

Iron Deficiency Anaemia in Inflammatory Bowel Disease in Children: A Systematic Review

Dahook Abdullah Abualsamh^{1*}, Mariam Mustafa Ageel², Mohammed Mansour Alfadhel³, Mohammed Saleh Al Wadai⁴, Ali Saeed Alamri⁴, Shahad Abdulaziz Aloufi⁵, Aljawharah Mohammed Aljohani⁶, Omar Khalid Alsaawi³, Fatimah Fawzi Alfaleh⁴, Fatimah Husni Rajab⁷ and Ahmed Abdulaziz Alassiri⁸

¹Department of Paediatrics, East Jeddah Hospital, Jeddah, Saudi Arabia

²College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

³College of Medicine, Qassim University, Qassim, Saudi Arabia

⁴College of Medicine, King Khalid University, Abha, Saudi Arabia

⁵College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia

⁶Department of Paediatrics, National Guard Hospital, Jeddah, Saudi Arabia

⁷College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia

⁸Department of Paediatrics, Hera General Hospital, Mecca, Saudi Arabia

***Corresponding Author:** Dahook Abdullah Abualsamh, Department of Paediatrics, East Jeddah Hospital, Jeddah, Saudi Arabia.

Received: December 07, 2019; **Published:** December 24, 2019

Abstract

Inflammatory bowel disease (IBD) incidence is widely increasing in pediatric populations in the past decade. This systematic review and meta-analysis was conducted according to the widely accepted Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA). On 20th November 2019, we searched for relevant articles in six electronic databases. Papers reporting iron deficiency anemia (IDA) in IBD patients, published articles after 2015 were only included. After screening 723 papers, we found 10 eligible studies with a male prevalence of 50%. The prevalence of IDA in IBA patients ranged from 8% to 52%. Moreover, treatment with iron supplementation showed good efficacy for the correction of IDA. Noteworthy, IDA in IBD is not rare. Therefore, more care should be devoted to diagnosis and treatment of IDA in IBD patients.

Keywords: Iron Deficiency Anemia; Inflammatory Bowel Disease; Systematic Review

Introduction

Inflammatory bowel diseases (IBD) comprise a major health care problem among clinicians especially pediatric populations. Recent years have witnessed a remarkable increase in IBD incidence. IBD patients incidence were tripled in 2003 compared to 1987 in Finland [1]. Furthermore, the incidence of Crohn's disease (CD) had increased by 0.5 from 1990 to 1998 in France [2]. Scotland as well had a significant rise of IBD patients and the increased rate estimated by 3/100000 from 1996 to 2008 [3].

Despite the multifactorial etiologies of IBD, genetic predisposition comprises the major role in IBD development [4]. Infections, diet and food allergy and helminths are known risk factors for IBD development [5]. Recently, Shaw, *et al.* indicated that the use of antibiotics in the first year of life was associated with a 2.9 risk of IBD affection derived from the loss of potentially protective flora from the frequent use of antibiotics [6]. Moreover, the meta-analysis of Barclay, *et al.* demonstrated that absence of breastfeeding is associated with an increase in the incidence of IBD [7].

IBD commonly presents with manifestations such as abdominal pain, diarrhea, rectal bleeding, weight loss, fever, and vomiting [8]. However, patients may be presented to extra-intestinal manifestations prior to IBD diagnosis such as musculoskeletal, dermatologic, oral, hepatobiliary and ophthalmic manifestations [9]. IBD patients are at greater risk of anemia development due to the continuous loss of blood [10]. The most common types of anemia in IBD patients were iron deficiency anemia (IDA), anemia of chronic disease or a combination of them [10]. The prevalence of IDA in IBD was 38%, out of the 76% were CD [11]. We aimed to conduct a systematic review of the recent publications regarding IDA in IBD patients.

