Formosa Journal of Science and Technology (FJST)
Vol. 4, No. 2, 2025: 559-578

Understanding Gastrointestinal Involvement in Juvenile Idiopathic Arthritis: A Perspective from Within the Gut

Saskia Ratna Desita*[1], Nadira Muthi Tsania[2]
Faculty of Medicine, Airlangga University
Corresponding Author: Saskia Ratna Desita,
saskia.ratna.desita-2020@fk.unair.ac.id

A R T I C L E I N F O

Keywords: Gastrointestinal Disease, Juvenile Idiopathic Arthritis, Gut Inflammation

Received : 21, January
Revised : 4, February
Accepted: 18, February

A B S T R A C T

Juvenile idiopathic arthritis (JIA) is the most common form of arthritis affecting the pediatric population. Gastrointestinal diseases such as Inflammatory Bowel Disease (IBD) and Celiac Disease (CD) are more prevalent in patients with JIA. Alteration in gut microbiota composition results in immune dysregulation, disruption of the gut mucosal barrier, and altered intestinal functionality. Furthermore, medication commonly prescribed for JIA patients impacts intestinal health. Management strategies have been suggested to address these complications, including proton pump inhibitors (PPIs), folic acid supplementation, and proper nutrition. This literature review aims to explore the mechanisms underlying gastrointestinal involvement in JIA, assess the impact of commonly used medications, and provide insights into the clinical implications and management.

ISSN-E: 2964-6804
DOI: https://doi.org/10.55927/fjst.v4i2.2
https://traformosapublisher.org/index.php/fjst

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disorder primarily characterized by joint inflammation. It is the most common form of chronic arthritis in children, with a global prevalence estimated to range from 3.8 to 400 cases per 100,000 and an incidence between 1.6 to 23 cases per 100,000. (Garner et al., 2021) A recent study approximated that 2,069,246 children worldwide are affected by JIA.(Dave et al., 2020)

JIA can present with extra-articular manifestations, depending on the subtype. (Thatayatikom et al., 2024) Among these, gastrointestinal involvement is a significant concern. Gastrointestinal manifestations in JIA arise from a complex process of inflammation, immune dysregulation, and therapeutic interventions. (Barut et al., 2017; Garner et al., 2021; Thatayatikom et al., 2024; Zaripova et al., 2021)

Recent studies show that gastrointestinal diseases such as Inflammatory Bowel Disease (IBD) and Celiac Disease (CD) have a higher incidence in JIA patients. (Maller et al., 2021; Naddei et al., 2022) They share a common genetic predisposition and overlapping pathophysiology mechanisms. (Naddei et al., 2022; van Straalen et al., 2021) This condition can confound diagnostic decision and is essential to ensure effective treatment strategies.

Beyond the potential for comorbidities, therapeutic interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and both conventional and biologics disease-modifying antirheumatic drugs (DMARDs) can contribute to gastrointestinal problems. (Aalto et al., 2017; Dallocchio et al., 2010; Thatayatikom et al., 2024; Wibrand et al., 2024) These conditions emphasize the importance of balancing effective disease management with minimizing gastrointestinal effects to achieve optimal patient outcomes.

Clinical manifestations of gastrointestinal problems in JIA patients are varied, abdominal pain is one of the most frequently reported gastrointestinal symptoms. Studies demonstrated that abdominal pain correlates with higher disability scores, greater arthritis-related pain, and lower scores in physical functioning, general health, vitality, and emotional well-being.(Rebane et al., 2022; Tharwat et al., 2024) Such manifestations impair quality of life and may also influence disease progression and response to therapy. (G. Ferrara et al., 2018)

A comprehensive understanding of the gastrointestinal involvement of JIA patients is crucial. Studies recommend that early screening may mitigate the impact of gastrointestinal complications. (G. Ferrara et al., 2018; Sadeghi et al., 2021; van Straalen et al., 2021) This literature review aims to explore the mechanisms underlying gastrointestinal involvement in JIA, assess the impact of commonly used medications, and provide insights into the clinical implications and management.

THEORETICAL REVIEW

Gastrointestinal Involvement in Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most prevalent arthritic condition within the pediatric population. JIA is diagnosed when the onset is before the age of 16 years old, persist for more than six weeks, and other potential diagnoses are excluded. There are seven subtypes of JIA, each presenting distinct clinical

manifestations, genetic predispositions, pathophysiology, disease progression, and prognostic outcomes. (Garner et al., 2021; Thatayatikom et al., 2024)

JIA is an autoimmune disorder characterized by a complex immunological process. The pathophysiology of JIA involves the abnormal activation of various immune cells, including T-cells, B-cells, natural killer (NK) cells, dendritic cells (DC), macrophages, and neutrophils. This dysregulation leads to excessive production of pro-inflammatory cytokines, resulting in joint destruction and systemic complications. Chemokines associated with JIA recruit T-helper 1 (Th-1) cells, which produce pro-inflammatory cytokines such as interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). Moreover, studies have identified an imbalance between regulatory T cells (T-reg), Th1, and Th17 cells as a crucial pathogenic mechanism. (Barut et al., 2017; Garner et al., 2021; Zaripova et al., 2021)

In addition to immunological dysfunctions, various external factors, including environmental stimuli, infections, stress, and trauma, have been implicated in the pathophysiology of JIA. Emerging evidence also highlights the significant role of gut microbiota in JIA. (Barut et al., 2017; Garner et al., 2021; Zaripova et al., 2021) Recent studies have demonstrated that JIA patients are also frequently associated with abdominal complications, prompting emerging research to explore the connection between intestinal health and JIA. (Soliman et al., 2021)

The intestinal microbiota is now recognized as an important mediator of host immune programming, with approximately 70% of immune cells residing in the gut. It plays a pivotal role in modulating both innate and adaptive immune responses, particularly T-reg cells and Th-cell differentiation. The development of JIA is hypothesized to involve abnormal immune responses to self-antigens. A recent study shows evidence of the formation of aggregates containing memory T cells and antigen-presenting cells, with Th1 cells and IFN-γ+ T cells demonstrating the highest abundance. T-reg is also elevated at the site of inflammation. (Stefanov et al., 2018) (Verwoerd et al., 2016)

Specific microbiota are also considered pivotal in the pathogenesis of JIA. A study has demonstrated that fecal microbiota composition in newly diagnosed JIA patients is significantly altered compared to healthy children.(Verwoerd et al., 2016; Xin et al., 2021) This altered gut microbiota composition, commonly referred to as dysbiosis, can compromise gut barrier integrity, immunological imbalances, and trigger inflammation. This condition can subsequently predispose the host to the development of intestinal disease. Dysbiosis is characterized by a reduction in beneficial symbionts and/or an increase in the harmful pathobionts, leading to a nonspecific inflammation state. This inflammatory environment heightens susceptibility to T-helper cell-mediated disease. (De Filippo et al., 2019) Recent study has shown that JIA patients, particularly the enthesitis-related arthritis (ERA) subtype, exhibit lower levels of the anti-inflammatory bacteria, *Faecalibacterium prausnitzii* compared to healthy children. This condition is compensated by increased abundance of the Bacteroidetes phylum and *Akkermansia muciniphila,* which contribute to promoting the inflammatory process by facilitating bacteria to the intestinal

immune system. (Stoll et al., 2014) These microbiota have the ability to enhance mucosal permeability, facilitating the internalization of enteric bacteria into the mucosa through mucin degradation. Studies have also found that JIA patients exhibited altered functional characteristics in their gut microbiota, such as changes in cell motility and flagellar assembly. These alterations will also disrupt the gut mucosal barrier and promote microbial dissemination. Additionally, disturbances in the metabolism of tryptophan and butyrate have been observed, which may impair tolerogenic immune responses. (De Filippo et al., 2019; Verwoerd et al., 2016) A study found that ERA patients exhibit distinct humoral responses to the gut bacteria, which contribute to gut inflammation. (Pichler et al., 2016)

