Diagnostic Considerations and Management Strategies of Pediatric Inflammatory Bowel Diseases

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Burden of inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic condition characterized by uncontrolled inflammation of the gastrointestinal tract. It can arise at any age, with increasing incidence in the pediatric population.[1,2] Over time, IBD has emerged as a global healthcare problem with a worldwide prevalence of 0.3%.[3] Females are reported to be more commonly affected than males.[4] The prevalence and incidence is increasing among the Hispanics and Asians.[5] High incidence of pediatric IBD has already been reported in western countries.[6] Earlier, the disease was reported to have a low incidence in Asia; however, a rising trend in both incidence and prevalence has been noted over the past decade. Among the Asian countries, India is projected to have the highest disease burden of IBD.[7,8] About 25% of IBDs have their onset in childhood or adolescence.[1] It has been estimated that IBD affects about 5 to 11 per 100000 children and adolescents under the age of 18 years.[9] Due to such high prevalence, pediatricians commonly come across children with IBD in their clinical practice.

Types of inflammatory bowel disease

Crohn's disease and ulcerative colitis are the two major subtypes of IBD.[1] These subtypes differ in terms of the location and nature of inflammatory changes. Ulcerative colitis is characterized by continuous and diffuse inflammation of the colon involving the rectum in almost all cases.[1] Erythema, friability, granularity, purulent exudates, and ulcers are the characteristic macroscopic features. Histologically, it presents as chronic inflammation limiting to the mucosa.[6] Mild inflammation of the upper gastrointestinal tract is present in 40-70% cases. Crohn's disease, on the other hand, refers to non-contiguous chronic inflammation in any part of the gastrointestinal tract. Most commonly, the terminal ileum or the perianal region are inflamed, and in a non-continuous manner. Histologically, there is thickened submucosa, transmural inflammation, fissuring ulceration and non-caseating granulomas in this type of IBD.[1] Patients who cannot be classified definitively as having any of these forms are grouped into another clinical category called indeterminate colitis or IBD-unclassified. The clinico-histopathological findings in indeterminate colitis are non-specific, and sometimes it demonstrates overlapping features of both subtypes.[10] Although there exist many similarities among the different forms, there are unique pathophysiological mechanisms underlying pediatric IBD.

