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Review

# Inflammatory bowel disease in primary immunodeficiency disorders is a heterogeneous clinical entity requiring an individualized treatment strategy: A systematic review

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CBT
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ABSTRACT

*Objective:* To describe the prevalence, clinical presentation and current treatment regimens of inflammatory bowel disease (IBD) in patients with primary immunodeficiency disorders (PIDs).
*Methods:* A systematic review was conducted. The following databases were searched: MEDLINE, Embase, Web of Science, the Cochrane Library and Google Scholar.
*Results:* A total of 838 articles were identified, of which 36 were included in this review. The prevalence of IBD in PIDs ranges between 3.4% and 61.2%, depending on the underlying PID. Diarrhea and abdominal pain were reported in 64.3% and 52.4% of the patients, respectively. Colon ulceration was the most frequent finding on endoscopic evaluation, while cryptitis, granulomas, ulcerations and neutrophilic/lymphocytic infiltrates were the most frequently reported histopathological abnormalities. Described treatment regimens included oral corticosteroids and other oral immunosuppressive agents, including mesalazine, azathioprine and cyclosporin, leading to clinical improvement in the majority of patients. In case of treatment failure, biological therapies including TNF- α blocking agents, are considered.
*Conclusions:* The overall prevalence of IBD in patients with PID is high, but varies between different PIDs. Physicians should be aware of these complications and focus on characteristic symptoms to reduce diagnostic delay and delay in initiation of treatment. Treatment of IBD in PIDs depends on severity of symptoms and may differ between various PIDs based on distinct underlying pathogenesis. An individualized diagnostic and therapeutic approach is therefore warranted.

## 1. Introduction

Primary immunodeficiency disorders (PIDs) encompass a heterogeneous group of more than 430 inheritable defects of immunity caused by variants in genes encoding functional proteins of human immune cells [1–3]. PIDs are characterized by a compromised or entirely absent function of a part of the immune system and are generally characterized by an increased risk of infectious complications [4,5]. Patients may present in childhood or at later stages in life. Patients with PIDs may also present with features of immune dysregulation, resulting in autoimmunity, autoinflammation, (hematological) malignancies and allergic disorders [6]. Inflammatory bowel disease (IBD), an autoinflammatory condition, is reported in various PIDs [7,8]. Symptoms may vary from mild to severe, necessitating adequate treatment. Physicians may not always be aware of the relation between IBD and PID where in some cases IBD can even be the presenting symptom of PID. Early recognition of PID-associated IBD could result in earlier treatment and even reduce diagnostic delay for PID.

In general, IBD comprises two types of chronic inflammatory disorders of the gastrointestinal tract: ulcerative colitis (UC) and Crohn's disease (CD) [9]. Distinct features may differentiate between both conditions, including disease phenotype, localization, endoscopic and histologic features. Cases with colitis that cannot be classified into UC or CD are diagnosed with unclassified (IBD-U). For rapid induction therapy

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and control of inflammation in IBD, glucocorticoids, e.g. budesonide and prednisone, are prescribed. Mesalazine is the mainstay of treatment in UC, and a step-up approach is commonly reserved for severe or therapy-refractory cases. During step-up, thiopurines and TNF-α blocking agents are frequently prescribed, followed by newer biologicals including vedolizumab (integrin α4β7 inhibitor) and ustekinumab (anti- IL12/23) as well as treatment with Tofacitinib (JAK inhibitor) [6,10–12]. Newer therapies with Filgotinib (JAK inhibitor) and Ozanimod (sfingosine-1-fosfaat-receptor antagonist) are awaited in the near future [13]. For CD, initial choice of therapy depends on severity of inflammation, disease phenotype, localization, and extraintestinal manifestations. Although very effective in treatment of UC, mesalazine is insufficiently effective for CD. In addition, in the group of immunomodulators for CD, methotrexate is a valid choice when teratogenicity is not a contraindication [14–16]. TNF-α blocking agents have a rapid onset of action and are potent for both inducing remission, maintaining remission and reduce the need for hospitalization and surgery in patients with CD [17,18].

Currently, little is known about the prevalence of IBD in PID patients. In infants, children and occasionally in adults, PIDs including common variable immunodeficiency (CVID), chronic granulomatous disease (CGD) and Wiskott-Aldrich syndrome (WAS) can present as IBD or IBD-like colitis [19–24]. Another rather unexplored area is the treatment of IBD in PID patients.

Patients with IBD in PID are usually treated by a step-up approach, however, an individualized treatment approach may be better as proposed by Chellapandian et al. [25]. We aim to describe the prevalence, clinical presentation and treatment of IBD in patients with PID, in order to gain a better understanding of how to recognize these patients and how to optimize treatment regimens.