Inflammation itself can significantly impact the compositions of the gut microbiota, creating an environment that favors the proliferation of pathobionts. Furthermore, the gut microbiota itself has the ability to modulate both the local mucosal immune system and the systemic intestinal immune response. (De Filippo et al., 2019) A study revealed that ERA subtype patients exhibit subclinical intestinal inflammation, with evidence of elevated concentrations of circulating anti-core Lipopolysaccharide (LPS) antibodies and LPS binding protein (LBP). LPS is an outer-membrane component of Gram-negative bacteria that is able to induce matrix breakdown and chondrocyte apoptosis, leading to cartilage degradation. Systemic inflammation, a prominent feature in JIA, can increase intestinal permeability, resulting in elevated concentrations of anti-core LPS antibodies and/or LBP. These markers correlate with both gut inflammation and disease activity.(Fotis et al., 2017) Another study also identified alterations in gut mucosal integrity in JIA patients. These alterations include increased small intestinal intraepithelial γδ+ T cells and cytotoxic lymphocytes, as well as increased HLA-DR expression in the ileal mucosa. These findings have been shown to correlate with JIA disease activity. (Arvonen et al., 2016) Furthermore, during episodes of intestinal inflammation, there is a significant increase in the mucosal uptake of gut bacteria and their membrane molecule, such as LPS and peptidoglycan-polysaccharides (PG-PS). These components also contribute to the development of extra-intestinal inflammatory manifestations, such as arthritis.(De Filippo et al., 2019)

METHODOLOGY

This narrative review article focuses on Gastrointestinal involvement in Juvenile Idiopathic Arthritis (JIA). Comprehensive literature research was performed in PubMed, Scopus, and Google Scholar using the keywords "juvenile idiopathic arthritis" and "gastrointestinal involvement." Relevant studies from the peer-reviewed journal were selected based on their relevance. An analytical approach synthesized the underlying mechanism, clinical manifestations, diagnostic challenges, and management strategies from selected studies. This review highlights the mechanisms underlying gastrointestinal involvement in JIA and provides insights into the clinical implications and management.

RESULTS & DISCUSSION

Gastrointestinal-Related Diseases

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) and JIA have a significant relationship. A recent study has shown that the probability of developing IBD in JIA patients is approximately 4.6%. Notably, some patients with IBD may initially experience joint complaints as the primary symptom, leading to an initial misdiagnosis of JIA.(Biswas et al., 2018; van Straalen et al., 2021) Common genetic features are involved in the pathophysiology of both IBD and JIA.(van Straalen et al., 2021) Medication plays a significant role in the incidence of IBD in JIA patients. Several studies have shown that JIA patients who develop IBD are often associated with the use of etanercept treatment. (Armaroli et al., 2020; Dallocchio et al., 2010; Hügle et al., 2017; Maller et al., 2021; van Dijken et al., 2011; van Straalen et al., 2021) Recent data indicates that there were 1.9 new cases of IBD among 100 JIA patients treated with etanercept. (Dallocchio et al., 2010) Etanercept is a TNF-α blocker, which is able to bind and prolong the half-life of TNF-α and increase IFN-ɣ, which in IBD pathogenesis, IFN-γ plays a crucial role. IFN-γ provoke an excessive immune response, resulting in leucocyte infiltration and mucosal disruption. (Langer et al., 2019) The duration of etanercept treatment before the onset of IBD varied across studies. One study reported a range of 7-78 months, another indicated a duration ranging from 5 to 12 years, while a third study noted an average of 27 months. Studies observed remission in all patients after discontinuing etanercept and starting treatment for IBD. (Bieber et al., 2017; Dallocchio et al., 2010; Hügle et al., 2017) A study by Maller et al. revealed that IL-1 blockade also contributes to the incidence of IBD. Canakinumab showed a significant correlation with IBD in patients with systemic JIA (sJIA) in this study. (Maller et al., 2021)

Multivariate analysis revealed that ERA and a positive family history of autoimmune disease emerged as the most significant predictors of IBD development in patients with JIA. Furthermore, the study demonstrated a higher prevalence of IBD in male patients, those with positive HLA-B27, and those with an older age onset of JIA.(van Straalen et al., 2021) Studies show that the presenting symptoms experienced by patients are abdominal pain, fecal blood, diarrhea, anorexia, anal abscess, oral ulcers, and fever. (Dallocchio et al., 2010; G. Ferrara et al., 2018)

Early detection of IBD in JIA patients is crucial as the management strategies for these conditions are different. While etanercept demonstrates significant efficacy in treating JIA, its therapeutic effect is not evident in the context of bowel inflammation. A study has revealed that JIA patients with concurrent IBD exhibit elevated Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), IgA levels, platelet count, and decreased hemoglobin level, indicative of systemic inflammation. Furthermore, these patients showed significantly higher Juvenile Idiopathic Arthritis Disease Activity Scores (JADAS), suggesting a greater challenge in achieving optimal clinical control of their chronic arthritis. Diagnosis can be challenging due to the subclinical presentation in some patients. Therefore, regular screening for IBD in JIA patients

is crucial to ensure timely diagnosis and appropriate management. (G. Ferrara et al., 2018) Studies suggest that screening with fecal calprotectin should be performed at the onset and periodically, particularly in high-risk patients. (G. Ferrara et al., 2018; van Straalen et al., 2021)

Celiac Disease

Celiac Disease (CD) is an autoimmune disorder triggered by the consumption of gluten. This autoimmune leads to inflammation and intestinal disruption. CD incidence is more prevalent in Europe, North and South America, Australia, South-West Asia, and North Africa. (Poddighe et al., 2019) JIA patients have an increased risk of CD, meta-analysis showed that more than 2.5% of JIA patients were diagnosed with CD. (Poddighe et al., 2022) The concurrent occurrence of CD and JIA is more frequently observed in patients with a positive family history of autoimmune disorders. Furthermore, a study has shown that they often require an escalation of their DMARD therapy to achieve disease remission. This condition suggests a correlation between the presence of CD and a more severe clinical course of JIA. (Naddei et al., 2022)

The onset of CD and JIA frequently occurs within short intervals. This condition may be attributed to several factors, including shared genetic predispositions, ongoing systemic inflammation, and environmental triggers such as infection and dietary factors. (Naddei et al., 2022)

Studies suggest routine screening for CD in all JIA patients, even in the absence of symptoms. Over one-third of children with CD may remain asymptomatic, highlighting the limitations of relying solely on symptom-based diagnosis. Screening should be considered particularly in JIA patients presenting with specific red flags, such as chronic or intermittent diarrhea, abdominal distention, failure to thrive, stunted growth or short stature, or an inadequate response to standard JIA therapies. (Naddei et al., 2022; Sadeghi et al., 2021)

Medication-Related Gastrointestinal Complications

NSAIDs

NSAIDs are the initial therapy and are widely applied in JIA patients before further therapy is given. The mechanism of NSAIDs is blocking prostaglandin production through inhibition of the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), thereby producing anti-inflammation and analgesic effects. For anti-inflammatory effects, the dose is often prescribed twice the recommended analgesic dose. Giving a minimum dose at the initial therapy may considered to reduce adverse effects.(Jacobson & Pham, 2018) Inhibition of COX-1 reduces mucosal prostaglandin and decreases the protective bicarbonate mucus barrier in the small bowel, which leads to peptic ulcer and gastrointestinal perforation. Peptic ulcers on the mucosa provoke gastrointestinal perforation and bleeding, leading to impaired iron absorption and anemia. A study showed NSAIDs in children induce gastric lesions by 64%, followed by duodenal and esophageal. (Cardile et al., 2016) Chronic inflammation of the intestinal mucosa is associated with the formation of fibrostenotic tissue, resulting in obstruction of the small intestine. Patients on long-term NSAID

therapy experience intermittent abdominal pain and decreased appetite. (Tai & McAlindon, 2021)

