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Crohns Disease: An Overview

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Review article

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ABSTRACT

As Crohn's disease is mostly considered as the auto immune disease, there is a need to study the disease more deeply as it is also known to have no cure. It is a type of inflammatory bowel disease which is dissimilar to the Ulcerative Colitis which is also an inflammatory bowel disease.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of intestinal disorders that cause prolonged inflammation of the digestive tract. Inflammation anywhere along the digestive tract disturbs this normal process. IBD can be very painful and disruptive, and in some cases, may even be life-threatening [1-5]. The two most common diseases included in inflammatory bowel diseases are ulcerative colitis and Crohn's disease. It is important to know that Crohn's disease is not the same thing as ulcerative colitis. Crohn's disease forms inflammation in any part of the digestive tract. However, it mostly affects the tail end of the small intestine. Ulcerative colitis is only to the colon, also called the large intestine. Crohn's disease can also affect the whole thickness of the bowel wall, but ulcerative colitis only involves the innermost lining of the colon.

Symptoms of the Crohn's Disease

- Persistent Diarrhea
- Urgent need to move bowels
- Abdominal cramps
- Feeling of incomplete evacuation
- Rectal bleeding
- Constipation (can lead to bowel obstruction)

Diarrhea

Diarrhea can be defined in absolute or relative terms based on either the frequency of bowel movements or the consistency (looseness) of stools.

Abdominal Cramps

The term stomach cramps is nonspecific and is used to refer to a number of different symptoms or sensations rather than true muscle cramps of the stomach. People often refer to a "stomachache" or "abdominal cramps" to refer to pain that is perceived anywhere in the abdominal area [6-10]. As such, the list of potential causes is extremely varied. Organs of the abdomen include the stomach, small intestine, colon, liver, gallbladder, and pancreas, and problems or diseases of all of these organs may be the source of pain [11-15].

Incomplete Evacuation

Patients usually report constipation when there are changes to harder stool consistency, the presence of pellets, straining or feelings of incomplete evacuation, infrequent bowel movements and a sensation of “want to but can't.”

Rectal Bleeding

Rectal bleeding is the passage of blood through the anus. The bleeding may result in bright red blood in the stool as well as maroon colored or black stool. The bleeding also may be not visible with the human eye.

Constipation

Being constipated means your bowel movements are difficult or happen less often than normal. Almost everyone has it at some point in life, and it's usually not serious ^[16-20]. Still, you'll feel much better when your system is back on track.

The normal length of time between bowel movements varies widely from person to person. Some people have bowel movements three times a day. Others have them only once or twice a week. Going longer than three or more days without one is usually too long ^[21-25]. After three days, the stool or faeces become harder and tougher to pass.

Other symptoms associated with inflammatory bowel diseases are

- Fever
- Loss of appetite
- Weight Loss
- Fatigue
- Night sweats
- Loss of normal menstrual cycle

People suffering from Crohn's disease often experience loss of appetite and may lose weight as a result. A feeling of weakness and fatigue is also common. Among children, Crohn's may delay growth and development.

In more critical cases, Crohn's can lead to fissures in the lining of the anus, which may cause pain and bleeding, especially during bowel movements ^[25-30]. Inflammation may also lead to the formation of fistula. A fistula is a tunnel that leads from one loop of intestine to other intestine, or that connects the intestine to the bladder, vagina, or skin. This is a serious condition that requires immediate attention ^[31-35].

The symptoms of Crohn's disease depends upon the part of the GI tract that is affected.

The types of Crohn's disease are ileocolitis, ileitis, Gastroduodenal Crohn's disease, Jejunoileitis, Crohn's (granulomatous) colitis ^[36].

Ileocolitis

Ileocolitis is the most common type of Crohn's disease. It causes inflammation in the end of the small intestine (known as the ileum) and the colon (large intestine) - most often on the right side. Around 50% of people with Crohn's disease are diagnosed with ileocolitis. It is a life-long chronic condition which cannot currently be cured and is part of a group of conditions known as inflammatory bowel disease (IBD). Crohn's disease causes inflammation in the gastrointestinal (GI) tract ^[37-42]. It most commonly affects the small intestine and the beginning of the large intestine; however it can affect any part of the GI tract from the mouth to the anus.