## 2. Methods

### 2.1. Information source and search strategy

We performed a systematic search to identify all manuscripts that describe IBD in PID. The search was performed on October 27th 2020. We did not limit the search to a certain time frame or study design. The following databases were used: Embase, Medline (Ovid), Web-of-Science Core Collection, Cochrane Central, and Google Scholar, using specific search strings per database (Appendix 1). The diagnosis IBD had to be confirmed by biopsies. Articles had to be original full-text articles written in English.

### 2.2. Study selection

Two authors (T.B. and S.M.R.) were involved in selecting articles. Any disagreement was discussed until consensus was reached. Articles were screened by title and abstract. Articles were excluded from our review if they were not available to us, did not include human subjects or patients who had PID with IBD (or IBD with PID). Reviews were excluded. Duplicates were counted once. In the second stage of screening the full-text articles were assessed for eligibility. In addition, articles without biopsy-proven IBD were excluded. We scored the articles using a self-made scoring tool based on the QUADAS-2 tool, to assess the quality of studies [26]. We developed this tool since the QUADAS-2 tool is used for evaluation of diagnostic studies and we also intended to include studies reporting prevalence and treatment regimens of IBD in various PIDs. In this stage, articles were included with a score of 4 or higher based on our quality assessment of which question 1, 2 and 3 had to be answered by yes. We used the following questions in our quality assessment:

1. Were the methods of determining the diagnosis of PID described in the study?
2. Were the methods of determining the diagnosis of IBD described in the study?
3. Was the study population clearly and fully described, including a case definition?
4. Was the prevalence of IBD in patients with PID discussed?
5. Was the clinical presentation of IBD in patients with PID discussed?
6. Was the treatment of IBD in patients with PID discussed?

A study can be awarded a maximum of 1 point for each numbered item, with a total maximum score of 6 points. One point can be scored for each yes and 0 points can be scored for each no.

### 2.3. Data synthesis and analysis

We distributed the data for our statistical analysis into a Microsoft Office Excel spreadsheet. We investigated 1) the prevalence of IBD in patients with PID, 2) the clinical symptoms of IBD in patients with PID and 3) the treatment of IBD in patients with PID.

The data on prevalence were extracted from cohort studies including PID patients without a patient selection, to prevent bias. In absence of a reported prevalence, we calculated the prevalence from the described cohort. Data concerning the clinical presentation of IBD in PID were extracted from the individual studies and the prevalence of each symptom was calculated divided by the total number of patients. Finally, the percentage of patients who achieved remission after treatment for IBD was calculated. The studies that described primarily IBD patients, of whom some were diagnosed with a PID, were not included when data were not reported separately.

## 3. Results

After removal of duplicates, we identified 838 articles through our search. These articles were screened by title and abstract. After applying the exclusion criteria, 137 articles remained for full-text analysis. Forty articles did not describe patients with a PID and IBD and sixty-four articles were reviews. This led to the exclusion of these articles. Four articles were added by cross-reference checking. Eventually, thirty-seven articles were included in our review (Fig. 1). In Appendix 2, we summarized the included articles with their quality assessment scores.

### 3.1. Prevalence

Fifteen articles provided data on the prevalence of IBD in PIDs. All articles were retrospective cohort studies and are summarized in Table 1. Multiple studies described the prevalence of IBD in patients with CVID, X-linked agammaglobulinemia (XLA), WAS, CGD or lipopolysaccharide-responsive and beige-like anchor (LRBA) protein deficiency. The prevalence of IBD in these patients varies between 3.4 and 61.2%, depending on the type of underlying immunodeficiency (Table 1) [27–38]. One study reported on the prevalence of IBD in hyperIgM syndrome (3.5%) [39] and one study in Nuclear factor-kappa B Essential Modulator (NEMO) deficiency syndrome (28.6%) [40].

### 3.2. Clinical presentation

A total of seventeen articles (fifteen case-reports and two retrospective cohort studies) described the clinical presentation of IBD in PID patients in detail, Table 2 [31,33,36,41–54]. Since the symptoms of IBD did not differ between the different PID types, we present the data of all