The American College of Rheumatology recommends that NSAID trials to relieve symptoms in JIA patients should be concise due to potential harmful effects and the efficacy remains unclear. The duration of NSAIDs in initial therapy is still under debate as some experts prefer to avoid NSAIDs. (Onel et al., 2022) Another study demonstrated Ibuprofen use in children was linked to gastrointestinal symptoms including GI bleeding, epigastric pain and nonspecific abdominal pain. Furthermore, a meta-analysis of RCT studies reported that the most common side effects of NSAID use were gastrointestinal, headaches, and motion sickness, especially in aspirin, ibuprofen, and tolmetin. Selective COX-2 inhibitors were reported to lower GI toxicity due to their protective effect on intestinal mucosa. Gastrointestinal complications due to NSAIDs consumption are relatively mild, but if combine with glucocorticoids, leflunomide, or methotrexate, it can exacerbate gastrointestinal symptoms. (Shi et al., 2021)

Corticosteroids

Systemic glucocorticoids are widely used to manage severe JIA-associated complications while awaiting the full therapeutic effects of DMARDs. (Batu, 2019) Systemic glucocorticoids at high doses provide good short-term effects in JIA patients, but various studies show that systemic corticosteroids do not affect long-term disease outcomes. (Harris et al., 2013) However, glucocorticoids are used as an anti-inflammatory therapy in the chronic inflammatory condition, such as IBD.

Glucocorticoids are known to inhibit the release of TNF-α, increase tight junctions in the intestinal epithelium, and reduce intestinal permeability under basal conditions. In contrast, in vivo studies suggest that glucocorticoids reduce intestinal barrier function through decreasing IgA secretion, mucus production changes, and modulation of intestinal microbiota. Glucocorticoids tend to have a negative effect on wound proliferation, thereby increasing permeability and favoring bacterial translocation. (Tena-Garitaonaindia et al., 2022)

Administration of prednisone at high altitudes carries the complication of avascular necrosis and a higher risk of gastrointestinal bleeding. (Koshi et al., 2022) Other studies suggest that corticosteroid administration in children increases the risk of gastrointestinal bleeding within the first month. (Yao et al., 2021)

DMARDs

Gastrointestinal problems are the most frequent complication of Methotrexate (MTX) use in JIA patients. Gastrointestinal manifestations of MTX therapy include nausea, vomiting, and elevated transaminase enzymes. High-dose methotrexate has been reported to be associated with acid reflux and abdominal pain in Rheumatoid Arthritis patients. (Asai et al., 2019) In vivo studies reported that mice treated with methotrexate appear to have mucosal injury, massive microbiota changes, macrophage polarization, and inflammation. (Zhou et al., 2018) MTX induced mucositis by damaging basal

epithelial cells and submucosal tissue through DNA damage. Upregulation of pro-inflammatory cytokines causes damage to mucosal integrity, thereby increasing intestinal permeability, causing susceptibility to bacterial colonization and increased recruitment of immunocytes such as mononuclear phagocytes. Mononuclear phagocytes produce additional pro-inflammatory cytokines and disrupt the gut microbial community. This condition leads to increased recruitment of immunocytes and polarization of macrophages. (Higuchi et al., 2020; Nayak et al., 2021; Zhou et al., 2018)

Methotrexate intolerance, including gastrointestinal adverse effects, appears to be higher in JIA compared to acute lymphoblastic leukemia. (Kyvsgaard et al., 2019) A study by Mena et al. demonstrated gastrointestinal problems are the most common complication in JIA patients receiving MTX therapy, with children over six years of age starting new MTX having a higher risk.(Barral Mena et al., 2020) Study showed that children receiving MTX for JIA treatment developed hepatotoxicity by 28% and increased ALT, AST, and ALP enzymes significantly. (Noha Adel et al., 2021) In addition, more than half of JIA patients reported having MTX intolerance, evaluated by Methotrexate Intolerance Severity Score (MISS). However, this study revealed there is no significant increase in ALT enzymes between MTX-intolerance and MTX-tolerance groups. (Wibrand et al., 2023)

TNF-α is a new targeted treatment for JIA patients. TNF-α widely used in rheumatic autoimmune disorders. However, a histopathological study revealed that TNF-α may exacerbate gastrointestinal paradoxical reactions, including inflammatory bowel disease and sarcoid-like granulomas. Discontinuing TNF-α inhibitor was associated with symptom improvement and histopathological changes. (Hutchings et al., 2019)

Clinical Manifestation

Abdominal complications are frequently observed in JIA patients. A study of ERA patients reported a prevalence of 44.3% for abdominal pain complaints and 14% of patients experienced diarrhea. (Gonzalez et al., 2018) This finding is in line with previous study in JIA patients, which have reported that approximately 50% of patients complain about abdominal pain. Abdominal pain is a major complaint and is associated with female, fatigue, methotrexate, and sulfasalazine use. Notably, patients experiencing frequent abdominal pain have been found to exhibit higher disability scores, increased arthritis-related pain, and poorer quality of life. (Rebane et al., 2022)

A previous study reported that one-third of JIA patients with abdominal pain had higher levels of fecal calprotectin (FC), representing gut inflammation. Elevated FC was linked to abdominal pain and NSAID treatment. Discontinuing NSAIDs and methotrexate were reported to have lower FCs, decreased abdominal pain, and lower inflammatory markers.(Aalto et al., 2017) Increased FCs were associated with gut dysbiosis, food intolerance, and malabsorption. (Heinzel et al., 2024) Dysfunction of intestinal integrity leads to malabsorption and bacterial translocation, which contribute to malnutrition and infection. (Adedokun & Olojede, 2019) Elevated fecal calprotectin levels provide further evidence of intestinal inflammation, particularly in ERA and HLA-B27-positive

patients. However, it is crucial to acknowledge the potential influence of medications, such as NSAIDs and DMARDs on fecal calprotectin levels. (Aalto et al., 2017)

Some patients may have diarrhea symptoms. This symptom may suggest a condition associated with autoimmune-inflammatory gastrointestinal disorders. (Gonzalez et al., 2018; Pichler et al., 2016) Moreover, another study reported that JIA patients have oral ulcers and tend to avoid certain foods. (Leksell et al., 2008)

Pichler et al. conducted a study involving endoscopy in JIA patients presenting with gastrointestinal complaints. Their finding revealed that 85% of JIA patients exhibited histologically confirmed gut inflammation. The gastrointestinal indications for endoscopy in this study included persistent abdominal pain (42%), diarrhea (30%), growth faltering or weight loss (18%), and per-rectal bleeding (15%). Other less common gastrointestinal symptoms included mouth ulcers, hematemesis, and constipation. (Pichler et al., 2016) Another study has also demonstrated a significant prevalence of gut inflammation in patients with late-onset juvenile chronic arthritis, with colonoscopy findings indicating its presence in 75% of cases. Moreover, evidence of intestinal immune system activation has been observed in JIA patients, characterized by lymphoid nodular hyperplasia with specific CD3 lymphocytes within the intestinal mucosa. (Aalto et al., 2017; Pichler et al., 2016)