Crohn's disease affects the entire thickness of the digestive tract wall and may also skip areas - meaning you could have inflammation near your mouth and also in your small bowel but nowhere in between ^[42-48].

It is common for people with Crohn's disease to be diagnosed with more than one type of the condition if inflammation is present in several places in the GI tract.

Ileitis:

This type affects only the ileum. Symptoms are of ileocolitis. In severe cases, fistulas or inflammatory abscess in right lower part of abdomen may occur.

Gastroduodenal Crohn's disease

Gastroduodenal Crohn's disease is a form of Crohn's disease that causes inflammation to the oesophagus, stomach and/or duodenum (the first part of the small intestine). This type is not common - only up to around 5% of people with Crohn's disease have gastroduodenal Crohn's ^[48-53]. It is a lifelong chronic condition which cannot

currently be cured and is part of a group of conditions known as inflammatory bowel disease (IBD). Crohn's disease causes inflammation in the gastrointestinal (GI) tract. It most commonly affects the small intestine and the beginning of the large intestine; however it can affect any part of the GI tract from the mouth to the anus ^[54-60]. Crohn's disease also affect the entire thickness of the digestive tract wall and may also skip areas - meaning you could have inflammation near you mouth and also in your small bowel but nowhere in between. It is common for people with Crohn's disease to be diagnosed with more than one type of the condition if inflammation is present in several places in the GI tract.

Jejunoleitis

Jejunoleitis is a form of Crohn's disease, which causes inflammation in the jejunum (the upper half of the small intestine). This form of Crohn's disease is fairly uncommon and is more commonly diagnosed in children than adults. It is a lifelong chronic condition which cannot currently be cured and is part of a group of conditions known as inflammatory bowel disease (IBD) ^[61-65]. Crohn's disease causes inflammation in the gastrointestinal (GI) tract. It most commonly affects the small intestine and the beginning of the large intestine; however it can affect any part of the GI tract from the mouth to the anus. Crohn's disease can affect the entire thickness of the digestive tract wall and may also skip areas - meaning you could have inflammation near you mouth and also in your small bowel but nowhere in between ^[65-70]. It is common for people with Crohn's disease to be diagnosed with more than one type of the condition if inflammation is present in several places in the GI tract.

Crohn's (granulomatous) colitis

Crohn's (granulomatous) colitis occurs only in the colon (also known as the large intestine or large bowel). It is often just known as Crohn's colitis and is a form of Crohn's disease. It accounts for around 20% of Crohn's disease cases. Crohn's colitis is a lifelong chronic condition which cannot currently be cured and is part of a group of conditions known as inflammatory bowel disease (IBD) ^[71-75]. Crohn's disease causes inflammation in the gastrointestinal (GI) tract. It most commonly affects the small intestine and the beginning of the large intestine, however it can affect any part of the GI tract from the mouth to the anus. Crohn's disease can affect the entire thickness of the digestive tract wall and may also skip areas - meaning you could have inflammation near you mouth and also in your small bowel but nowhere in between ^[76-80]. It is common for people with Crohn's disease to be diagnosed with more than one type of the condition if inflammation is present in several places in the GI tract. When given a diagnosis of Crohn's colitis some people believe they have both Crohn's disease and ulcerative colitis. However, this isn't the case. Crohn's colitis is a form of Crohn's disease. Due to inflammation in the colon in Crohn's colitis bloody diarrhoea is a common symptom.

CAUSES OF CROHN'S DISEASE

Men and Women are equally likely to be affected, the disease can occur at any age. Crohn's is more prevalent among the young adults between the ages of 15 and 35. While the exact cause of the Crohn's disease is unknown, it seems to be due to a combination of environmental factors and genetical factors.

Genetics

Crohn's has a genetic effect. Because of this, siblings of the people with Crohn's are 30 times more likely to develop Crohn's than the general population ^[81-85]. Over thirty genes have been associated with Crohn's; a biological function is known for most of them. There is considerable overlap between susceptibility loci for IBD and mycobacterial infections ^[85-90]. Recent genome-wide association studies have proven that Crohn's disease is genetically linked to coeliac disease.