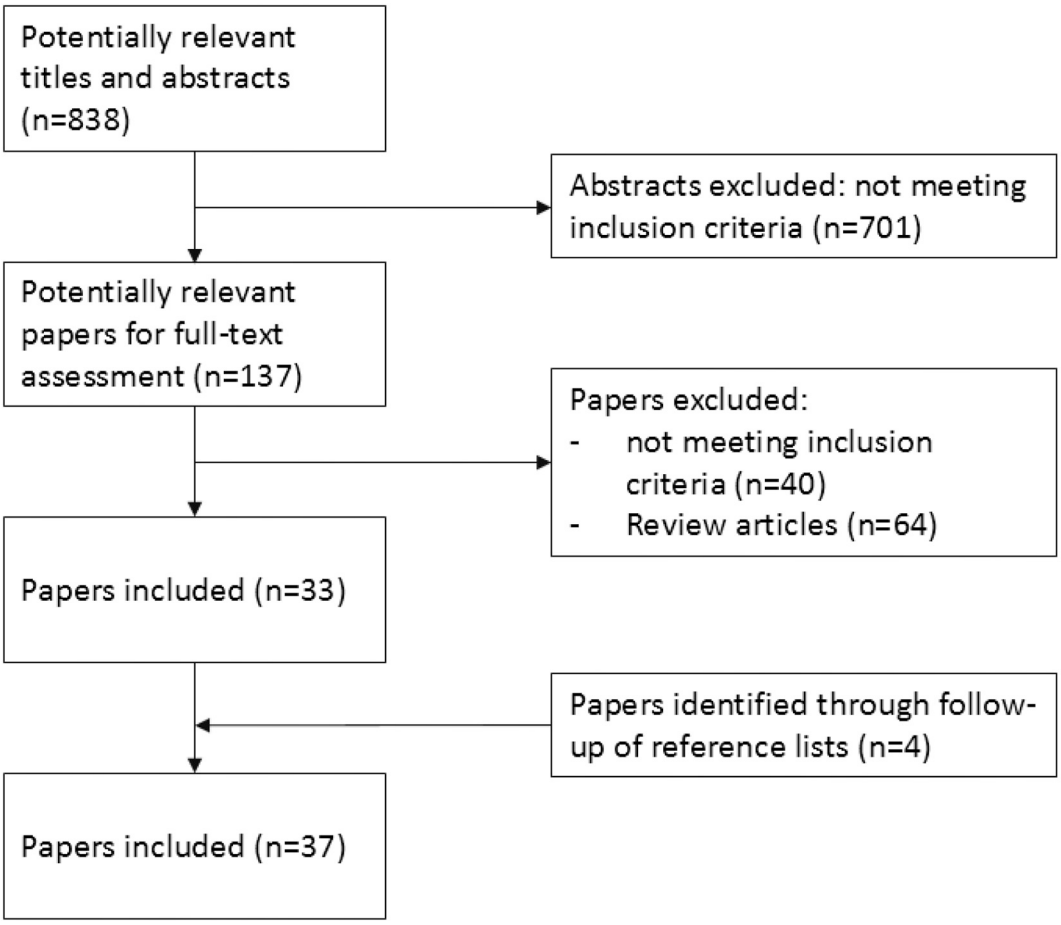


**Fig. 1.** Flowchart of study selection.

**Table 1**
Prevalence of IBD in PID.

| First author | Year of publication | PID type | Number of PID patients | Age range (years) | Number of IBD patients | Prevalence of IBD in PID (%) |
|---|---|---|---|---|---|---|
| Erdem [27] | 2019 | CVID | 28 | 0–9 | 3 | 10.3 |
| Habahbeh [29] | 2016 | CVID | 16 | 1–5 | 2 | 12.5 |
| Aydogan [30] | 2008 | CVID | 10 | 0–8 | 3 | 30 |
| Barmettler [57] | 2017 | XLA | 200 | NR | 19 | 9.5 |
| El-Sayed [70] | 2019 | XLA | 783 | 0–7 | 27 | 3.4 |
| Dupuis-Girod [31] | 2003 | WAS | 55 | 0–14 | 5 | 9.1 |
| Lee [32] | 2008 | WAS | 11 | 0–6 | 1 | 9.1 |
| Broides [33] | 2016 | CGD | 8 | 2–14 | 1 | 12.5 |
| Kawai [58] | 2015 | CGD | 35 | 0–17 | 16 | 45.7 |
| Magnani [35] | 2014 | CGD | 98 | 0–25 | 60 | 61.2 |
| Marciano [36] | 2004 | CGD | 140 | 0–27 | 8 | 57.1 |
| Cagdas [38] | 2019 | LRBA | 15 | 6–44 | 5 | 33.3 |
| Asgardoon [37] | 2020 | LRBA | 17 | 11–22 | 4 | 23.5 |
| Cheng [40] | 2009 | HyperIgM | 7 | 0–2 | 2 | 28.6 |
| Quartier [39] | 2004 | NEMO | 29 | 0–13 | 1 | 3.5 |

*Abbreviations:* CVID, Common Variable Immunodeficiency; WAS, Wiskott-Aldrich syndrome; CGD, Chronic Granulomatous Disease; XLA, X-linked agammaglobulinemia; LRBA, lipopolysaccharide-responsive and beige-like anchor protein deficiency; HyperIgM, Hyper IgM syndrome; NEMO, Nuclear factor-kappa B Essential Modulator deficiency syndrome; NR, not reported.
Studies are sorted by primary immunodeficiency disease.

patients combined ($n = 42$). Thirty-six patients had multiple symptoms.