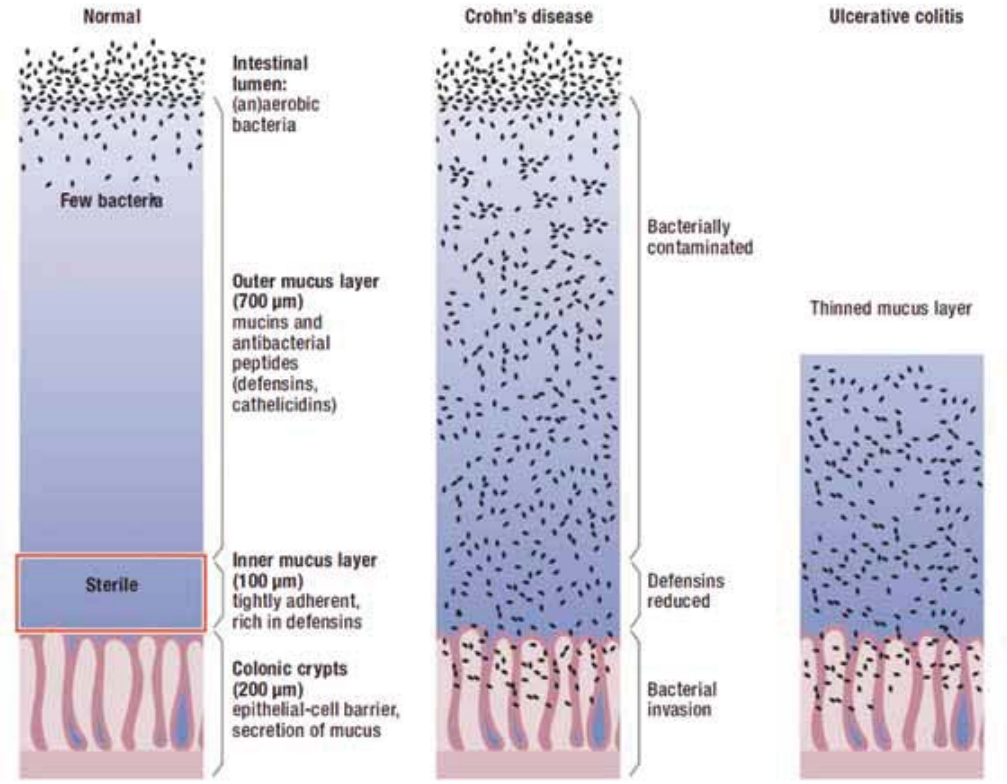
Risk factors and pathophysiology

The exact etiology of IBD is not known; however, the individual's genetic susceptibility, external environment, intestinal microbial flora and immune responses are considered to be involved and functionally integrated in IBD pathogenesis. Factors like cesarean delivery, lack of exposure to breast milk, dietary fat intake, obesity and early exposure to antibiotics have been implicated to increase the risk of IBD.[1,11] Recent evidences suggest that IBD is a complex barrier disorder with dysbiosis playing a central role in the initiation and maintenance of the chronic inflammatory process. Normally, the innermost mucosal barrier of the gastrointestinal tract consists of an epithelial layer above which lies a mucus layer made up of goblet cell mucins and epithelially secreted defensins. In ulcerative colitis, there is a thinning of the mucus layer while Crohn's disease is characterized by Paneth cells at the base of the epithelium and defective defensin production (Figure 1). These defects in the epithelial wall lead to altered mucus secretion and bacterial invasion into the mucosal epithelium. The invading microorganisms induce an inflammatory response mediated by several types of immune cells, thereby resulting in a chronic inflammatory condition and IBD symptoms.[12,13]

Clinical manifestations in children

The most common initial symptoms of IBD in children are nonspecific, including chronic abdominal pain, diarrhea, rectal bleeding and loss of weight.[14] Other systemic symptoms include fever, fatigue, pale skin and mucous membranes, abdominal tenderness on palpation,

Figure 1: Normal mucosal barrier and alterations in Crohn's disease and ulcerative colitis



Adapted from: Wehkamp J, Götz M, Herrlinger K, *et al*. Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int*. 2016;113(5):72–82.

resistance (particularly in lower right abdomen), nausea/vomiting, anorexia, constipation, tenesmus, and perianal disease manifesting as fistulae, fissures and abscesses. Extraintestinal manifestations are also common in children and adolescents with IBD. They are reported in about 10% of pediatric IBD cases. Some of the extraintestinal manifestations of pediatric IBD are shown in Box 1.[1,15]

Lactose intolerance in pediatric inflammatory bowel disease

Lactose malabsorption has been reported to influence the severity of disease activity in patients with ulcerative colitis and to cause abdominal pain in children. Hence, milk and other dairy products are eliminated from the diet of children with IBD.[16] Similarly, Crohn's disease has been reported to be a cause of secondary lactose intolerance, thereby resulting in decreased expression of lactase enzyme levels.[17,18] King *et al*[19] reported decreased lactase enzyme activity in 50 and 54% of children with Crohn's disease and ulcerative colitis, respectively (Figure 2). Similar results were obtained in another study[20] wherein decreased activity of lactase enzyme was found in 33% of biopsies taken from the small intestine mucosa of pediatric patients with Crohn's disease. Findings of these studies suggest that lactose intolerance should be evaluated as a part of the diagnostic work-up of IBD in children.

Diagnostic considerations

The objective of this review is to highlight the importance of early and accurate diagnosis of pediatric IBD in order to improve the prognosis. IBD has serious long-term consequences on the child's growth and development. Childhood onset IBD is also associated with an increased risk of cancer, both in young age and later life. Furthermore, children and adolescents with IBD have been reported to experience high levels of stress and psychosocial problems mainly due to the relapsing and unpredictable course and potentially embarrassing symptoms. Diagnosis is particularly challenging in pediatric patients who present with atypical symptoms and/or extraintestinal manifestations instead of gastrointestinal symptoms.[14] Furthermore, symptoms of pediatric IBD may often overlap with various other disorders (Box 2).[15] Hence, initial evaluation comprising of a thorough clinical history regarding symptom onset, recent travel, food intolerance, contact with enteric illnesses, medications, and a detailed family history of IBD is important.[1,14]

In addition, a complete physical examination including inspection of the abdomen, perianal and rectal region, and

Box 1: Extraintestinal manifestations of pediatric inflammatory bowel disease

Dermatologic
- Erythema nodosum
- Pyoderma gangrenosum
- Metastatic Crohn's disease