Immune system

There was a prevailing talk that Crohn's disease is a primary T cell autoimmune disorder, however, a newer theory hypothesizes that Crohn's results from an impaired innate immunity ^[91-95]. The later study describes impaired cytokine secretion by macrophages, which is impaired innate immunity and leads to a sustained microbial-induced inflammatory response in the colon, where the bacterial load is more. Another theory is that Crohn's inflammation was caused by an overactive Th1 and Th17 cytokine response.

Environmental factors

The increased incidence of Crohn's in the industrialized world indicates an environmental component. Crohn's disease is associated with an increased intake of animal protein, milk protein and an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids ^[95-98]. People who consume vegetable proteins appear to have a lower incidence of Crohn's disease. Consumption of fish protein has no effect. Smoking increases the risk of the return of active disease (flares). Isotretinoin is associated with Crohn's. Although stress is sometimes claimed to exacerbate Crohn's disease, there is no concrete evidence to support such claim.

Different diagnostic studies can be done for the Crohn's disease such as Endoscopy, Radiologic tests and Blood tests.

Medication

Normal antibiotics to treat any infection and amino salicylate anti-inflammatory drugs and corticosteroids to reduce inflammation.

Alternative medicine

These include diets, probiotics, fish oil and other herbal and nutritional supplements. Few scientists have suggested more research into these is needed to discriminate between effective therapies and ineffective therapies.

PROGNOSIS

Crohn's disease is a chronic condition for which there is no cure. It is characterised by periods of improvement followed by episodes when symptoms flare up. With treatment, most people achieve a healthy weight, and the mortality rate for the disease is relatively low. It can vary from being benign to very severe and people with CD could experience just one episode or have continuous symptoms ^[98,99]. It usually reoccurs, although some people can remain disease free for years or decades. Most people with Crohn's live a normal lifespan. However, Crohn's disease is associated with a small increase in risk of small bowel and colorectal carcinoma (bowel cancer).

CONCLUSION

The percentage of people with Crohn's disease has been determined in Norway and the United States and is similar at 6 to 7.1:100,000. The Crohn's and Colitis Foundation of America cites this number as approximately 149:100,000; NIH cites 28 to 199 per 100,000. Crohn's disease is more common in northern countries, and with higher rates still in the northern areas of these countries. The incidence of Crohn's disease is thought to be similar in Europe but lower in Asia and Africa. It also has a higher incidence in Ashkenazi Jews and smokers. Crohn's disease begins most commonly in people in their teens and 20s, and people in their 50s through to their 70s. It is rarely diagnosed in early childhood. It usually affects female children more severely than males. However, only slightly more women than men have Crohn's disease. Parents, siblings or children of people with Crohn's disease are 3 to 20 times more likely to develop the disease. Twin studies find that if one has the disease there is a 55% chance the other will too. The incidence of Crohn's disease is increasing in Europe. Patient education about use of medications, expectations of efficacy and tolerability issues and long-term management options will help achieve adherence and therapeutic success.

REFERENCES

1. Daniel A. Intestinal Tuberculosis and Crohns Disease. *J Clin Case Rep.* 2015;5:578.
2. Daniel T, et al. Sweet Syndrome and Pulmonary Tuberculosis in a Crohns Disease Patient Treated with Anti-TNF α . *J Gastrointest Dig Syst.* 2015;5:262.
3. Toru S. Autoimmune Thyroid Diseases Concomitant with Crohns Disease and Ulcerative Colitis. *Thyroid Disorders Ther.* 2015;4:169.
4. Yuan L, et al. Crohns Disease Complicated by Gastrointestinal Non-Hodgkins Lymphoma: Report of a Case. *J Gerontol Geriatric Res.* 2012;1:109.
5. Skroza N, et al. Psoriasis and Inflammatory Bowel Diseases: Epidemiological, Genetic and Pathogenetic Correlations: A Review of Literature. *J Clin Exp Dermatol Res.* 2016;7:335.
6. Desideri F, et al. Anti TNF α for Inflammatory Bowel Diseases in Cirrhotic Patients: A Feasible Option. *J Colitis Diverticulitis.* 2016;1:e003.