The most frequently reported symptoms included diarrhea, abdominal pain, weight-loss or failure to thrive (in children) and bloody diarrhea. Less frequently reported symptoms included oral lesions, loss of appetite, fever, anal fistulae, perianal fissures, perianal ulcerations and perianal skin tags. Four studies reported imaging studies (MR-enterography) in eight patients of which the most common findings were nodular thickening, ulcerations and strictures of the small

**Table 2**
Most common clinical presentation of IBD ($n = 42$ patients) in PID. Most patients (36/42 = 85.7%) had multiple symptoms.

| Symptom | Frequency of the clinical symptom[a] | Prevalence (%) | Number of studies |
|---|---|---|---|
| Diarrhea | 27 | 64.3 | 12 [31,41–47,49,52–54] |
| Abdominal pain | 22 | 52.4 | 12 [33,41,43–45,48–53,55] |
| Weight loss/ failure to thrive | 17 | 40.5 | 10 [41–46,48,52,54,55] |
| Bloody diarrhea | 10 | 23.8 | 7 [33,44,49–53] |
| Oral lesions | 7 | 16.7 | 2 [44,52] |
| Loss of appetite | 4 | 9.5 | 4 [41,42,45,48] |
| Fever | 3 | 7.1 | 3 [48,49,53] |

*Abbreviations:* NA, not applicable.
[a] Symptoms of IBD in 42 patients with PID were extracted from seventeen articles.

intestine.

[41,43,48,55]. All grades of inflammation varying from edema, erosions to ulcerations, which were localized in both the upper gastrointestinal tract or small bowel, and colon were noticed by endoscopy. In several cases, granulomas were reported in the mucosal biopsies. Endoscopic features and histopathological reports of different PIDs are summarized in Table 3.

### 3.3. Treatment

All patients with IBD in PID were initially treated with antibiotics, usually as pre-emptive therapy and discontinued after negative cultures/PCRs or proven IBD as well as nutritional optimization. Based on the initial response or severity of IBD additional immunosuppressive drugs were initiated. The results of 134 individual patients, receiving 178 treatment regimens are summarized in Fig. 2 and Table 4. Four patients with CVID started on budesonide monotherapy after optimization of immunoglobulin replacement therapy (IGRT). However, no clinical improvement was described and corticosteroid and/or mesalazine therapy was initiated with good effect (Table 4) [41,42,56]. Furthermore, two patients with NEMO deficiency syndrome responded well after treatment with budesonide in combination with corticosteroids and mesalazine, respectively (Table 4) [40]. Nine patients including the patients who failed on budesonide (seven with CVID, two with XLA) received corticosteroid monotherapy (prednisone) with good effect (Table 4) [41,46,57]. Corticosteroid therapy is usually initiated for swift relieve of symptoms by decreasing inflammation activity. This therapy is frequently followed by corticosteroid sparing agents. Furthermore, in most patients on corticosteroid monotherapy subtle symptoms remained, also requiring additional immunosuppressive agents. We identified thirty-two patients who were treated with mesalazine of whom twenty-six patients (81%) achieved complete remission (Table 4) [40,42,50–53,55,56,58,59]. We identified twelve patients using azathioprine (three patients improved), six patients using cyclosporine (one patient improved) and three patients using 6-mercaptopurin (one patient improved) (Table 4) [43,44,52,56,58–61].

Sixteen patients who failed on oral immunosuppressive agents switched to biologicals (most frequently described drugs included adalimumab ($n = 6$) and infliximab ($n = 6$; both TNF-α blocking agents) or abatacept ($n = 4$; anti-CTLA4) (Fig. 2). Six of these patients (38%) improved (two with adalimumab, one with infliximab and three with abatacept), ten patients did not respond and required additional therapy [38,43,44,48,55,56,58,60,61] (Fig. 2). Three patients with refractory disease after treatment with corticosteroids, oral immunosuppressive agents and biologicals switched to other biologicals [48,56,59]. Two patients were treated with vedolizumab (integrin α4β7 inhibitor) and one patient received ustekinumab (anti-IL12/23) resulting in relieve of

**Table 3**
Results of radiological, endoscopic and histopathologic tests.

| PID | Number of patients | Radiological abnormalities | Endoscopic abnormalities | Histopathological abnormalities |
|---|---|---|---|---|
| CVID [28,41–43,45–47,49] | 14 | Duodenal stricture, small bowel nodular thickening, skip lesions, ulcers and edema ($n = 5$) | Fibrinoid ulcer ileum, colon ulcers and edema ($n = 3$) | Gastritis/duodenitis, villous atrophy, crypt hyperplasia, cryptitis, small bowel (non) transmural infiltrates/granuloma, lymphocyte/neutrophil infiltrates colon ($n = 14$) |
| XLA [41,48] | 2 | Small bowel nodular thickening and stricture ($n = 2$) | NR | Duodenitis, small bowel non-transmural infiltrates/granuloma, lymphocyte infiltrates colon ($n = 2$) |
| CGD [33,36,51,52,60] | 21 | NR | Gastritis/duodenitis, small bowel ulcers and erosions, colitis, colon ulcers and bleeding ($n = 9$) | Small bowel and colon granuloma, cryptitis, lymphocyte/neutrophil infiltrates colon ($n = 21$) |
| WAS [31,50] | 6 | Colon thickening ($n = 1$) | Colon ulcers, bleeding ($n = 1$) | Colon ulcers ($n = 1$) |
| LRBA [46] | 2 | NR | NR | Duodenitis, villous atrophy, lymphocytic infiltration colon, patchy thickening ($n = 2$) |

*Abbreviations:* CVID, Common Variable Immunodeficiency; WAS, Wiskott-Aldrich syndrome; CGD, Chronic Granulomatous Disease; XLA, X-linked agammaglobulinemia; LRBA, lipopolysaccharide-responsive and beige-like anchor protein deficiency; NR, not reported.
The table reports all available data concerning radiological, endoscopic and histopathologic tests of IBD in patients with PIDs.
($n$) = number of patients of which results are reported.