Methotrexate use was reported to correlate with oral ulcer incidence.(Kikuchi et al., 2023) A cohort study reported methotrexate intolerance was found to be 42% in one year and more than half reported nausea and 27% reported vomiting. (van Dijkhuizen et al., 2015) In addition, a study by Mulligan et al. demonstrated that more than 30% of parents reported their children had nausea and 15% reported vomiting weekly due to methotrexate medication.(Mulligan et al., 2013) This phenomenon leads to poor adherence to treatment. A study reported that half of the JIA patients experienced adverse effects, including gastrointestinal symptoms and 35% of them had to stop the treatment due to methotrexate. (Barral Mena et al., 2020) Patients experience nausea, vomiting, and abdominal pain due to methotrexate therapy, which leads to discontinuation and lower quality of life. (Falvey et al., 2017)

Chronic inflammation and increased of IL-6 and TNF-α in JIA patients leads to gut leakage. Therefore, some nutrients are unable to be absorbed efficiently. Previous study reported that anemia in JIA patients is due to gut inflammation which result in malabsorption of Fe. Additionally, long-term use of NSAIDs can cause abdominal pain, peptic ulcer, and gastrointestinal bleeding, which also affect the nutrient absorbance. (Albokhari & Muzaffer, 2021)

A study reported that iron deficiency was found in JIA patients. (Albokhari & Muzaffer, 2021) The elevation of IL-6 in JIA patients stimulates hypoxia-induced erythropoietin and proliferation of erythroid progenitors. This condition induces increased ferritin expression, enhanced hepatic uptake, and leads to reticuloendothelial iron block. Moreover, IL-6 induces hepcidin to inhibit iron absorption from the intestine and prevent the release of recycled iron from

macrophages. Furthermore, these mechanisms result in reduced serum iron availability. (Zandonadi, 2022)

The prevalence of anemia in JIA is approximately 50%, predominantly in younger patients with elevated ESR and CRP. (Albokhari & Muzaffer, 2021) A study by Tbini et al. revealed that anemia was reported in 69% of JIA patients with hypochromic microcytic blood count. This study found that anemia is associated with females, absence of antinuclear antibodies, and corticosteroid therapy. (Tbini et al., 2022)

Gastrointestinal symptoms often occur in JIA patients, predominantly due to pharmacological adverse effects. Poor adherence was found in one-fourth of pediatric rheumatic disease and associated with joint pain and low functional activity. (Manatpreeprem et al., 2023) The most common barriers to patients' adherence to JIA oral treatments were poor taste, difficulty managing side effects, and pain. (Favier et al., 2018)

Screening and monitoring

Gastrointestinal involvement in JIA is a challenging issue as a manifestation and complication of the disease. Regularly screening and monitoring gastrointestinal involvement is essential to reduce the risks of complications and enhance their quality of life.

History taking to screen the gastrointestinal involvement in JIA patients is essential. Chronic and severe diarrhea suggested an inflammatory bowel disease or secondary infection. Observing the types, frequency, consistency, and other additional symptoms of diarrhea is essential to differentiate it from secondary infection. Monitoring nausea and vomiting symptoms in JIA patients is crucial since some patients may develop methotrexate intolerance.(Wibrand et al., 2024) Continuous nausea and vomiting leads to low drug compliance, which affects severity of the disease. In addition, children with frequent nausea and vomiting may have loss of appetite. This situation leads to malnutrition, low functional status, and exacerbates the severity. (Hügle & van Dijkhuizen, 2020)

A comprehensive physical examination should be performed to identify clinical findings on JIA patients. A previous study reported methotrexate induced hepatotoxicity. Observing the icteric or hepatomegaly might reveal the methotrexate hepatotoxicity. Examining the liver enzymes could confirm the hepatotoxicity. (Noha Adel et al., 2021)

Blood examination should be performed in JIA patients to investigate anemia. (Tbini et al., 2022) Liver function test can be valuable for monitoring patient taking MTX. An observational study demonstrated that children with methotrexate treatment had higher levels of ALT, AST, and lower levels of ALP compared to non-methotrexate treatment. (Noha Adel et al., 2021) Ultrasound could be performed to find hepatic steatosis or fibrosis. Niyasom et al. reported that hepatic steatosis was observed commonly in JIA patients receiving methotrexate. However, it is not associated with hepatic fibrosis. (Niyasom et al., 2024) A colonoscopy is examined to identify JIA-associated inflammatory bowel disease. Moreover, fecal calprotectin can be performed to evaluate gut inflammation. Elevated levels of fecal calprotectin were observed in ERA and may coexist with joint inflammation. (Lamot et al., 2021)

Management

Proton Pump Inhibitor

Strategic management to alleviate symptoms and other gastrointestinal problems should be essential to prevent complications and increase their quality of life. Proton Pump Inhibitor (PPI) is an effective treatment to reduce peptic ulcers induced by NSAIDs. A previous study reported that a fix-dose combination of Naproxen/Esomeprazole effectively treated gastric ulcers in JIA patients aged 12-16.(Lovell et al., 2018) However, another study reported that regular use of PPI may alter gut microbiota, which develops severity of autoimmune disease. (Räisänen et al., 2023) pH changes after PPI treatment could affect the gastric barrier, resulting in microorganisms invading the gastrointestinal tract. Moreover, PPI induced hormonal changes which could affect intestinal osmolality as in the metabolism of calcium and phosphorus, which modify gut microbiota. (Tian et al., 2023)

Folic Acid

Methotrexate is a folate antagonist that is regularly used to treat JIA. Folic acid supplementation is widely accepted to manage methotrexate intolerance. Meta-analysis in Rheumatoid Arthritis patients demonstrated that folic acid supplementation reduces hepatotoxicity and gastrointestinal symptoms due to methotrexate intolerance. (Liu et al., 2019) A study reported that administering folic acid 48 hours before methotrexate in JIA patients significantly reduced gastrointestinal symptoms and achieved complete remission without decreasing drug efficacy. (Martini et al., 2023)

Antiemetics

Another strategy to treat methotrexate intolerance is prescribing antiemetics. A study by Amin et al. stated that 21% of JIA patients start using anti-emetics frequently. (Amin et al., 2015) Ondansetron is a first-line antiemetic widely used in children and tends to be effective compared to metoclopramide and chlorpromazine. Ondansetron was reported to reduce methotrexate intolerance significantly in inflammatory rheumatoid arthritis. Premedication ondansetron was significantly potent in reducing nausea-induced methotrexate. Moreover, ondansetron was effective in treating nausea-induced methotrexate in patients who were not initially given premedication. (Saif et al., 2022)

Probiotics

Previous study suggested there is an altered gut microbiota in JIA patients. Alteration of gut microbiota was correlated with disease severity. Probiotic supplementation attempts to modify gut microbiota, hence could reduce inflammation and severity of the disease. (Qian et al., 2020) A study revealed that probiotic supplementation in JIA is well tolerated, although there is no significant clinical improvement in disease activity when combined with NSAIDs. This study reported that IL-10 was significantly lower after probiotics treatment. However, there is no difference in adverse effects between probiotics and control groups.

(Shukla et al., 2016) Another study reported that probiotics supplementation increased IgA and decreased mucosal tissue damage. (Mazziotta et al., 2023)

Nutrition

Nutritional aspects play a crucial role and adversely affect the long-term outcomes of JIA patients. Anti-inflammatory diets promote gut health, support healing processes, and strengthen the immune system. Giving suboptimal nutrition could enhance recovery, prevent flare-up, and reduce severity in JIA patients. (Zandonadi, 2022) Anti-inflammatory diets and omega-3 fatty acids were reported to reduce inflammation and improve clinical manifestations of JIA. This study demonstrated that giving omega-3 supplementation 2g/day for 12 weeks could decrease the daily use of NSAIDs. (Gheita et al., 2012) It is suggested that giving omega-3 supplementation could prevent abdominal pain, gastric ulcers, and gastrointestinal bleeding due to NSAIDs. Moreover, a study revealed that the increase in omega-3 and omega-6 levels was correlated with the reduction of CRP and ESR levels. (Gorczyca et al., 2017) A randomized controlled trial revealed dietary supplements of omega-3 improved immunology status. (Yarema et al., 2018)

This part allows you to elaborate on your results findings academically. You must not put numbers related to your statistical tests here; instead, you have to explain that numbers here. You have to compile your discussion with academic supports to your study and a good explanation according to the specific area you are investigating.