Musculoskeletal
- Arthritis
- Growth retardation
- Osteopenia
- Osteoporosis
- Ankylosing spondylitis
- Arthralgia

Hepatic
- Primary sclerosing cholangitis
- Cholelithiasis
- Autoimmune hepatitis

Ocular
- Episcleritis
- Uveitis
- Conjunctivitis

Renal
- Nephrolithiasis
- Obstructive hydronephrosis
- Enterovesical fistula
- Urinary tract infection
- Amyloidosis

Pulmonary
- Pulmonary vasculitis
- Pulmonary thrombosis

Pancreatic
- Pancreatitis

Hematologic
- Iron deficiency anemia
- Anemia of chronic disease
- Autoimmune hemolytic anemia
- Vitamin B12 deficiency
- Venous thromboembolism

Oral
- Aphthous stomatitis
- Cheilitis

Adapted from: 1. Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr*. 2015;169(11):1053–1060. **2.** Däbritz J, Gerner P, Enninger A, *et al*. Inflammatory Bowel Disease in Childhood and Adolescence: Diagnosis and Treatment. *Dtsch Arztebl Int.* 2017;114(19):331–338.

evaluation of height and weight with the help of age- and sex-specific percentile curves may help in better understanding of the underlying pathologic features.[1,15] Laboratory investigations should include markers of inflammation (such as C-reactive protein, erythrocyte sedimentation rate, fecal leukocytes, lactoferrin, calprotectin), complete blood count, nutritional laboratory tests, and stool examination. Non-invasive serological and genetic tests may also be useful in pediatric patients. However, endoscopic evaluation of the upper and lower gastrointestinal tracts (esophagogastroduodenoscopy and ileocolonoscopy) with

Box 2: Differential diagnoses of pediatric inflammatory bowel disease

- Carbohydrate malabsorption
- Infectious colitis, enterocolitis
- Cow's milk protein allergy
- Celiac disease
- Henoch–Schönlein purpura
- Appendicitis
- Anal fissures
- Intestinal polyps
- Hemorrhoids
- Intussusception
- Meckel diverticulum
- Immunological diseases
- Functional diseases
- Intestinal tuberculosis
- Adverse drug reactions

Adapted from: Däbritz J, Gerner P, Enninger A, *et al*. Inflammatory Bowel Disease in Childhood and Adolescence: Diagnosis and Treatment. *Dtsch Arztebl Int*. 2017;114(19):331–338.

mucosal biopsy for histopathologic confirmation remain the mainstay for diagnosing IBD in children. Small bowel imaging is useful for assessing extent and severity of the disease and identifying possible complications.[1,14] A diagnostic algorithm derived from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines is shown in Figure 3.[21] These stepwise approaches can help in shortening the time to diagnosis and initiating prompt treatment in children with IBD.

