A European Survey on Digestive Perianastomotic Ulcerations, a Rare Crohn-like Disorder Occurring in Children and Young Adults

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ABSTRACT

Objectives: Digestive perianastomotic ulcerations (DPAU) resembling Crohn disease lesions are long-term complications of intestinal resections, occurring in children and young adults. They are known to be uncommon, severe and difficult to treat.

Methods: In the absence of recommendations, we performed a large European survey among the members of the ESPGHAN working group on inflammatory bowel disease (IBD) in order to collect the experience of expert pediatric gastroenterologists on DPAU.

Results: Fifty-one patients (29 boys and 22 girls) were identified from 19 centers in 8 countries. Most patients were followed after necrotizing enterocolitis (n = 20) or Hirschsprung disease (n = 11). The anastomosis was performed at a median age (interquartile range) of 6 [1–23] months, and first symptoms occurred 39 [22–106] months after surgery. Anemia was the most prevalent symptom followed by diarrhea, abdominal pain, bloating, and failure to thrive. Hypoalbuminemia, elevated CRP, and fecal calprotectin were common. Deep ulcerations were found in 59% of patients usually proximally to the anastomosis (68%). During a median follow-up of 40 [19–67] months, treatments reported to be the most effective included exclusive enteral nutrition (31/35, 88%), redo anastomosis (18/22, 82%), and alternate antibiotic treatment (37/64, 58%).

Conclusions: Unfortunately, persistence of symptoms, failure to thrive, and abnormal laboratory tests at last follow-up in most of patients show the burden of DPAU lacking optimal therapy and incomplete understanding of the pathophysiology.

Key Words: abdominal surgery, Crohn disease, digestive perianastomotic ulcerations, enteral nutrition, gut inflammation, Hirschsprung disease, ileocaecal valve, intestinal resection, necrotizing enterocolitis, short bowel syndrome

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What Is Known

- Digestive perianastomotic ulcerations are rare complications occurring months or years after an intestinal resection with anastomosis.
- A limited number of cases have been reported in the literature with heterogeneous descriptions.
- No recommendations are available on how to treat this severe condition.

What Is New

- This international survey describes the causes and clinical, biological, endoscopic, and histological findings in a large series of 51 cases.
- The reported best therapeutic options include enteral nutrition, antibiotics, and redo-anastomosis.
- By some aspects, digestive perianastomotic ulcerations are very resemblant to Crohn Disease lesions.

Digestive perianastomotic ulcerations (DPAU) are long-term complications of intestinal resections. A first series of 4 patients was reported by Parashar et al (1) in 1988. Then after, other cases were documented by Couper et al (2) in 1989, Hamilton et al (3) in 1992, Paterson et al (4) in 1993, Sondheimer et al (5) in 1995, Chari and Keate (6) in 2000, Freeman et al (7) in 2014, Chabrit-Henrion et al (8) in 2014, Frémond et al (9) in 2014, Bass et al (10)

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in 2015, and Fusaro et al (11) in 2018. In all, 70 patients have been reported. In addition, Crohn disease (CD)-like phenotypes were reported in 66 patients with Hirschprung disease (12). Most of these patients (86%) exhibited a total colonic or a long segment aganglionosis with Duhamel procedure (84%).

According to the pooled literature (1–11), DPAU usually occur in children or young adults (median age at diagnosis: 10.5 years) especially in boys (sex ratio = 1.71). Most patients underwent a resection of the ileocecal valve with an anastomosis between small bowel (SB) and large bowel (LB) in infancy (median age at surgery: 2 months). DPAU then occur months or years after surgery. They can be revealed by a large panel of clinical complaints including chronic anemia (45%), diarrhea (30%), abdominal pain (29%), bloating (11%), or various other symptoms like failure to thrive, chronic inflammation, or hypoalbuminemia. The diagnosis is based on ileocolonoscopy and/or videocapsule endoscopy (10). Ulcerations look like CD lesions, at least macroscopically (see below) and NOD2 mutations have been identified in some patients (9).