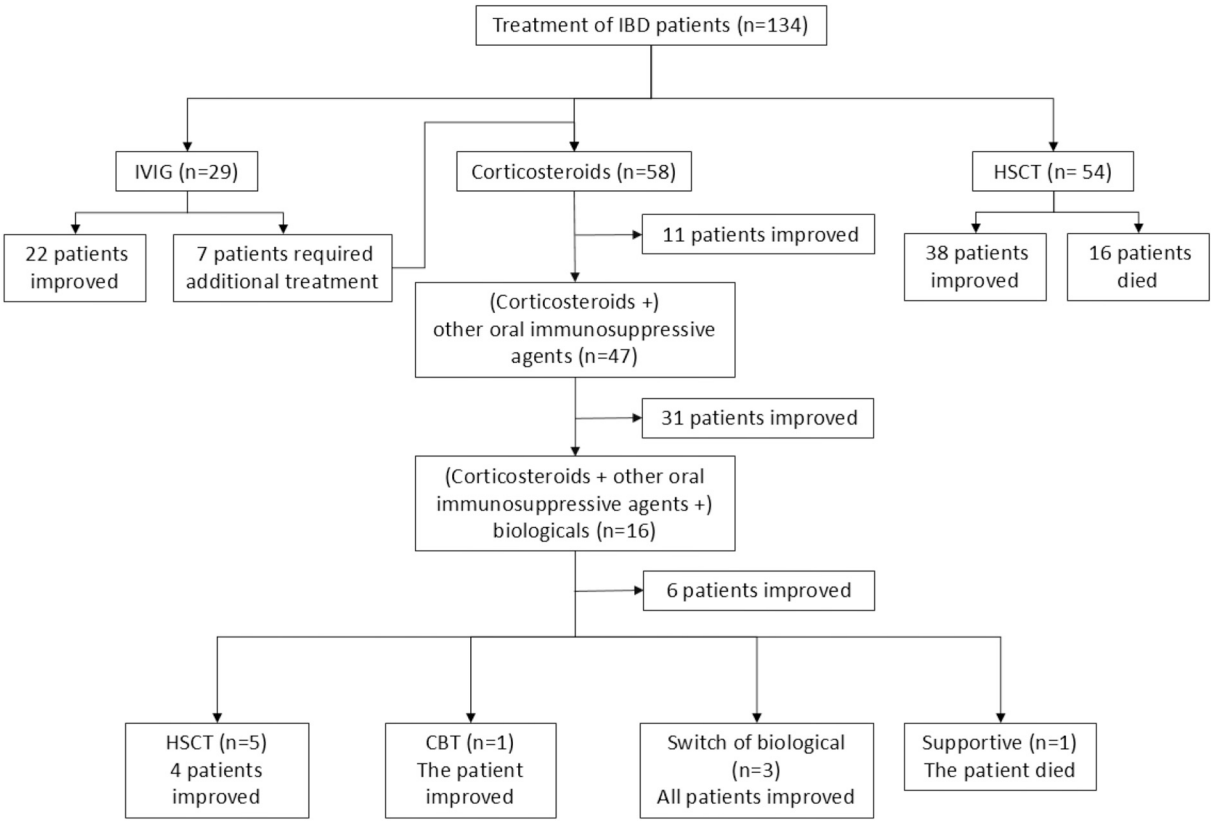


**Fig. 2.** Flowchart of treatment effects.

symptoms in all three patients without significant side-effects. Of the remaining seven patients, six (pediatric) patients received stem cell transplantation because of their PID (Fig. 2) with complete recovery from their IBD, the other patient received supportive care and died.

A total of twenty-nine patients were treated with IGRT because of PID (CVID, XLA, LRBA-deficiency) before signs of IBD were present. After development of IBD, IGRT dosage was increased leading to clinical improvement in twenty-two patients (76%) [32,45,46,57]. The other seven patients were subsequently treated with corticosteroids, other oral immunosuppressive agents, anti-TNF agents and finally five patients (all children) received hematopoietic stem cell transplantation (HSCT) of whom four improved [38,47,54,62].