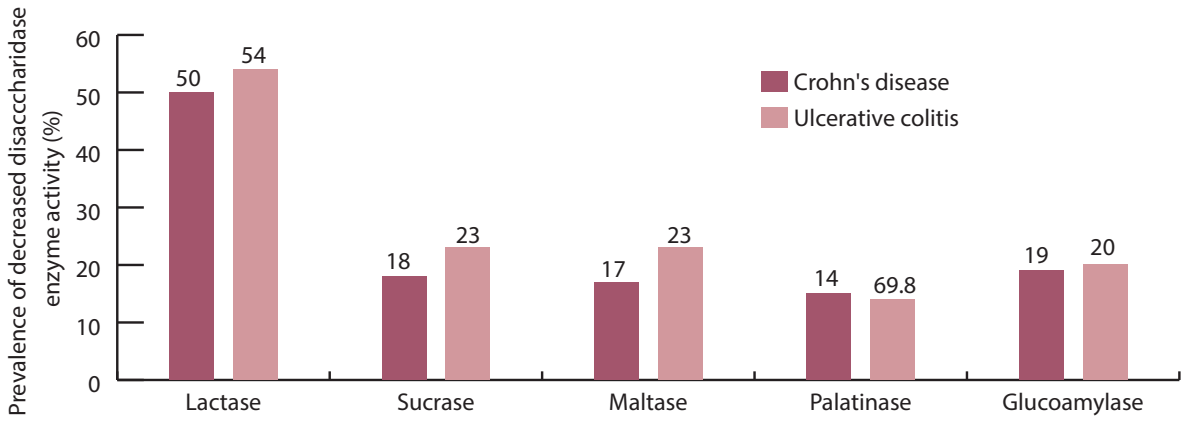
Management options

Treatment approaches for IBD in pediatric patients differ substantially from the adult population. Previously, the goal of therapy was solely to reduce symptoms. Currently, the management is aimed at relieving symptoms, restoring normal growth, reducing risk of surgery and improving psychosocial functioning and overall quality of life of the child. Current pharmacological therapies comprise of agents used to achieve remission and those used to maintain remission.[1] These include corticosteroids such as budesonide and prednisolone; 5-aminosalicylates like balsalazide; immunomodulators like thiopurines or methotrexate; and biologics like infliximab adalimumab, certolizumab pegol, and golimumab.[1,15] Although these agents can rapidly ameliorate symptoms, they are associated with limited improvements in mucosal healing. Moreover, prolonged use of these agents has been reported to cause undesirable side-effects in children.[11] Hence, alternative therapeutic options are required.

Nutritional modifications in pediatric inflammatory bowel disease

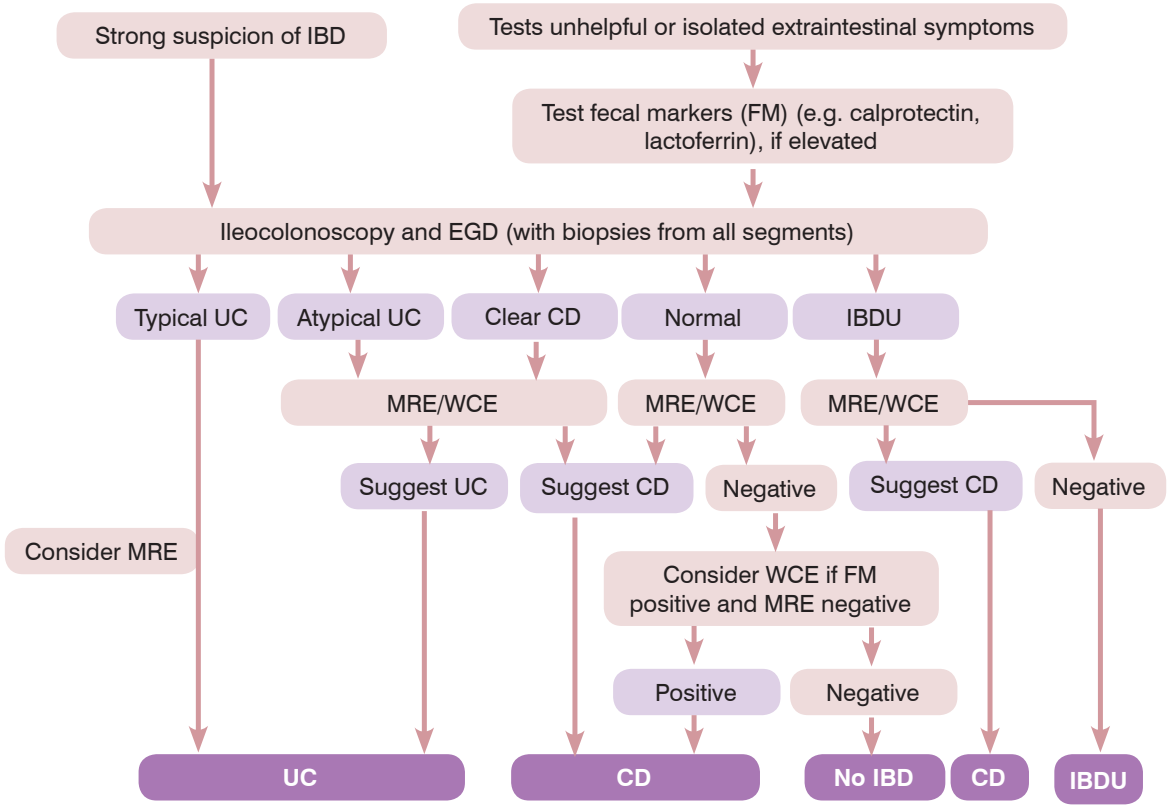
Enteral nutrition therapy is found to be a well-tolerated and effective therapeutic option in reducing mucosal inflammation

Figure 2: Prevalence of decreased disaccharidase enzyme activity in children with inflammatory bowel disease



Adapted from: King J, He Z, Raman Sreedharan, *et al*. Disaccharidase measurement in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2006;43(4):E53.