7. Dworzanski T, et al. Advances in Nutrition of Patients with Inflammatory Bowel Diseases. *J Nutr Food Sci.* 2016;6:451.
8. Vuanghao L. Journal of Inflammatory Bowel Diseases and Disorder: A New Paradigm Platform from Bench to Bedside. *J Inflamm Bowel Dis & Disord.* 2016.
9. Atzori L, et al. Cutaneous Adverse Reactions during Anti-Tnf Alpha Treatment for Inflammatory Bowel Diseases: The Experience of the Dermatology Clinic of Cagliari. *J Pharmacovigilance.* 2015;S2:004.
10. Antoni S and Izabela S. Autacoids in Inflammatory Bowel Diseases. *J Autacoids.* 2014;5:e127.
11. Alexander EB and Eugene IP. Micro RNA as Biomarkers and Tool for Target-Based Treatment in Patients with Inflammatory Bowel Diseases. *Biol Med (Aligarh).* 2015;6:231.
12. Rebecca HS, et al. Pharmacokinetics of Monoclonal Antibodies Used for Inflammatory Bowel Diseases in Pregnant Women. *J Clin Toxicol.* 2014;4:209.
13. Antonella G, et al. Role of Fecal Calprotectin in Monitoring Response to Therapy in Inflammatory Bowel Diseases. *J Clin Cell Immunol.* 2014;5: 252.
14. Dapeng J, et al. Manipulation of Microbiome, a Promising Therapy for Inflammatory Bowel Diseases. *J Clin Cell Immunol.* 2014;5:234.
15. Souad B and Tom GM. Ethnic Differences in Inflammatory Bowel Diseases. *J Gastrointest Dig Syst.* 2014;4:173.
16. Flavio C, et al. Targeting T cells in Chronic Inflammatory Bowel Diseases. *J Clin Cell Immunol.* 2013;4:155.
17. Vincent B. Do Anti-TNF Therapies Increase the Risk of Postoperative Complications in Inflammatory Bowel Diseases?. *J Gastrointest Dig Syst.* 2012;2:112.
18. Bouzid D, et al. Replication of Identified Inflammatory Bowel Diseases Genetic Associations: A Case-Control Study in the Tunisian Population. *J Clin Cell Immunol* 2013;S10:001.
19. Tara MC, et al. Genetic and Demographic Correlates of Quality of Life after Ileal Pouch Anal Anastomosis for Ulcerative Colitis. *J Inflamm Bowel Dis & Disord.* 2016.
20. Liu Y, et al. Associations between Markers of Colorectal Cancer Stem Cells, Mutations, Mirna, and Clinical Characteristics of Ulcerative Colitis. *Transl Med* 2016;6:168.
21. Zhu M, et al. The Regulatory Role of Casein Glycomacropptide (CGMP) in the Fecal Flora of Mice with Ulcerative Colitis. *Journal of Microbiology and Biotechnology* 2015.
22. Love BL, et al. Adherence to 5-Aminosalicylic Acid Treatment in Ulcerative Colitis. *J Hepatol Gastroint Dis* 2015;1:107.
23. Abu TM, et al. An Unusual Presentation of Ulcerative Colitis with Numerous Colon Polyps and Formation of Multiple Band and Septum Like Structures in the Colonic Lumen. *J Hepatol Gastroint Dis* 2015;1:i101.
24. Alaa EI, et al. Role of Autologous Bone Marrow Stem Cell Transplantation in the Treatment of Active Ulcerative Colitis. *J Stem Cell Res Ther* 2015;5:313.
25. Masayuki S, et al. Endoscopic Findings during the Early Induction Phase of Infliximab Therapy may Predict its Efficacy for Refractory Ulcerative Colitis. *J Gastrointest Dig Syst* 2015;5:324.
26. Ahmad AH, et al. Synchronous Perforation of Transverse and Sigmoid Colon due to Ulcerative Colitis: A Rare Case Report. *Surgery* 2015;11:1.
27. Toru S. Autoimmune Thyroid Diseases Concomitant with Crohn's Disease and Ulcerative Colitis. *Thyroid Disorders Ther* 2015;4:169.
28. Robert L, et al. Treatment of Ulcerative Colitis Patients by Local Application of the Toll like Receptor-9 Agonist DIMS0150. *J Gastrointest Dig Syst* 2014;4:243.
29. Hanan EB, et al. Interleukin 23 P 19 Expression in Patients with Ulcerative Colitis and Its Relation to Disease Severity. *J Mol Biomark Diagn.* 2014; 5:191.
30. Anita A, Tamás M. Pathogenesis of Ulcerative Colitis and Crohn's Disease: Similarities, Differences and a Lot of Things We Do Not Know Yet. *J Clin Cell Immunol.* 2014; 5:253.
31. Toru Shizuma. Coexistence of Graves' Disease (Basedow's Disease) and Ulcerative Colitis. *Intern Med.* 2014; 4:166.
32. Paul Z, et al. Novel Approach for Designing Supportive Care in Genetic Disorders of Gastrointestinal Tract: Three-Dimensional Polymer Model of Nutritional Therapies in Cystic Fibrosis, Ulcerative Colitis, and Crohn's Disease. *J Nanomedicine Biotherapeutic Discov.* 2014; 4:128.
33. Mihaela L and Pascu. Full Clinical and Endoscopic Remission Following Fecal Microbiota Transplant with Moderate-Severe Treatment-Resistant Ulcerative Colitis. *J Gastrointest Dig Syst.* 2014; 4:183.