CONCLUSIONS AND RECOMMENDATIONS

Gastrointestinal involvement in JIA patients is a significant complication that requires close attention. The mechanisms between JIA and gastrointestinal involvement were complex including systemic inflammation, medication side effects, and genetic variants. Commonly prescribed medications in JIA therapy can also contribute to gastrointestinal complications, highlighting the importance of achieving disease control while minimizing adverse effects. Early screening for gastrointestinal problems and appropriate management strategies are essential to improve clinical outcomes in JIA patients.

FURTHER STUDY

Further studies need to be conducted to explore the biological specific mechanism of gastrointestinal involvement in JIA. Longitudinal studies should be performed to measure the gastrointestinal effects due to treatment, including the patient's quality of life and future disease progression. Developing safer treatment options to minimize gastrointestinal complication

ACKNOWLEDGMENT

The authors would like to acknowledge to Faculty of Medicine, Airlangga University for the support

REFERENCES

Aalto, K., Lahdenne, P., & Kolho, K.-L. (2017). Fecal calprotectin in juvenile idiopathic arthritis patients related to drug use. *Pediatric Rheumatology*, *15*(1), 9. https://doi.org/10.1186/s12969-016-0132-2

Adedokun, S. A., & Olojede, O. C. (2019). Optimizing gastrointestinal integrity in poultry: the role of nutrients and feed additives [Review]. *Frontiers in Veterinary Science*, *5*. https://doi.org/10.3389/fvets.2018.00348

Albokhari, S., & Muzaffer, M. A. (2021). Anemia in juvenile idiopathic arthritis (JIA) and other pediatric rheumatologic diseases: a retrospective study. *Open Journal of Rheumatology and Autoimmune Diseases*, *11*, 188-202. https://doi.org/10.4236/ojra.2021.114019

Amin, T. S., Shenton, S., Mulligan, K., Wedderburn, L. R., Wood, M., VanRooyen, V., & Leone, V. (2015). Strategies for the prevention and management of methotrexate-related nausea and vomiting in juvenile idiopathic arthritis: results of a UK Paediatric Rheumatology prescriber survey. *Rheumatology*, *54*(11), 2108-2109. https://doi.org/10.1093/rheumatology/kev259

Armaroli, G., Klein, A., Ganser, G., Ruehlmann, M. J., Dressler, F., Hospach, A., Minden, K., Trauzeddel, R., Foeldvari, I., Kuemmerle-Deschner, J., Weller-Heinemann, F., Urban, A., & Horneff, G. (2020). Long-term safety and effectiveness of etanercept in JIA: an 18-year experience from the BiKeR registry. *Arthritis Research & Therapy*, *22*(1), 258. https://doi.org/10.1186/s13075-020-02326-5

Asai, S., Nagai, K., Takahashi, N., Watanabe, T., Matsumoto, T., Asai, N., Sobue, Y., Ishiguro, N., & Kojima, T. (2019). Influence of methotrexate on gastrointestinal symptoms in patients with rheumatoid arthritis. *Int J Rheum Dis*, *22*(2), 207-213. https://doi.org/10.1111/1756-185x.13380

Barral Mena, E., García Cárdaba, L. M., Canet Tarrés, A., Enríquez Merayo, E., Cruz Utrilla, A., & de Inocencio Arocena, J. (2020). Methotrexate in juvenile idiopathic arthritis. Adverse effects and associated factors. *Anales de Pediatría (English Edition)*, *92*(3), 124-131. https://doi.org/https://doi.org/10.1016/j.anpede.2019.05.011

Barut, K., Adrovic, A., Şahin, S., & Kasapçopur, Ö. (2017). Juvenile idiopathic arthritis. *Balkan Med J*, *34*(2), 90-101. https://doi.org/10.4274/balkanmedj.2017.0111

Batu, E. D. (2019). Glucocorticoid treatment in juvenile idiopathic arthritis. *Rheumatol Int*, *39*(1), 13-27. https://doi.org/10.1007/s00296-018-4168-0

Bieber, A., Fawaz, A., Novofastovski, I., & Mader, R. (2017). Antitumor necrosis factor-α therapy associated with inflammatory bowel disease: three cases and a aystematic literature review. *J Rheumatol*, *44*(7), 1088-1095. https://doi.org/10.3899/jrheum.160952

Biswas, S., Qureshi, Z. A., Reyes, S., Bodepudi, S. L., & Thomas, S. E. (2018). IBD-associated arthritis misdiagnosed as juvenile idiopathic arthritis: a case report and literature review: 2091. *Official journal of the American College of Gastroenterology | ACG*, *113*, S1188-S1189. https://journals.lww.com/ajg/fulltext/2018/10001/ibd_associated_arthritis_misdiagnosed_as_juvenile.2090.aspx

Cardile, S., Martinelli, M., Barabino, A., Gandullia, P., Oliva, S., Di Nardo, G., Dall'Oglio, L., Rea, F., de'Angelis, G. L., Bizzarri, B., Guariso, G., Masci, E., Staiano, A., Miele, E., & Romano, C. (2016). Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol*, *22*(5), 1877-1883. https://doi.org/10.3748/wjg.v22.i5.1877

Dallocchio, A., Canioni, D., Ruemmele, F., Duquesne, A., Scoazec, J.-Y., Bouvier, R., Paraf, F., Languepin, J., Wouters, C., Guillot, M., & Quartier, P. (2010). Occurrence of inflammatory bowel disease during treatment of juvenile idiopathic arthritis with etanercept: A French retrospective study. *Rheumatology (Oxford, England)*, *49*, 1694-1698. https://doi.org/10.1093/rheumatology/keq136

Dave, M., Rankin, J., Pearce, M., & Foster, H. E. (2020). Global prevalence estimates of three chronic musculoskeletal conditions: club foot, juvenile idiopathic arthritis and juvenile systemic lupus erythematosus. *Pediatric Rheumatology*, *18*(1), 49. https://doi.org/10.1186/s12969-020-00443-8

De Filippo, C., Di Paola, M., Giani, T., Tirelli, F., & Cimaz, R. (2019). Gut microbiota in children and altered profiles in juvenile idiopathic arthritis. *Journal of Autoimmunity*, *98*, 1-12. https://doi.org/https://doi.org/10.1016/j.jaut.2019.01.001

Falvey, S., Shipman, L., Ilowite, N., & Beukelman, T. (2017). Methotrexate-induced nausea in the treatment of juvenile idiopathic arthritis. *Pediatric Rheumatology*, *15*(1), 52. https://doi.org/10.1186/s12969-017-0180-2

Favier, L. A., Taylor, J., Loiselle Rich, K., Jones, K. B., Vora, S. S., Harris, J. G., Gottlieb, B. S., Robbins, L., Lai, J. T., Lee, T., Kohlheim, M., Gill, J., Bouslaugh, L., Young, A., Griffin, N., Morgan, E. M., & Modi, A. C. (2018). Barriers to adherence in juvenile idiopathic arthritis: a multicenter collaborative experience and preliminary results. *J Rheumatol*, *45*(5), 690-696. https://doi.org/10.3899/jrheum.171087