In total, fifty-nine patients (all children) were treated with HSCT and one with cord-blood transplantation because of PID-associated IBD (fifty-two CGD, four LRBA deficiency, two CD3 gamma deficiency, one RIPK1 deficiency, one LAD-deficiency) [38,44,58,60,61,63,64]. Forty-three patients completely recovered from their IBD (71.6%), however, multiple severe side-effects are reported such as pulmonary infections (aspergillosis) and graft-versus-host.

## 4. Discussion

Patients with PID may present with IBD [19–22,24]. In this study we reviewed articles that discussed the prevalence, clinical presentation and treatment of IBD in patients with a PID. These insights could lead to better awareness of IBD in PID patients and reduce diagnostic delay. Prevalence of IBD in PID varied depending on the underlying PID. These percentages are summarized in Table 1. The prevalence of IBD seems to differ between various PIDs, although the number of cohort studies per PID is small which could influence the results.

The two most common clinical symptoms of IBD in patients with a PID were diarrhea without blood loss and abdominal pain. These symptoms are common and could be explained by gastro-intestinal infections, celiac disease or functional gastrointestinal disorders, however, physicians should, after excluding infections, look for other signs of IBD. In patients with persistent gastro-intestinal symptoms, a colonoscopy or MR-enterography should be performed. Increased awareness of these presenting symptoms could lead to a faster diagnosis of IBD in patients with PID.

Patients with a PID and IBD were most commonly treated with corticosteroids such as prednisolone and other oral immunosuppressive agents such as mesalazine. Biologicals are widely used in the treatment of IBD, however, data on the effects of TNF-α blocking agents in PID patients are limited. As presented in this review, only 3/14 (=21%) patients treated with adalimumab or infliximab showed improvement, which is lower when compared to the reported efficacy of TNF-α blocking agents in patients with CD (71%) [66,67]. However, it should be noted that the number of patients on anti-TNF-α treatment is small and is initiated in patients that have a more therapy refractory disease. Of the four patients treated with abatacept three showed improvement, while this medication is generally not prescribed in CD and UC without PID [38]. These data support the hypothesis that IBD in PID results from specific defects in pathways involved in PID [8], necessating individualized treatment strategies. Our limited data from radiological, endoscopic and histopathological evaluations also support this theory. Indeed, Chellapandian et al. reported the beneficial effects of precision therapy of autoinflammation in certain PIDs [25]. Patients who did not respond to standard therapy as described above were treated with recently introduced biologicals including vedolizumab and ustekinumab. Although large trials and a meta-analysis showed beneficial effects in patients with IBD [68,69], data on vedolizumab or ustekinumab in PID patients with IBD are scarce. Two PID patients were treated with vedolizumab and one with ustekinumab (all successfully) [48,56,59]. However, the effect of these biologicals may be exaggerated due to the limited number of publications and possible positive publication bias should be taken into account. A rigorous but effective treatment for PID

**Table 4**
Treatment outcome of 178 treatment strategies for IBD in 134 patients with PID.

| Treatment | PID (number of patients) | Number of treatments[a] | Treatment response (%) | Number of studies |
|---|---|---|---|---|
| Corticosteroids | | | | |
| Budesonide | CVID (4), NEMO (2) | 6 | 2 (33) | 4 [40–42,56] |
| Prednisone | CVID (7), XLA (2) | 9 | 9 (100) | 3 [41,46,57] |
| Other oral immunosuppressive agents | | | | |
| Mesalazine | CVID (2), WAS (1), CGD (25), DiGeorge (1), NEMO (1), LAD-1 def (1), IL-12R def (1) | 32 | 26 (81) | 10 [40,42,50–53,55,56,58,59] |
| Azathioprine | CVID (2) RIPK1 def (2), CGD (6), XLA (1), LAD-def (1) | 12 | 3 (25) | 6 [43,44,52,56,59,60] |
| Cyclosporin | CGD (4), LRBA-def (4) | 6 | 1 (17) | 2 [38,58] |
| 6-mercaptopurin | CVID (1), DiGeorge (1), LAD-1 def (1) | 3 | 1 (33) | 3 [47,59,61] |
| Biologicals | | | | |
| Adalimumab | CVID (2), XLA (1), RIPK1 def (2), CGD (2), LAD-1 def (1) | 8 | 2 (25) | 6 [43,44,48,56,60,61] |
| Infliximab | CVID (1), CGD (2), LAD-1 def (2), XLA (1) | 6 | 1 (17) | 5 [48,55,56,60,61] |
| Abatacept | LRBA-def (4) | 4 | 3 (75) | 1 [38] |
| Ustekinumab | CVID (1) | 1 | 1 (100) | 1 [56] |
| Vedolizumab | XLA (1), DiGeorge (1) | 2 | 2 (100) | 2 [48,59] |
| Other | | | | |
| IVIG | XLA (17), CVID (8), LRBA-def (4) | 29 | 22 (88) | 8 [32,38,45–47,54,57,62] |
| HSCT | CGD (52), LRBA-def (4), CD3gamma def (2), RIPK1-def (1), LAD-1 def (1) | 59 | 42 (71) | 8 [38,44,54,58,60,63,64] |
| CBT | LAD-1 def (1) | 1 | 1 (100) | 1 [61] |
| Total | | 178 | 116 (65) | |