34. Ibtisam Al-Thubaiti and Farah Al-Eissa. A Patient with NMO and Ulcerative Colitis: Is it only Autoimmunity?. *J Clin Case Rep.* 2013; 3:322.
35. Silvestro C, et al. Ulcerative Colitis in the Elderly. *J Gerontol Geriatric Res.* 2014;3:e125.
36. Ayako S, et al. Generalized Pustular Psoriasis Associated with Ulcerative Colitis. *J Clin Exp Dermatol Res.* 2013;4:192.
37. Lamdhade SJ, et al. Successful Treatment of Listeria Meningitis in a Pregnant Woman with Ulcerative Colitis Receiving Infliximab. *Gen Med.* 2013;1:116.
38. Tomotaka T, et al. Adacolumn Therapeutic Leucocytapheresis for Ulcerative Colitis: Clinical and Endoscopic Features of Responders and Unresponders to this Nonpharmacologic Intervention. *J Gastrointest Dig Syst.* 2011;1:104.
39. Tamás M, et al. Management of Patients with Ulcerative Colitis after Proctocolectomy: Pouchitis is a Real Danger. *J Gastrointest Dig Syst.* 2011;1:102.
40. Cezary S. Contribution of Neuropeptides and Neurotransmitters in colitis. *J Veterinar Sci Technol.* 2011;S5-001.
41. Aaron MW, et al. Methodological Challenges in Conducting Case-Control Studies in Necrotizing Enterocolitis, Microscopic colitis. *Epidemiol.* 2012;2:e107.
42. Hak LM, et al. CRTH2 is Critical to the Development of Colitis Induced by Dextran Sodium Sulfate (DSS). *J Clin Cell Immunol.* 2012; 3:131.
43. Xiao MB, et al. The Benefits of Expressed Maternal Milk and Donor Breast Milk for Preventing Necrotizing Enterocolitis in Preterm Infants: Systematic Review and Meta- Analysis. *J Nutrition Disorder Ther.* 2012; 2:110.
44. Tamas J, et al. Intestinal Epithelial Cell Apoptosis, Immunoregulatory Molecules, and Necrotizing Enterocolitis. *J Clin Cell Immunol.* 2012; S3:007.
45. Tomotaka T, et al. Adacolumn Therapeutic Leucocytapheresis for Ulcerative Colitis: Clinical and Endoscopic Features of Responders and Unresponders to this Nonpharmacologic Intervention. *J Gastrointest Dig Syst.* 2011;1:104.
46. Ibtisam AT, et al. A Patient with NMO and Ulcerative Colitis: Is it only Autoimmunity?. *J Clin Case Rep.* 2013;3:322.
47. Toru S and Naoto F. Anticarcinogenic and Anti-Colitis Effects of the Japanese Vinegar Kurozu. *J Rice Res.* 2013;1:113.
48. Silvestro C, et al. Ulcerative Colitis in the Elderly. *J Gerontol Geriatric Res.* 2014;3:e125.
49. Ayako S, et al. Generalized Pustular Psoriasis Associated with Ulcerative Colitis. *J Clin Exp Dermatol Res.* 2013;4:192.
50. Lamdhade SJ, et al. Successful Treatment of Listeria Meningitis in a Pregnant Woman with Ulcerative Colitis Receiving Infliximab. *Gen Med.* 2013;1:116.
51. Ghiath B, et al. The Effect of Intravenous Vancomycin in the Reduction of the Incidence of Clostridium difficile Colitis. *J Infect Dis Ther.* 2016;4:286.
52. Tara MC, et al. Genetic and Demographic Correlates of Quality of Life after Ileal Pouch Anal Anastomosis for Ulcerative Colitis. *J Inflamm Bowel Dis & Disord.* 2014.
53. Suvradeep M, et al. Fulminant Amoebic colitis: A Rarity in the Pediatric Population. *J Microb Biochem Technol.* 2016; 8:166-168.
54. Abdel Maksod YH, et al. Stepwise Management of Necrotizing Enterocolitis Could Improve Outcome of this Life-Threatening Disease. *Med Rep Case Stud.* 2016;1:113.
55. Galanopoulos M, et al. A Successful Treatment of Anterior nodular Scleritis with Topical Corticosteroids in a patient with Crohn's Colitis. *J Inflamm Bowel Dis & Disord.* 2016.
56. Jan M. Vrolijk. Amoebic Enterocolitis Mimicking Crohn's Disease - Case Report. *J Gastrointest Dig Syst.* 2016;6:422.
57. Ashraf MU, et al. Microscopic Colitis: An Overview. *Interdiscip J Microinflammation.* 2014;1:108.
58. Mona Z Zaghoul. Pseudomembranous colitis. *Trop Med Surg.* 2014;3:e120.
59. Yeong JL, et al. Neutropenic Enterocolitis Associated with Methotrexate Therapy for Rheumatoid Arthritis: A Case Report. *J Arthritis.* 2014;3:126.
60. Mihaela L and Pascu. Full Clinical and Endoscopic Remission Following Fecal Microbiota Transplant with Moderate-Severe Treatment-Resistant Ulcerative Colitis. *J Gastrointest Dig Syst.* 2014; 4:183.