Methods

Search strategy and study selection

This systematic review and meta-analysis was conducted according to the widely accepted Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) [12]. On 20th November 2019, we searched for relevant articles in six electronic databases including PubMed, Institute of Science Index (ISI), Scopus, System for Information on Grey Literature in Europe (SIGLE), Virtual Health Library (VHL) and Google Scholar using the following search term: "Inflammatory Bowel Diseases" AND "Anemia OR Iron-Deficiency". We conducted a manual search of references from the included articles by searching the primary studies that had cited our included papers and scanning references of the relevant papers in PubMed and Google Scholar to avoid missing any relevant publications [13].

We included all relevant original articles which reported iron deficiency anemia in pediatric inflammatory bowel diseases. There were no restrictions on study design, race, sex, ethnicity, place, language or date of publication. Papers were excluded if one of the following exclusion criteria was met: i) published before 2015 ii) *in vitro* and animal studies, iii) data duplication, overlapping or unreliably extracted or incomplete data, iv) abstract only articles, reviews, thesis, books, conference papers, and articles without available full texts (conferences, editorials, author response, letters, and comments). Initial title and abstract screening was done by at least four independent reviewers and checked by a fifth reviewer to ensure accuracy. Four independent reviewers screened full texts of eligible articles for inclusion in the meta-analysis. Controversies arising during the process were resolved by discussion and consensus.

Data extraction

Two authors developed a data extraction sheet using Microsoft Excel by performing a pilot extraction of random studies. The extraction sheet was divided into three parts. The first part included study characteristics (study design, sample size, age of patients and gender), the second part included the outcome of interest and the third part included the risk of bias for each included study. Four reviewers independently extracted data from the included studies using the excel sheet. Before the initiation of analysis, data rechecking was carried out by at least four different authors. All disagreements and discrepancies were resolved by discussion and consultation with a senior reviewer when necessary.

Quality assessment

Four independent reviewers evaluated the risk of bias in the included studies. National Institutes of Health (NIH) quality assessment tool was used to determine the quality of each included study [14]. Quality assessment of each study was obtained through a scoring system including 14 questions. The criterion was judged as following; a score of 13 to 14 was good, 9 to 12 was fair, and studies scoring below 9 are considered of poor quality for cohort studies [15]. Any discrepancy between the reviewers was solved by consensus.

Results

Characteristics of included studies

Our search yielded 723 records after excluding of 198 duplicates via endnote software. Of these 208 reports were included for full-text screening after exclusion of 515 reports which resulted in the inclusion of 9 eligible studies. Another paper was included after doing manual searches. In total, we have included 10 studies for our systematic review (Figure 1).