Figure 3: European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline-based algorithm for diagnosis of inflammatory bowel disease in children



Abbreviations: CD-Crohn's disease; EGD-esophagogastroduodenoscopy; FM-fecal marker; IBD-inflammatory bowel disease; MRE-magnetic resonance enterography; UC-ulcerative colitis; WCE-wireless capsule endoscopy; IBDU-inflammatory bowel disease unclassified

Adapted from: Levine A, Koletzko S, Turner D, *et al*. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014;58(6):795-806.

in children with IBD. This form of therapy involves the consumption of a liquid diet consisting of an elemental or polymeric formula, exclusively for a prolonged duration of 8 to 12 weeks. This approach permits avoidance of medication-associated adverse effects; furthermore, it also allows superior mucosal healing and nutritional improvements in children with IBD.[1,11] It is considered to be the first-line treatment to induce remission in children and adolescents with Crohn's disease.[15] Other nutritional modifications have also been proposed for pediatric IBD. Avoidance of high-fat diet and foods or beverages containing large amounts of emulsifiers may be considered.

Furthermore, since symptoms of lactose malabsorption overlap with those of IBD, a diet with reduced lactose intake may be initiated in children/adolescents with IBD and symptoms suggestive of lactose malabsorption. The ESPGHAN guidelines suggest the use of lactase treated products or enzyme replacements in children with IBD and associated lactase deficiency or lactose intolerance.[22]

Conclusion

Inflammatory bowel diseases are common chronic conditions that can arise at any age, with increasing incidence in the pediatric population. Crohn's disease and ulcerative colitis are the two major subtypes of IBD. Unique pathophysiological mechanisms underlie pediatric IBD. IBD has varied clinical manifestations in children. Early and accurate diagnosis of pediatric IBD is essential as the disease has serious consequences on the child's growth and development. Treatment approaches for IBD in pediatric patients differ substantially from the adult population. Pharmacological agents can rapidly ameliorate symptoms; however, they are associated with undesirable side-effects. Enteral nutrition therapy is found to be a well-tolerated and effective therapeutic option in reducing mucosal inflammation in children with IBD. Lactose intolerance is a common feature of pediatric IBD. Guidelines suggest the use of lactase treated products or enzyme replacements in children with IBD and associated lactase deficiency or lactose intolerance.