61. Dokyoon K, et al. Pilot Application of Magnetic Nanoparticle-Based Biosensor for Necrotizing Enterocolitis. *J Proteomics Bioinform.* 2015;5:002.
62. Deepak S, et al. Lactoferrin and Neonates: Role in Prevention of Neonatal Sepsis and Necrotizing Enterocolitis. *J Neonatal Biol.* 2014;3:E110.
63. Hanan EB, et al. Interleukin 23 P 19 Expression in Patients with Ulcerative Colitis and Its Relation to Disease Severity. *J Mol Biomark Diagn.* 2014;5:191.
64. Anita A and Tamás M. Pathogenesis of Ulcerative Colitis and Crohn's Disease: Similarities, Differences and a Lot of Things We Do Not Know Yet. *J Clin Cell Immunol.* 2014;5:253.
65. Toru S. Coexistence of Graves' Disease (Basedow's Disease) and Ulcerative Colitis. *Intern Med.* 2014;4:166.
66. Toru S. Anti-Colitis Effects of Brown Rice Reported by Experimental Studies. *J Rice Res.* 2014;2:127.
67. Ciurans CC, et al. Chronic Constipation in Pediatrics - Not Always a Trivial Discomfort. *J Community Med Health Educ.* 2016;6:415.
68. Peter K and George K. The Clinical Challenge of Opioid-induced Constipation: Insights from the Opioid-induced Constipation Clinical Audit. *J Gen Pract.* 2016;4:221.
69. Hideaki I, et al. A New Acid-Resistant Seamless Capsule of Bifidobacterium Improves Chronic Constipation in Patients on Maintenance Hemodialysis. *J Prob Health.* 2016.
70. Anne-Marie JW, et al. Preventive Prescribing of Laxatives for Opioid-induced Constipation Using Electronic Clinical Rule Implementation by Clinical Pharmacists. *Adv Pharmacoepidemiol Drug Saf.* 2014;3:159.
71. Tatsuya A, et al. Efficacy of Lubiprostone in Chronic Constipation: Clinical and Work Productivity Outcomes. *J Gastrointest Dig Syst.* 2014;4:223.
72. Miharuru I, et al. Prophylactic Effects of Kefir-Fermented Milk on Constipation among Mentally and Physically Handicapped Persons. *J Prob Health.* 2015.
73. Marta E, et al. Diarrhea and Symptomatic Coagulopathy: An Uncommon Presentation of Celiac Disease. *J Gastrointest Dig Syst.* 2015;5:358.
74. Pinchuk LM, et al. All is Not Butter that Comes from the Cow: The Bovine Viral Diarrhea. Understanding the Pathogenesis of Cytopathic and Non-Cytopathic Infection. *J Anc Dis Prev Rem.* 2015;3:126.
75. Anuradha SD, et al. Bacterial Etiology of Diarrhea in Children Admitted in Hematologic Unit in a Tertiary Care Hospital. *J Leuk.* 2015;S1-005.
76. Geetha V, et al. Pylori Associated Spruelike Duodenitis Presenting with Chronic Diarrhea, Hypoalbuminemia and Edema ? A Case Report. *J Clin Exp Pathol.* 2015;5:223.
77. Nikhil GS. Diarrheal Epidemic Grips Ghallour Sub-centre, Jawalamukhi Block, Kangra District, Himachal Pradesh, India. *Fam Med Med Sci Res.* 2015;4:157.
78. Hernandez PM and Gomez TV. Diarrhea as the Main Initial Manifestation of Meningococemia: 2 Case Reports. *J Clin Diagn Res.* 2014;2:113.
79. Sumera AA, et al. Surveillance System Proposed To Monitor The Burden Of Diarrheal Diseases In Pakistan: A Short Communication. *J Gen Pract.* 2016;4:258.
80. Monteleone G, et al. Mongersen Oral SMAD7 Antisense Oligonucleotide, and Crohn's Disease. *The New England Journal Of Medicine.* 2015; 372:1104-1113.
81. Julian LS. Disorders of Fluids and Electrolytes: Integration of Acid-Base and Electrolyte Disorders. *The New England Journal Of Medicine.* 2014;371:1821-1831.
82. William JS, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. *The New England Journal Of Medicine.* 2013;369:711-721.
83. Jean FC, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *The New England Journal Of Medicine.* 2010;362:1383-1395.
84. Glocker EO, et al. Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor. *NEJM.* 2009;361:2033-2045.
85. Mark WB, et al. Case 35-2007 — A 30-Year-Old Man with Inflammatory Bowel Disease and Recent Onset of Fever and Bloody Diarrhea. *N Engl J Med.* 2007;357:2068-2076.
86. Daniel KP, et al. 8-2006 — A 71-Year-Old Woman with Crohn's Disease and Altered Mental Status. *N Engl J Med* 354:1178-1184.
87. Timo V, et al. Safety and Efficacy of a Pentavalent Human-Bovine (WC3) Reassortant Rotavirus Vaccine. *N Engl J Med.* 2006;354:23-33.