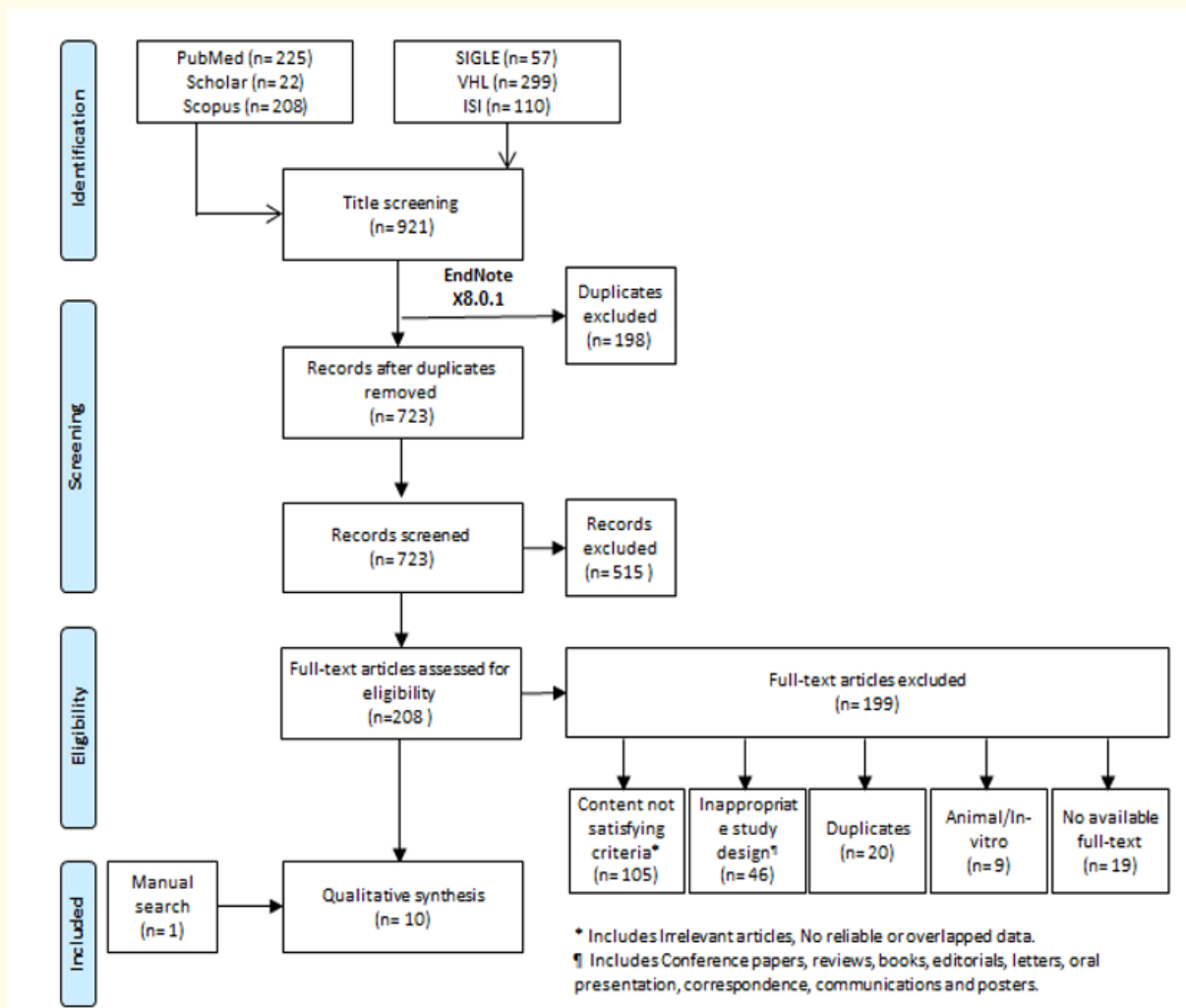


Figure 1: PRISMA flow chart showing the process of the review.

There were 8 cohort studies (6 retrospective and 2 prospective) and 2 cross-sectional studies. The total sample size was 3133 and ranged from 16 to 2424 with a male prevalence of 50%. Follow up duration was reported in 2 studies. Quality assessment for all included papers was of fair criterion (Table 1).

Prevalence of IDA in IBD

Seven studies reported the prevalence of IDA in IBD (Table 2). The prevalence ranges between 8% to 52% of patients. Martinelli, *et al.* indicated that 6.6% had IDA and 26.6% had a combination of IBD and anemia of chronic disease [16]. Miller, *et al.* reported that the prevalence of IDA in CD was higher than patients with UC with a percentage of 9% and 7%, respectively [17]. Moreover, 52% of IBD patients had IDA (ferritin < 15 µg/L or sTfR > 8.3 mg/L) [18]. Aljomah, *et al.* revealed that 29% of patients had IDA with or without anemia of chronic disease [19]. 36.6% of IBD patients experienced IDA reported by Venturieri, *et al* [20]. The prevalence of IDA in Carvalho, *et al.* study was 43.5% [21]. 44% had IDA demonstrated by Carman, *et al* [22].