*Abbreviations:* CVID, Common Variable Immunodeficiency; WAS, Wiskott-Aldrich syndrome; CGD, Chronic Granulomatous Disease; LRBA-def, lipopolysaccharide-responsive and beige-like anchor protein deficiency; LAD-1 def, Leukocyte adhesion deficiency 1 deficiency; XLA, X-linked agammaglobulinemia; RIPK1-def, Receptor-interacting serine/threonine-protein kinase 1 deficiency; NEMO, Nuclear factor-kappa B Essential Modulator; HSCT, hematopoietic stem cell transplantation; CBT, cord-blood transplantation.

[a] The table reports 178 treatment schedules of 134 unique patients. The outcome is reported for each treatment. As shown in Fig. 2, 47 patients used at least two treatment schedules.

(and its associated IBD) is HSCT. However, indication for HSCT in these pediatric patients was the severity of the underlying PID itself. In this study, the majority of patients receiving a HSCT was cured of their PID and associated IBD. The remaining patients died after transplantation because of either severe graft-versus-host or a fulminant infection.

This systematic review has certain strengths and limitations. Previous reviews focused on prevalence, symptoms or treatment response in subgroups of PID patients. An overview including the prevalence, clinical symptoms and treatment schedules for IBD in PIDs was lacking. This systematic review is, to the best of our knowledge, the first review evaluating prevalence, clinical presentation and treatment of IBD in PID patients.

One of the limitations is, the number of cohort studies on this topic is limited. Therefore, it was difficult to assess the prevalence of IBD in patients with a PID. In addition, it was difficult to evaluate which treatment leads to the best outcome because the treatments were not evaluated in a large group of patients. Another limitation is that most studies did not discuss the duration of the treatments, which is why we did not include treatment duration in our results. In addition, most of the studies reporting a certain treatment did not describe the effects of previous treatment schedules of which the patient may have benefited as well. Furthermore, it could be that in some patients minimal disease activity was accepted and no treatment was given while remission was not achieved since this was not always clearly reported. Therefore, the term improvement was used in this review instead of remission. In addition, surgical interventions were not reported in this review, as details on this topic were lacking in most of the studies. Lastly, almost all studies were retrospective and therefore lacked power.

In the studies included in this review patients are mainly treated according to IBD schemes with a step-up approach used in patients without PID. However, as was discussed, it is likely that patients with PID could benefit more from an individualized treatment regimen, based on the underlying pathogenic defects.

Larger prospective studies are needed to evaluate individual treatment strategies in PID patients. In absence of these studies we recommend to treat patients with PID-associated IBD by an individualized treatment scheme. Further research should be performed to assess these treatment strategies in PID-associated IBD.

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## Appendix 1. Search term

Embase

(('immune deficiency'/exp AND 'genetics'/exp) OR (PID OR PIDs OR ((primar*) NEAR/3 (immuno* OR immune* OR antibod*))):ab,ti,kw) AND ('inflammatory bowel disease'/exp OR (IBD OR crohn* OR Terminal-Ileit* OR ((ulcera*) NEAR/6 (colit* OR colorec* OR procto*)) OR ((inflamm*) NEAR/3 (bowel*))):ab,ti,kw) NOT (('child'/exp OR 'pediatrics'/exp) NOT ('adult'/exp)) AND [ENGLISH]/lim NOT ([Conference Abstract]/lim)

Medline(OVID)

(exp "Primary Immunodeficiency Diseases"/ OR (PID OR PIDs OR ((primar*) ADJ3 (immuno* OR immune* OR antibod*))).ab,ti,kf.) AND (exp "Inflammatory Bowel Diseases"/ OR (IBD OR crohn* OR Terminal-Ileit* OR ((ulcera*) ADJ6 (colit* OR colorec* OR procto*)) OR ((inflamm*) ADJ3 (bowel*))).ab,ti,kf.) NOT ((exp "Child"/ OR exp

"Infant"/ OR exp "Pediatrics"/) NOT ("Adolescent"/ OR exp "Adult"/)) AND (english).lg NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.