88. Mark P, et al. Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation. *N Engl J Med.* 2011;364:22-32.
89. Brian GF, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med.* 2013;369:699-710.
90. Lawrence M, et al. Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation. *N Engl J Med.* 2006;354:2225-2234.
91. Giovanni M, et al. Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn's Disease. *N Engl J Med.* 2015; 372:1104-1113.
92. William JS, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. *N Engl J Med.* 2012;367:1519-1528.
93. Michael C. Mechanisms of Disease: Peripheral Mechanisms in Irritable Bowel Syndrome. *N Engl J Med.* 2012;367:1626-1635.
94. Danny OJ. Diverticulitis. *N Engl J Med.* 2007;357:2057-2066.
95. Brian K. Interleukin-10 in Inflammatory Bowel Disease. *N Engl J Med.* 2009;361:2091-2093.
96. Benjamin AN, et al. Case 39-2014 — A 9-Year-Old Girl with Crohn's Disease and Pulmonary Nodules. *N Engl J Med.* 2014;371:2418-2427.
97. William JS, et al. Certolizumab Pegol for the Treatment of Crohn's Disease. *N Engl J Med.* 2007;357:228-238.
98. Brian GF, et al. Methotrexate for the Treatment of Crohn's Disease. *N Engl J Med.* 1995;332:292-297.
99. Brian GF, et al. A Comparison of Budesonide and Mesalamine for Active Crohn's Disease. *N Engl J Med.* 2000;342:1627-1632.