Author ID	Country	Study design	Type of IBD	Sample size	Age (mean (SD))	Males(n)	Follow up duration	Quality assessment
Martinelli/2016	Italy	Cross-sectional	UC	28	12.6 (3.5)	27	NR	Fair
			CD	20				
			IBD-U	2				
Miller/2019	USA	Retrospective cohort	UC	886	1 - 21*	413	2 years	Fair
			CD	1560		805		
Stein/2019	USA	Retrospective cohort	UC	11	14.5 (3.6)	32	NR	Fair
			CD	53				
			IBD-U	8				
Syed/2017	Georgia	Cross-sectional	UC	19	5 - 19*	36	NR	Fair
			CD	43				
Azevedo/2017	Portugal	Prospective cohort	CD	19	15.5#	9	18 months	Fair
Aljomah/2018	USA	Retrospective cohort	UC	49	1 - 18*	86	NR	Fair
			CD	92				
			IC	12				
Venturieri/2019	Brazil	Retrospective cohort	UC	4	6.6 (5.4)	10	NR	Fair
			CD	12				
Carvalho/2017	Portugal	Retrospective cohort	UC	20	13.3	NR	NR	Fair
			CD	49				
Carman/2018	Australia	Prospective cohort	UC	26	14#	64	NR	Fair
			CD	75				
Danko/2016	USA	Retrospective cohort	UC	10	15.4	3	NR	Fair
			CD	2		74		
			CD	122		7		
			IC	11				

Table 1: Characteristics and findings of included studies.

UC: Ulcerative Colitis; CD: Crohn Disease; IBD-U: Inflammatory Bowel Disease Unclassified;

IC: Intermediate Colitis; *: Range; #: Median; NR: Not Reported.

Treatment of IDA in IBD

Seven studies reported the treatment of IDA. Treatment of IDA in IBD by iron sucrose was associated with significant improvement in the levels of hemoglobin, mean corpuscular volume, total iron-binding capacity, serum iron, transferrin saturation and ferritin [23]. After the application of intravenous iron treatment as a therapeutic agent for IDA, significant improvement of serum ferritin, transferrin saturation and serum iron were noticed among IBD patients [24]. Iron therapy had decreased the prevalence of IDA with or without anemia of chronic disease [19]. Treatment of IDA with Noripurum resulted in significant improvement of Hb, serum iron and ferritin [20]. Ferric carboxymaltose was associated with a decrease in the prevalence of IDA [22]. Intravenous iron treatment had significantly reduced IDA after 1 year of follow up [21]. After application of intravenous Iron Sucrose as a treatment of IDA a significant increase was noted in Hb levels and serum ferritin [25].

Author ID	Main findings
Martinelli/2016	The prevalence of iron deficiency anemia was higher in IBD patients rather than celiac disease group and healthy controls. IBD with PCDAI/PUCAI≥30 had significantly higher levels of serum hepcidin compared to PCDAI/PUCAI<30, celiac disease group and healthy controls.
Miller/2019	IDA was higher in CD compared to UC.
Stein/2019	Patients treated with iron sucrose have significant improvement in the levels of hemoglobin, mean corpuscular volume, total iron-binding capacity, serum iron, transferrin saturation, and ferritin after a 4-month duration of treatment with Intravenous Iron Sucrose.
Syed/2017	IDA prevalence was 52% CHR was significantly associated with some inflammatory biomarkers.
Azevedo/2017	Treatment with intravenous iron indicated a significant improvement of serum ferritin, transferrin saturation, and serum iron.
Aljomah/2018	29% of IBD patients have IDA or IDA and anemia of chronic disease. Significant decrease of IDA after iron therapy.
Venturieri/2019	36.6% IBD patients suffers from IDA. Significant improvement in the levels of Hb, serum iron and ferritin after treatment of Noripurum EVVR.
Carvalho/2017	The prevalence of IDA in IBD patients was 43% Iron treatment had decreases significantly the prevalence of IDA after 1 year of follow up.
Carman/2018	The prevalence of IDA was 44%. Treatment of IDA by Ferric carboxymaltose resulted in the decline of the prevalence of IDA by 64%
Danko/2016	Treatment of IDA by intravenous iron sucrose resulted in a significant increase in Hb levels and serum ferritin.

Table 2: Findings of each study.