Ferrara, G., Mastrangelo, G., Barone, P., La Torre, F., Martino, S., Pappagallo, G., Ravelli, A., Taddio, A., Zulian, F., Cimaz, R., & On behalf of the Rheumatology Italian Study, G. (2018). Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. *Pediatric Rheumatology*, *16*(1), 46. https://doi.org/10.1186/s12969-018-0255-8

Ferrara, G., Pastore, S., Sancin, L., Torelli, L., Radillo, O., Bramuzzo, M., Bibalo, C., Tommasini, A., Ventura, A., & Taddio, A. (2018). Fecal calprotectin to detect inflammatory bowel disease in juvenile idiopathic arthritis. *J Rheumatol*, *45*(10), 1418-1421. https://doi.org/10.3899/jrheum.171200

Fotis, L., Shaikh, N., Baszis, K. W., Samson, C. M., Lev-Tzion, R., French, A. R., & Tarr, P. I. (2017). Serologic evidence of gut-driven systemic inflammation in juvenile idiopathic arthritis. *J Rheumatol*, *44*(11), 1624-1631. https://doi.org/10.3899/jrheum.161589

Garner, A. J., Saatchi, R., Ward, O., & Hawley, D. P. (2021). Juvenile idiopathic arthritis: a review of novel diagnostic and monitoring technologies. *Healthcare (Basel)*, *9*(12). https://doi.org/10.3390/healthcare9121683

Gheita, T., Kamel, S., Helmy, N., El-Laithy, N., & Monir, A. (2012). Omega-3 fatty acids in juvenile idiopathic arthritis: effect on cytokines (IL-1 and TNF-α), disease activity and response criteria. *Clin Rheumatol*, *31*(2), 363-366. https://doi.org/10.1007/s10067-011-1848-5

Gonzalez, T., Malagon, C., Guarnizo, P., Mosquera, A. C., Chila-Moreno, L., & Romero-Sanchez, C. (2018). Autoantibodies and gastrointestinal symptoms in colombian children with juvenile idiopathic arthritis. *Curr Rheumatol Rev*, *14*(2), 163-171. https://doi.org/10.2174/1573397114666180108110429

Gorczyca, D., Postepski, J., Czajkowska, A., Mariola, P., Prescha, A., Olesińska, E., Gruenpeter, A., Lachór-Motyka, I., & Szponar, B. (2017). The profile of polyunsaturated fatty acids in juvenile idiopathic arthritis and association with disease activity. *Clinical Rheumatology*, *36*. https://doi.org/10.1007/s10067-017-3586-9

Harris, J. G., Kessler, E. A., & Verbsky, J. W. (2013). Update on the treatment of juvenile idiopathic arthritis. *Current Allergy and Asthma Reports*, *13*(4), 337-346. https://doi.org/10.1007/s11882-013-0351-2

Heinzel, S., Jureczek, J., Kainulainen, V., Nieminen, A. I., Suenkel, U., von Thaler, A.-K., Kaleta, C., Eschweiler, G. W., Brockmann, K., Aho, V. T. E., Auvinen, P., Maetzler, W., Berg, D., & Scheperjans, F. (2024). Elevated fecal calprotectin is associated with gut microbial dysbiosis, altered serum markers and clinical outcomes in older individuals. *Scientific Reports*, *14*(1), 13513. https://doi.org/10.1038/s41598-024-63893-0

Higuchi, T., Yoshimura, M., Oka, S., Tanaka, K., Naito, T., Yuhara, S., Warabi, E., Mizuno, S., Ono, M., Takahashi, S., Tohma, S., Tsuchiya, N., & Furukawa, H. (2020). Modulation of methotrexate-induced intestinal mucosal injury by dietary factors. *Hum Exp Toxicol*, *39*(4), 500-513. https://doi.org/10.1177/0960327119896605

Hügle, B., Speth, F., & Haas, J.-P. (2017). Inflammatory bowel disease following anti-interleukin-1-treatment in systemic juvenile idiopathic arthritis. *Pediatric Rheumatology*, *15*(1), 16. https://doi.org/10.1186/s12969-017-0147-3

Hügle, B., & van Dijkhuizen, E. H. P. (2020). MTX intolerance in children and adolescents with juvenile idiopathic arthritis. *Rheumatology*, *59*(7), 1482-1488. https://doi.org/10.1093/rheumatology/keaa139

Hutchings, D., Miller, J. A., & Voltaggio, L. (2019). Paradoxical gastrointestinal reactions in patients taking tumor necrosis factor inhibitors: a rare event that broadens the histologic spectrum of medication–associated injury. *Human Pathology*, *85*, 202-209. https://doi.org/https://doi.org/10.1016/j.humpath.2018.11.003

Jacobson, J. L., & Pham, J. T. (2018). Juvenile idiopathic arthritis: a focus on pharmacologic management. *J Pediatr Health Care*, *32*(5), 515-528. https://doi.org/10.1016/j.pedhc.2018.02.005

Kikuchi, H., Oliveira, L. A., Santos-Silva, A. R., Lopes, M. A., Faustino, I. S. P., Teixeira, V. P., & Júnior, J. N. R. A. (2023). Oral ulcerations associated with the use of methotrexate: a series of 4 cases. *Oral Surgery, Oral Medicine,*

Oral Pathology and Oral Radiology, *136*(1), e66. https://doi.org/10.1016/j.oooo.2023.03.228

Koshi, E. J., Young, K., Mostales, J. C., Vo, K. B., & Burgess, L. P. (2022). Complications of corticosteroid therapy: a comprehensive literature review. *J Pharm Technol*, *38*(6), 360-367. https://doi.org/10.1177/87551225221116266

Kyvsgaard, N., Mikkelsen, T. S., Thastum, M., Christensen, A. E., Wehner, P. S., Nysom, K., & Herlin, T. (2019). Increased methotrexate intolerance in juvenile idiopathic arthritis compared to acute lymphoblastic leukaemia in children. *PLoS One*, *14*(7), e0219539. https://doi.org/10.1371/journal.pone.0219539

Lamot, L., Miler, M., Vukojević, R., Vidović, M., Lamot, M., Trutin, I., Gabaj, N. N., & Harjaček, M. (2021). The increased levels of fecal calprotectin in children with active enthesitis related arthritis and MRI signs of aacroiliitis: the results of a single center cross-sectional exploratory study in juvenile idiopathic arthritis patients [Brief Research Report]. *Frontiers in Medicine*, *8*. https://doi.org/10.3389/fmed.2021.650619

Langer, V., Vivi, E., Regensburger, D., Winkler, T. H., Waldner, M. J., Rath, T., Schmid, B., Skottke, L., Lee, S., Jeon, N. L., Wohlfahrt, T., Kramer, V., Tripal, P., Schumann, M., Kersting, S., Handtrack, C., Geppert, C. I., Suchowski, K., Adams, R. H., . . . Stürzl, M. (2019). IFN-γ drives inflammatory bowel disease pathogenesis through VE-cadherin-directed vascular barrier disruption. *J Clin Invest*, *129*(11), 4691-4707. https://doi.org/10.1172/jci124884

Leksell, E., Ernberg, M., Magnusson, B., & Hedenberg-Magnusson, B. (2008). Intraoral condition in children with juvenile idiopathic arthritis compared to controls. *Int J Paediatr Dent*, *18*(6), 423-433. https://doi.org/10.1111/j.1365-263X.2008.00931.x