Web-of-Science

TS=(((PID OR PIDs OR ((primar*) NEAR/2 (immuno* OR immune* OR antibod*)))) AND ((IBD OR crohn* OR Terminal-Ileit* OR ((ulcera*) NEAR/5 (colit* OR colorec* OR procto*)) OR ((inflamm*) NEAR/2 (bowel*))))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(English)

Cochrane

((PID OR PIDs OR ((primar*) NEAR/3 (immuno* OR immune* OR antibod*))):ab,ti,kw) AND ((IBD OR crohn* OR Terminal NEXT Ileit* OR ((ulcera*) NEAR/6 (colit* OR colorec* OR procto*)) OR ((inflamm*) NEAR/3 (bowel*))):ab,ti,kw)

Google Scholar

"inflammatory bowel"|IBD|crohn|"ulcera colitis" " Primary Immunodeficiency"

## Appendix 2. Summary of the reviewed articles

| First author | Year | Study design | PID | Number of patients | Age range | Number of patients with IBD | Quality assessment score |
|---|---|---|---|---|---|---|---|
| Asgardoon | 2020 | Retrospective cohort study | CVID/LRBA-def | 27 | 11–22 | 4 | 4 |
| Barmettler | 2017 | Retrospective cohort study | XLA | 200 | NR | 19 | 5 |
| Cagdas | 2019 | Retrospective cohort study | LRBA-def | 15 | 6–44 | 5 | 5 |
| Erdem | 2019 | Retrospective cohort study | CVID | 28 | 0–9 | 3 | 4 |
| Akkelle | 2018 | Retrospective cohort study | CVID/PIK3CD | 47 | 2–12 | 15 | 4 |
| Broides | 2016 | Retrospective cohort study | CGD | 8 | 2–14 | 1 | 5 |
| Dupuis-Girod | 2003 | Retrospective cohort study | WAS | 55 | 0–14 | 5 | 5 |
| Habahbeh | 2016 | Retrospective cohort study | CVID | 16 | 4.5 | 2 | 4 |
| Kawai | 2015 | Retrospective cohort study | CGD | 35 | 0–17 | 16 | 5 |
| Lee | 2008 | Retrospective cohort study | WAS | 11 | 0–6 | 1 | 5 |
| Magnani | 2014 | Retrospective cohort study | CGD | 98 | 0–25 | 60 | 4 |
| El-Sayed | 2019 | Retrospective cohort study | XLA | 783 | 0–7 | 27 | 4 |
| Aydogan | 2008 | Retrospective cohort study | CVID | 10 | 0–8 | 3 | 4 |
| Quartier | 2004 | Retrospective cohort study | HyperIgM | 29 | 0–13 | 1 | 4 |
| Cheng | 2009 | Retrospective cohort study | NEMO | 7 | 0–2 | 2 | 5 |
| Marciano | 2004 | Retrospective cohort study | CGD | 140 | 2 | 8 | 4 |
| Conlong | 1999 | Case-series | CVID/XLA | 5 | 19–60 | 5 | 5 |
| Sanges | 2015 | Case-report | CVID | 1 | 28 | 1 | 5 |
| Vázquez | 2013 | Case-report | CVID | 1 | 6 | 1 | 5 |
| Li | 2019 | Cohort study | RIPK-def | 8 | 0–10 | 7 | 5 |
| Filipovic | 2009 | Case-report | CVID | 1 | 39 | 1 | 5 |
| Alangari | 2012 | Case-study | CVID/LRBA-def | 5 | 7–22 | 4 | 5 |
| Folwaczny | 2002 | Case-report | WAS | 1 | 18 | 1 | 5 |
| Imanzade | 2015 | Case-report | CGD | 1 | 2 | 1 | 5 |
| Cekic | 2019 | Case-report | XLA | 1 | 4 | 1 | 5 |
| Comunoglu | 2015 | Case-report | CVID | 1 | 0.5 | 1 | 4 |
| Bosworth | 2006 | Case-report | CVID | 1 | 0–70 | 1 | 5 |
| Angelino | 2017 | Case-series | CGD | 9 | 0–24 | 9 | 5 |
| Ozgur | 2008 | Case-report | CD-3 chain def | 1 | 1 | 1 | 5 |
| Khoshnevisian | 2019 | Case-report | IL-12RB1 def | 1 | 26 | 1 | 5 |
| Marsili | 2014 | Case-report | LAD-1 def | 1 | 0.5 | 1 | 5 |
| Marsh | 2019 | Retrospective cohort study | CGD | 49 | 1–26 | 32 | 4 |
| Hauck | 2016 | Case-report | CGD | 2 | 18–43 | 2 | 4 |
| Jain | 2013 | Case-report | LAD-1 def | 1 | 0 | 1 | 4 |
| Ruiz de Morales | 2017 | Case-report | CVID | 1 | 10–40 | 1 | 4 |
| Thau | 2019 | Letter | DiGeorge | 1 | 0–8 | 1 | 4 |
| Bakhtiar | 2017 | Case-report | LRBA-def | 1 | 0 | 1 | 4 |

*Abbreviations:* CVID, Common Variable Immunodeficiency; WAS, Wiskott-Aldrich syndrome; CGD, Chronic Granulomatous Disease; LRBA-def, lipopolysaccharide-responsive and beige-like anchor protein deficiency; LAD-1 def, Leukocyte adhesion deficiency 1 deficiency; XLA, X-linked agammaglobulinemia; RIPK1-def, Receptor-interacting serine/threonine-protein kinase 1 deficiency; NEMO, Nuclear factor-kappa B Essential Modulator.

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