IBD: Inflammatory Bowel Disease; sTfR: Soluble Transferrin Receptor; PCDAI: Paediatric Crohn’s Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index; IDA: Iron Deficiency Anemia; CD: Crohn Disease; UC: Ulcerative Colitis; CHR: Hemoglobin Content of Reticulocytes; Hb: Hemoglobin.

Discussion

IBD patients usually have micronutrients deficiency [26]. The multifactorial theory of this deficiency hardens it is treatment strategies. IDA is considered one of the most common types of anemia associated with IBD in addition to anemia of chronic diseases.

The associated IDA in IBD patients was built upon several hypotheses. IBD diseases are associated with bleeding of the bowel which results in frequent blood loss [27]. The intestinal mucosal damage plays also an important role in decreasing the absorption of food contents [28]. Moreover, adequate supplementation of food was decreased in IBD patients due to the associated anorexia [29]. Additionally, the immunosuppressive drugs prescribed for IBD patients may result in iron malabsorption [30].

The diagnosis of IDA should be considered based upon several clinical and laboratory parameters. Signs and symptoms such as Koilonychia, increase cardiac output, tachycardia, loss of appetite, pica, irritability, and lead intoxication can help in the diagnosis of IDA [31]. Akin to that, a complete blood picture comprises a key role in the diagnosis of IDA. Microcytic hypochromic anemia, anisocytosis, low serum iron, ferritin, transferrin saturation, and high total iron-binding capacity are the main clues in diagnosis of IDA [31].

The wide variability of IDA prevalence was reported among different pediatric clinical studies. Our updated study that included published studies after 2015 indicated that the prevalence of IDA in pediatric IBD patients ranges from 8% to 52%. The highest prevalence of IDA in our study was reported by Syed, *et al.* [18] and the lowest prevalence was found in Martinelli, *et al* [16]. However, the prevalence of IDA was higher in the study of Goodhand, *et al.* which recruited different age groups of IBD patients with a prevalence of 64%. More-

over, IDA constitutes the major part of anemia among the pediatric, adolescents and adults IBD patients with a prevalence of 88%, 83%, and 55%, of all anemia types respectively [32]. Moreover, the published systematic review in 2004 by Wilson, *et al.* indicated that the prevalence of IDA among IBD patients ranged from 9 - 74% [33]. The difference in the prevalence of IDA in IBD patients originates from the different types of IBD patients among each published study where CD had more prevalence of IDA rather than UC [17]. Furthermore, the different socioeconomic levels of the reported populations can play an important role in determining the prevalence of IDA and the management strategy as well [34]. Moreover, the prevalence of preterm in the recruited populations can affect the prevalence of IDA where the prevalence was higher among preterm infants compared to term infants [35].

Treatment of IDA in IBD patients based commonly iron supplementation and treatment of IBD. Oral iron therapy showed good efficacy in treating iron deficiency in IBD patients [36]. Moreover, intravenous iron treatment demonstrated a good therapeutic option for the treatment of IBD especially in patients with marked anorexia in addition to critically ill patients that require rapid iron correction. Intravenous iron treatment revealed a remarkable increase in serum ferritin, transferrin saturation and serum iron [24]. Despite the election of rapid therapeutic response, 18% of patients experienced adverse reactions such as hypotension, hypertension, pain at the peripheral intravenous site, bradycardia and chills, however not any of these adverse reactions were life-threatening [23].

Conclusion

IDA is a common finding in patients with IBD. Frequent examination and monitoring of high-risk patients for developing iron deficiency anemia is important. Moreover, iron replacement therapy should be considered for correction of IDA.

Funding

None.

Conflicts of Interest

No conflicts related to this work.