Liu, L., Liu, S., Wang, C., Guan, W., Zhang, Y., Hu, W., Zhang, L., He, Y., Lu, J., Li, T., Liu, X., Xuan, Y., & Wang, P. (2019). Folate supplementation for methotrexate therapy in patients with rheumatoid arthritis: a systematic review. *J Clin Rheumatol*, *25*(5), 197-202. https://doi.org/10.1097/rhu.0000000000000810

Lovell, D. J., Dare, J. A., Francis-Sedlak, M., Ball, J., LaMoreaux, B. D., Von Scheven, E., Reinhardt, A., Jerath, R., Alpan, O., Gupta, R., Goldsmith, D., Zeft, A., Naddaf, H., Gottlieb, B., Jung, L., & Holt, R. J. (2018). A 6-month, multicenter, open-label study of fixed dose naproxen/esomeprazole in adolescent patients with juvenile idiopathic arthritis. *Pediatric Rheumatology*, *16*(1), 41. https://doi.org/10.1186/s12969-018-0260-y

Maller, J., Fox, E., Park, K. T., Paul, S. S., Baszis, K., Borocco, C., Prahalad, S., Quartier, P., Reinhardt, A., Schonenberg-Meinema, D., Shipman-Duensing, L., Terreri, M. T., Simard, J., Lavi, I., Chalom, E., Hsu, J., Zisman, D., & Mellins, E. D. (2021). Inflammatory bowel disease in children with systemic juvenile idiopathic arthritis. *J Rheumatol*, *48*(4), 567-574. https://doi.org/10.3899/jrheum.200230

Manatpreeprem, R., Lerkvaleekul, B., & Vilaiyuk, S. (2023). Factors associated with medication adherence among children with rheumatic diseases [Original Research]. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1149320

Martini, G., Meneghel, A., Fastiggi, M., Dell'Apa, F., Vittadello, F., & Zulian, F. (2023). Strategic use of levofolinic acid for methotrexate-induced side effects in juvenile idiopathic arthritis: a prospective observational study. *Pediatric Rheumatology*, *21*(1), 18. https://doi.org/10.1186/s12969-023-00800-3

Mazziotta, C., Tognon, M., Martini, F., Torreggiani, E., & Rotondo, J. C. (2023). Probiotics mechanism of action on immune cells and beneficial effects on human health. *Cells*, *12*(1). https://doi.org/10.3390/cells12010184

Mulligan, K., Kassoumeri, L., Etheridge, A., Moncrieffe, H., Wedderburn, L. R., & Newman, S. (2013). Mothers' reports of the difficulties that their children experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. *Pediatr Rheumatol Online J*, *11*(1), 23. https://doi.org/10.1186/1546-0096-11-23

Naddei, R., Di Gennaro, S., Guarino, A., Troncone, R., Alessio, M., & Discepolo, V. (2022). In a large Juvenile Idiopathic Arthritis (JIA) cohort, concomitant celiac disease is associated with family history of autoimmunity and a more severe JIA course: a retrospective study. *Pediatr Rheumatol Online J*, *20*(1), 31. https://doi.org/10.1186/s12969-022-00689-4

Nayak, R. R., Alexander, M., Deshpande, I., Stapleton-Gray, K., Rimal, B., Patterson, A. D., Ubeda, C., Scher, J. U., & Turnbaugh, P. J. (2021). Methotrexate impacts conserved pathways in diverse human gut bacteria leading to decreased host immune activation. *Cell Host & Microbe*, *29*(3), 362-377.e311. https://doi.org/10.1016/j.chom.2020.12.008

Niyasom, C., Soponkanaporn, S., Vilaiyuk, S., Lertudomphonwanit, C., Getsuwan, S., Tanpawpong, P., Kaewduang, P., & Sobhonslidsuk, A. (2024). Use of transient elastography to assess hepatic steatosis and fibrosis in patients with juvenile idiopathic arthritis during methotrexate treatment. *Clinical Rheumatology*, *43*(1), 423-433. https://doi.org/10.1007/s10067-023-06835-x

Noha Adel, Y., Mai, H., & Azza, E. (2021). Methotrexate hepatotoxicity in children with juvenile idiopathic arthritis: a single-center study. *Current Rheumatology Reviews*, *17*(2), 242-246. https://doi.org/http://dx.doi.org/10.2174/1573397116666201211123142

Onel, K. B., Horton, D. B., Lovell, D. J., Shenoi, S., Cuello, C. A., Angeles-Han, S. T., Becker, M. L., Cron, R. Q., Feldman, B. M., Ferguson, P. J., Gewanter, H., Guzman, J., Kimura, Y., Lee, T., Murphy, K., Nigrovic, P. A., Ombrello, M. J., Rabinovich, C. E., Tesher, M., . . . Reston, J. T. (2022). 2021 American College of Rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*, *74*(4), 521-537. https://doi.org/10.1002/acr.24853

Pichler, J., Ong, C., Shah, N., Sebire, N., Kiparrissi, F., Borrelli, O., Pilkington, C., & Elawad, M. (2016). Histopathological features of gastrointestinal mucosal biopsies in children with juvenile idiopathic arthritis. *Pediatric Research*, *79*(6), 895-901. https://doi.org/10.1038/pr.2016.27

Poddighe, D., Rakhimzhanova, M., Marchenko, Y., & Catassi, C. (2019). Pediatric celiac disease in Central and East Asia: current knowledge and prevalence. *Medicina (Kaunas)*, *55*(1). https://doi.org/10.3390/medicina55010011

Poddighe, D., Romano, M., Dossybayeva, K., Abdukhakimova, D., Galiyeva, D., & Demirkaya, E. (2022). Celiac disease in juvenile idiopathic arthritis and other pediatric rheumatic disorders. *J Clin Med*, *11*(4). https://doi.org/10.3390/jcm11041089

Qian, X., Liu, Y.-X., Ye, X., Zheng, W., Lv, S., Mo, M., Lin, J., Wang, W., Wang, W., Zhang, X., & Lu, M. (2020). Gut microbiota in children with juvenile idiopathic arthritis: characteristics, biomarker identification, and usefulness in clinical prediction. *BMC Genomics*, *21*(1), 286. https://doi.org/10.1186/s12864-020-6703-0

Räisänen, L., Viljakainen, H., & Kolho, K.-L. (2023). Exposure to proton pump inhibitors is associated with the development of pediatric autoimmune diseases [Brief Research Report]. *Frontiers in Pediatrics*, *11*. https://doi.org/10.3389/fped.2023.1157547

Rebane, K., Tuomi, A.-K., Kautiainen, H., Peltoniemi, S., Glerup, M., & Aalto, K. (2022). Abdominal pain in Finnish young adults with juvenile idiopathic arthritis. *Scandinavian Journal of Gastroenterology*, *57*(10), 1189-1194. https://doi.org/10.1080/00365521.2022.2072691

Sadeghi, P., Salari, K., Ziaee, V., Rezaei, N., & Eftekhari, K. (2021). Serological screening of celiac disease in patients with juvenile idiopathic arthritis. *Arch Iran Med*, *24*(10), 783-785. https://doi.org/10.34172/aim.2021.116

Saif, S., Kakalia, S., Kitchlew, R., Khan, H. A., Fida, S., & Siddique, M. (2022). Role of ondansetron in reducing methotrexate intolerance in patients with inflammatory arthritis. *J Coll Physicians Surg Pak*, *32*(10), 1308-1312. https://doi.org/10.29271/jcpsp.2022.10.1308

Shi, C.-l., Zhang, Y., Zhang, Z.-y., Zhou, J., & Tang, X.-m. (2021). Comparative efficacy and safety of non-steroidal anti-inflammatory drugs in patients with juvenile idiopathic arthritis: a systematic review and network meta-analysis. *Indian Pediatrics*, *58*(2), 162-168. https://doi.org/10.1007/s13312-021-2155-0