References

1. Rosen MJ, Dhawan A, Saeed SA. Inflammatory Bowel Disease in Children and Adolescents. *JAMA Pediatr.* 2015;169(11):1053–1060.
2. Wehkamp J, Götz M, Herrlinger K, *et al*. Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int.* 2016;113(5):72–82.
3. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2018;390(10114):2769-2778.
4. Hosseini-Carroll P, Mutyala M, Seth A, et al. Pregnancy and inflammatory bowel diseases: Current perspectives, risks and patient management. World J Gastrointest Pharmacol Ther. 2015;6(4):156–171.
5. Hou JK, El-Serag H, Thirumurthi S. Distribution and manifestations of inflammatory bowel disease in Asians, Hispanics, and African Americans: a systematic review. Am J Gastroenterol. 2009;104(8):2100-9.
6. Aziz DA, Moin M, Majeed A, *et al*. Paediatric Inflammatory Bowel Disease: Clinical Presentation and Disease Location. *Pak J Med Sci*. 2017;33(4):793–797.
7. Ray G. Inflammatory bowel disease in India - Past, present and future. *World J Gastroenterol.* 2016;22(36):8123–8136.
8. Singh P, Ananthakrishnan A, Ahuja V. Pivot to Asia: inflammatory bowel disease burden. *Intest Res.* 2017;15(1):138–141.
9. Buderus S, Scholz D, Behrens R, *et al*. Inflammatory Bowel Disease in Pediatric Patients: Characteristics of Newly Diagnosed Patients From the CEDATA-GPGE Registry. *Dtsch Arztebl Int.* 2015;112(8):121–127.
10. Romano C, Famiani A, Gallizzi R, *et al*. Indeterminate colitis: a distinctive clinical pattern of inflammatory bowel disease in children. *Pediatrics.* 2008;122(6):e1278-81.
11. Nahidi L, Day AS, Lemberg DA, Leach ST. Paediatric Inflammatory Bowel Disease: A Mechanistic Approach to Investigate Exclusive Enteral Nutrition Treatment. *Scientifica (Cairo)*. 2014;2014:423817.
12. Wehkamp J, Götz M, Herrlinger K, *et al*. Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis. *Dtsch Arztebl Int.* 2016;113(5):72–82.
13. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. *J Inflamm Res.* 2014;7:113–120.
14. Cuffari C. Diagnostic Considerations in Pediatric Inflammatory Bowel Disease Management. *Gastroenterol Hepatol (N Y).* 2009;5(11):775–783.
15. Däbritz J, Gerner P, Enninger A, *et al*. Inflammatory Bowel Disease in Childhood and Adolescence: Diagnosis and Treatment. *Dtsch Arztebl Int.* 2017;114(19):331–338.
16. Kirschner BS, DeFavaro MV, Jensen W. Lactose malabsorption in children and adolescents with inflammatory bowel disease. *Gastroenterology*. 1981;81(5):829-32.
17. Heine RG, AlRefaee F, Bachina P, *et al*. Lactose intolerance and gastrointestinal cow's milk allergy in infants and children – common misconceptions revisited. *World Allergy Organ J.* 2017;10(1):41.
18. Usai-Satta P, Scarpa M, Oppia F, Cabras F. Lactose malabsorption and intolerance: What should be the best clinical management? *World J Gastrointest Pharmacol Ther.* 2012; 3(3): 29–33.
19. King J, He Z, Raman Sreedharan, *et al*. Disaccharidase measurement in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2006;43(4):E53.
20. Wiecek S, Wos H, Radziewicz Winnicki I, *et al*. Disaccharidase activity in children with inflammatory bowel disease. *Turk J Gastroenterol.* 2014;25(2):185-91.
21. Levine A, Koletzko S, Turner D, *et al*. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014;58(6):795-806.
22. Miele E, Shamir R, Aloi M, *et al*. Nutrition in Pediatric Inflammatory Bowel Disease: A Position Paper on Behalf of the Porto Inflammatory Bowel Disease Group of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;66(4):687-708.

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20. Management and Screening of Primary Vesicoureteral Reflux in Children. Available at: http://www.auanet.org/guidelines/vesicoureteral-reflux-(2010-amended-2017)#x3333. Accessed on 31/8/2018.
21. Cheng CH, Tsai MH, Huang YC, et al. Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. *Pediatrics.* 2008;122:1212-7.
22. Cooper CS, Chung BI, Kirsch AJ, et al. The outcome of stopping prophylactic antibiotics in older children with vesicoureteral reflux. *J Urol.* 2000; 163:269-272.
23. Thompson RH, Chen JJ, Pugach J, et al. Cessation of prophylactic antibiotics for managing persistent vesicoureteral reflux. *J Urol.* 2001; 166:1465-9.
24. Al-Sayyad AJ, Pike JG, Leonard MP. Can prophylactic antibiotics safely be discontinued in children with vesicoureteral reflux? *J Urol.* 2005; 174 (4 Pt 2):1587-9.
25. Peters CA, Skoog SJ, Arant BS Jr, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. *J Urol.* 2010;184(3): 1134-44.
26. Gökçe İ, Çiçek N, Güven S, et al. Changes in Bacterial Resistance Patterns of Pediatric Urinary Tract Infections and Rationale for Empirical Antibiotic Therapy. *Balkan Med J*. 2017;34:432-5.
27. Falakaflaki B, Fallah R, Jamshidi MR, et al. Comparison of Nitrofurantoin and Trimethoprim-Sulphamethoxazole for Long-Term Prophylaxis in Children with Recurrent Urinary Tract Infections. *International Journal of Pharmacology.* 2007;3:179-182.
28. Fransen F, Melchers MJB, Lagarde CMC, et al. Pharmacodynamics of Nitrofurantoin at different pH levels against pathogens involved in urinary tract infections. *J Antimicrob Chemother*. 2017;72(12):3366-3373.
29. Calzi A, Grignolo S, Caviglia I, et al. Resistance to oral antibiotics in 4569 Gram-negative rods isolated from urinary tract infection in children. *Eur J Pediatr.* 2016;175(9):1219-1225.
30. Shariff V A AR, Shenoy MS, Yadav T, MR. The antibiotic susceptibility patterns of uropathogenic Escherichia coli, with special reference to the fluoroquinolones. *J Clin Diagn Res*. 2013;7(6):1027-30.