Bibliography

1. Lehtinen Pieta., *et al.* "Incidence Trends of Pediatric Inflammatory Bowel Disease in Finland, 1987–2003, a Nationwide Study". *Inflammatory Bowel Diseases* 17.8 (2010): 1778-1783.
2. Auvin Stéphane., *et al.* "Incidence, Clinical Presentation and Location at Diagnosis of Pediatric Inflammatory Bowel Disease: A Prospective Population-Based Study in Northern France (1988-1999)". *Journal of Pediatric Gastroenterology and Nutrition* 41.1 (2005): 49-55.
3. Henderson Paul., *et al.* "Rising Incidence of Pediatric Inflammatory Bowel Disease in Scotland". *Inflammatory Bowel Diseases* 18.6 (2011): 999-1005.
4. Shih David Q., *et al.* "Recent Advances in Ibd Pathogenesis: Genetics and Immunobiology". *Current Gastroenterology Reports* 10.6 (2008): 568-575.
5. Korzenik and Joshua R. "Past and Current Theories of Etiology of Ibd: Toothpaste, Worms, and Refrigerators". *Journal of Clinical Gastroenterology* 39.4 (2005): S59-S65.
6. Shaw Souradet Y., *et al.* "Association between the Use of Antibiotics in the First Year of Life and Pediatric Inflammatory Bowel Disease". *The American Journal of Gastroenterology* 105.12 (2010): 2687.
7. Barclay Andrew R., *et al.* "Systematic Review: The Role of Breastfeeding in the Development of Pediatric Inflammatory Bowel Disease". *The Journal of Pediatrics* 155.3 (2009): 421-426.

8. Gupta Neera., *et al.* "Presentation and Disease Course in Early- Compared to Later-Onset Pediatric Crohn's Disease". *The American Journal of Gastroenterology* 103.8 (2008): 2092-2098.
9. Jose Folashade Adebisi., *et al.* "Development of Extraintestinal Manifestations in Pediatric Patients with Inflammatory Bowel Disease". *Inflammatory Bowel Diseases* 15.1 (2008): 63-68.
10. Bager Palle., *et al.* "The Prevalence of Anemia and Iron Deficiency in Ibd Outpatients in Scandinavia". *Scandinavian Journal of Gastroenterology* 46.3 (2011): 304-309.
11. Ott Claudia., *et al.* "High Prevalence but Insufficient Treatment of Iron-Deficiency Anemia in Patients with Inflammatory Bowel Disease: Results of a Population-Based Cohort". *Gastroenterology Research and Practice* (2012).
12. Liberati Alessandro., *et al.* "The Prisma Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration". *PLoS Medicine* 6.7 (2009): e1000100.
13. Vassar Matt., *et al.* "Manual Search Approaches Used by Systematic Reviewers in Dermatology". *Journal of the Medical Library Association: JMLA* 104.4 (2016): 302.
14. Health National Institutes of. "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies". *National Heart, Lung, and Blood Institute* (2014).
15. Leung Amy., *et al.* "A Systematic Review of Patient-Related Risk Factors for Catheter-Related Thrombosis". *Journal of Thrombosis and Thrombolysis* 40.3 (2015): 363-373.
16. Martinelli Massimo., *et al.* "Serum Hepcidin and Iron Absorption in Paediatric Inflammatory Bowel Disease". *Journal of Crohn's and Colitis* 10.5 (2016): 566-574.
17. Miller, Steven D., *et al.* "Anemia Screening, Prevalence, and Treatment in Pediatric Inflammatory Bowel Disease in the United States, 2010–2014". *Pediatric Gastroenterology, Hepatology and Nutrition* 22.2 (2019): 152-161.
18. Syed, Sana., *et al.* "Use of Reticulocyte Hemoglobin Content in the Assessment of Iron Deficiency in Children with Inflammatory Bowel Disease". *Journal of Pediatric Gastroenterology and Nutrition* 64.5 (2017): 713-720.
19. Aljomah Ghanim., *et al.* "Anemia in Pediatric Inflammatory Bowel Disease". *Journal of Pediatric Gastroenterology and Nutrition* 67.3 (2018): 351-355.
20. Venturieri, Maissara O., *et al.* "Treatment with Noripurum Ev® Is Effective and Safe in Pediatric Patients with Inflammatory Bowel Disease and Iron Deficiency Anemia". *Scandinavian Journal of Gastroenterology* 54.2 (2019): 198-204.
21. Carvalho Fábila Susana Ginja de., *et al.* "Prevalence of Iron Deficiency Anemia and Iron Deficiency in a Pediatric Population with Inflammatory Bowel Disease". *Scandinavian Journal of Gastroenterology* 52.10 (2017): 1099-1103.
22. Carman Nicholas., *et al.* "Ferric Carboxymaltose in the Treatment of Iron Deficiency in Pediatric Inflammatory Bowel Disease". *Translational Pediatrics* 8.1 (2019): 28-34.
23. Stein, Ronen E., *et al.* "Intravenous Iron Sucrose for Treatment of Iron Deficiency Anemia in Pediatric Inflammatory Bowel Disease". *Journal of Pediatric Gastroenterology and Nutrition* 66.2 (2018): e51-e55.
24. Valério de Azevedo., *et al.* "Pediatric Crohn's Disease, Iron Deficiency Anemia and Intravenous Iron Treatment: A Follow-up Study". *Scandinavian Journal of Gastroenterology* 52.1 (2017): 29-33.