Shukla, A., Gaur, P., & Aggarwal, A. (2016). Effect of probiotics on clinical and immune parameters in enthesitis-related arthritis category of juvenile idiopathic arthritis. *Clin Exp Immunol*, *185*(3), 301-308. https://doi.org/10.1111/cei.12818

Soliman, Y. A., Hassan, W. A. S., & Elsayed, D. G. (2021). Gastro-intestinal manifestations of pediatric rheumatic diseases. *Benha Journal of Applied Sciences*, *6*(6), 375-383. https://doi.org/10.21608/bjas.2021.214842

Stefanov, S., Ganeva, M., Stoilov, N., Boyadzhieva, V., & Telcharova-Mihaylovska, A. (2018). The role of gut microbiota in juvenile idiopathic

arthritis. *Biotechnology & Biotechnological Equipment*, *32*(5), 1081-1086. https://doi.org/10.1080/13102818.2018.1512376

Stoll, M. L., Kumar, R., Morrow, C. D., Lefkowitz, E. J., Cui, X., Genin, A., Cron, R. Q., & Elson, C. O. (2014). Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis. *Arthritis Res Ther*, *16*(6), 486. https://doi.org/10.1186/s13075-014-0486-0

Tai, F. W. D., & McAlindon, M. E. (2021). Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Clinical Medicine*, *21*(2), 131-134. https://doi.org/https://doi.org/10.7861/clinmed.2021-0039

Tbini, H., Rahmouni, S., Boussaid, S., Ammou, A. B., Jemmali, S., Rekik, S., Zouaoui, K., Sahli, H., & Elleuch, M. (2022). 17 Anemia in juvenile idiopathic arthritis: analysis of associated factors. *Rheumatology*, *61*(Supplement_2). https://doi.org/10.1093/rheumatology/keac496.013

Tena-Garitaonaindia, M., Arredondo-Amador, M., Mascaraque, C., Asensio, M., Marin, J. J. G., Martínez-Augustin, O., & Sánchez de Medina, F. (2022). Modulation of intestinal barrier function by glucocorticoids: Lessons from preclinical models. *Pharmacological Research*, *177*, 106056. https://doi.org/https://doi.org/10.1016/j.phrs.2022.106056

Tharwat, S., Nassar, M. K., Salem, K. M., & Nassar, M. K. (2024). Extraarticular manifestations of juvenile idiopathic arthritis and their impact on health-related quality of life. *Clin Rheumatol*, *43*(7), 2295-2305. https://doi.org/10.1007/s10067-024-07008-0

Thatayatikom, A., Modica, R., & Leucio, A. D. (2024). Juvenile idiopathic arthritis. In StatPearls (Ed.). StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK554605/

Tian, L., Huang, C., Fu, W., Gao, L., Mi, N., Bai, M., Ma, H., Zhang, C., Lu, Y., Zhao, J., Zhang, X., Jiang, N., Lin, Y., Yue, P., Yuan, J., & Meng, W. (2023). Proton pump inhibitors may enhance the risk of digestive diseases by regulating intestinal microbiota [Review]. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/fphar.2023.1217306

van Dijken, T. D., Vastert, S. J., Gerloni, V. M., Pontikaki, I., Linnemann, K., Girschick, H., Armbrust, W., Minden, K., Prince, F. H. M., Kokke, F. T. M., Nieuwenhuis, E. E. S., Horneff, G., & Wulfraat, N. M. (2011). Development of inflammatory bowel disease in patients with juvenile idiopathic arthritis treated with etanercept. *The Journal of Rheumatology*, *38*(7), 1441-1446. https://doi.org/10.3899/jrheum.100809

van Dijkhuizen, E. H. P., Bulatović Ćalasan, M., Pluijm, S. M. F., de Rotte, M. C. F. J., Vastert, S. J., Kamphuis, S., de Jonge, R., & Wulffraat, N. M. (2015). Prediction of methotrexate intolerance in juvenile idiopathic arthritis: a prospective, observational cohort study. *Pediatric Rheumatology*, *13*(1), 5. https://doi.org/10.1186/s12969-015-0002-3

van Straalen, J. W., Krol, R. M., Giancane, G., Panaviene, V., Ailioaie, L. M., Doležalová, P., Cattalini, M., Susic, G., Sztajnbok, F. R., Maritsi, D., Constantin, T., Sawhney, S., Rygg, M., Oliveira, S. K., Nordal, E. B., Saad-Magalhães, C., Rubio-Perez, N., Jelusic, M., de Roock, S., . . . Organisation,

f. t. P. R. I. T. (2021). Increased incidence of inflammatory bowel disease on etanercept in juvenile idiopathic arthritis regardless of concomitant methotrexate use. *Rheumatology*, *61*(5), 2104-2112. https://doi.org/10.1093/rheumatology/keab678

Verwoerd, A., Ter Haar, N. M., de Roock, S., Vastert, S. J., & Bogaert, D. (2016). The human microbiome and juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*, *14*(1), 55. https://doi.org/10.1186/s12969-016-0114-4

Wibrand, C., Kyvsgaard, N., Christensen, A. E., & Herlin, T. (2023). The role of liver transaminase levels in methotrexate intolerance in juvenile idiopathic arthritis—a cross-sectional study. *Rheumatology International*, *43*(5), 875-880. https://doi.org/10.1007/s00296-023-05297-3

Wibrand, C., Kyvsgaard, N., Herlin, T., & Glerup, M. (2024). Methotrexate intolerance in juvenile idiopathic arthritis: definition, risks, and management. *Pediatric Drugs*, *26*(5), 479-498. https://doi.org/10.1007/s40272-024-00643-9

Xin, L., He, F., Li, S., Zhou, Z. X., & Ma, X. L. (2021). Intestinal microbiota and juvenile idiopathic arthritis: current understanding and future prospective. *World J Pediatr*, *17*(1), 40-51. https://doi.org/10.1007/s12519-020-00371-3

Yao, T. C., Wang, J. Y., Chang, S. M., Chang, Y. C., Tsai, Y. F., Wu, A. C., Huang, J. L., & Tsai, H. J. (2021). Association of oral corticosteroid bursts with severe adverse events in children. *JAMA Pediatr*, *175*(7), 723-729. https://doi.org/10.1001/jamapediatrics.2021.0433

Yarema, N., Fedortsiv, O., & Palasiuk, B. (2018). Influence of ω-3 polyunsaturated fatty acids on the structure of immunocompetent cell membranes and the parameters of cellular and humoral immunity in children with rheumatoid arthritis [journal article]. *Family Medicine & Primary Care Review*, *20*(1), 78-82. https://doi.org/10.5114/fmpcr.2018.73707

Zandonadi, R. P. (2022). An overview of nutritional aspects in juvenile idiopathic arthritis. *Nutrients*, *14*(20), 4412. https://www.mdpi.com/2072-6643/14/20/4412

Zaripova, L. N., Midgley, A., Christmas, S. E., Beresford, M. W., Baildam, E. M., & Oldershaw, R. A. (2021). Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. *Pediatric Rheumatology*, *19*(1), 135. https://doi.org/10.1186/s12969-021-00629-8

Zhou, B., Xia, X., Wang, P., Chen, S., Yu, C., Huang, R., Zhang, R., Wang, Y., Lu, L., Yuan, F., Tian, Y., Fan, Y., Zhang, X., Shu, Y., Zhang, S., Bai, D., Wu, L., Xu, H., & Yang, L. (2018). Induction and amelioration of methotrexate-induced gastrointestinal toxicity are related to immune response and gut microbiota. *eBioMedicine*, *33*, 122-133. https://doi.org/10.1016/j.ebiom.2018.06.029