25. Danko Istvan. "Response of Iron Deficiency Anemia to Intravenous Iron Sucrose in Pediatric Inflammatory Bowel Disease". *The Journal of Pediatric Pharmacology and Therapeutics* 21.2 (2016): 162-168.
26. Weisshof Roni and Irit Chermesh. "Micronutrient Deficiencies in Inflammatory Bowel Disease". *Current Opinion in Clinical Nutrition and Metabolic Care* 18.6 (2015): 576-581.
27. Robert JR., et al. "Severe Gastrointestinal Hemorrhage in Crohn's Disease". *Annals of Surgery* 213.3 (1991): 207-211.
28. Semrin Gaith., et al. "Impaired Intestinal Iron Absorption in Crohn's Disease Correlates with Disease Activity and Markers of Inflammation". *Inflammatory Bowel Diseases* 12.12 (2006): 1101-1106.
29. Jenkins AP., et al. "Crohn's Disease Presenting as Anorexia Nervosa". *British Medical Journal (Clinical Research Edition)* 296.6623 (1988): 699-700.
30. Gionchetti Paolo., et al. "Use of Corticosteroids and Immunosuppressive Drugs in Inflammatory Bowel Disease: Clinical Practice Guidelines of the Italian Group for the Study of Inflammatory Bowel Disease". *Digestive and Liver Disease* 49.6 (2017): 604-617.
31. Özdemir Nihal. "Iron Deficiency Anemia from Diagnosis to Treatment in Children". *Turkish Archives of Pediatrics/Türk Pediatri Arşivi* 50.1 (2015): 11.
32. Goodhand James R., et al. "Prevalence and Management of Anemia in Children, Adolescents, and Adults with Inflammatory Bowel Disease". *Inflammatory Bowel Diseases* 18.3 (2011): 513-519.
33. Wilson Alisa., et al. "Prevalence and Outcomes of Anemia in Inflammatory Bowel Disease: A Systematic Review of the Literature". *The American Journal of Medicine* 116.7.1 (2004): 44-49.
34. Skalicky Anne., et al. "Child Food Insecurity and Iron Deficiency Anemia in Low-Income Infants and Toddlers in the United States". *Maternal and Child Health Journal* 10.2 (2005): 177.
35. Ozdemir Hulya., et al. "Iron Deficiency Anemia in Late-Preterm Infants". *The Turkish Journal of Pediatrics* 55.5 (2013): 500-505.
36. DE SILVA AD., et al. "Efficacy and Tolerability of Oral Iron Therapy in Inflammatory Bowel Disease: A Prospective, Comparative Trial". *Alimentary Pharmacology and Therapeutics* 22.11-12 (2005): 1097-105.

Volume 16 Issue 1 January 2020

©All rights reserved by Dahook Abdullah Abualsamh., et al.