DPAU are difficult to treat. Surgical resection of the ulcerations with redo anastomosis may be useful (43%) but recurrences are frequent, and its indication is usually restricted to a unique anastomotic ulceration accompanied by severe bleeding and/or resistance to medical treatments. Several drugs have been proposed to control the disease. Considering the clinical and endoscopic resemblance between DPAU and CD (9), 5ASA (34%), prednisone (20%), budesonide (16%), immunosuppressors (13%), and anti-TNF antibodies (7) (14%) have been proposed with variable success rates. Use of antibiotics (27%), probiotics (3%), cholestyramine (9%), sucralfate, and others has also been reported. In general, based on the up-to-date clinical experience, no firm recommendation can be drawn.

In order to better understand the clinical response to different therapeutic options, we performed a large European survey among pediatric gastroenterologists who are members of the French ''Pediatric Groupe d'Etudes Therapeutique des Affections Inflammatoires Digestives'' (GETAID) and the ESPGHAN working group on Inflammatory Bowel Disease (IBD). We identified 51 cases for which we recorded the clinical findings and responses to treatments.

PATIENTS AND METHODS

The survey was sent out to all members of the Pediatric GETAID and ESPGHAN working group on IBD. Patients with a history of IBD were excluded. For each patient, a standard form collected information on family medical history whenever relevant; birth events; digestive disease(s) and surgical interventions; clinical, biological, endoscopic, and histological findings at diagnosis. Finally, we recorded treatments and their efficacy. Anemia was defined by a hemoglobin concentration under the limits for the age. Efficacy was defined by the partial or full resolution of symptoms. Unfortunately, most often, no endoscopic control was available to confirm ulcer healing. Data were presented as median [1st–3rd quartiles]. The study was approved by the French ethic committee at hospital Robert Debré (ref 2018-386) and adhered to the French ethic laws.

RESULTS

Patients were identified from 19 centers in 8 countries. The cohort consisted of 29 boys and 22 girls (sex ratio 1.32) with a median age at inclusion of 13 [9–17] years. The anastomosis had been performed at median age of 6 [1–23] months. Most patients had a past history of necrotizing enterocolitis or Hirschsprung disease (Fig. 1A). As expected for a disease related to necrotizing enterocolitis, preterm birth was observed in two-third of cases. Birth weights were appropriate for gestational age. An ileocecal resection had been performed in 47 (92%) patients with often a transient stoma (n = 32). Stomas were closed at a median of 5 [2–15] months after the first surgical procedure. Tenty-four (48%) patients had a short bowel syndrome. Four of them were operated for intestinal lengthening and 6 were dependent of home parenteral nutrition. The anastomoses were usually between SB and LB (SB-LB anastomoses, n = 47, 92%) including 12 (24%) Duhamel procedures while SB-SB and LB-LB anastomoses were both found in 5 (10%) of cases (note that 8 patients had more than 1 anastomosis at time of survey).

First symptoms occurred at median 39 [22–106] months after surgery. The diagnosis was made at median 7.5 [1–17] months later based on ileocolonoscopy (n = 49) or videocapsule endoscopy (n = 2). Symptoms at diagnostic were numerous and variable from 1 child to another (Fig. 1B). Anemia was the most prevalent followed by diarrhea, abdominal pain, and bloating. Values of the main laboratory tests frequently indicated anemia, hypoalbuminemia, elevated CRP, and fecal calprotectin (Fig. 1C). Failure to thrive was also common (Fig. 1D).

The anastomosis was visible during endoscopic examinations in all cases. Deep ulcerations as defined by the CD Endoscopic Index of Severity (CDEIS) (13) were found in 59% of patients (Fig. 2), superficial ulcerations in 59%, and stenosis in 8%. Ulcerations were most often proximally to the anastomosis (n = 35, 68%) but less often distally (n = 4, 8%) or on both sides of the anastomosis (n = 6, 12%). Few patients exhibited ulcerations limited only on the anastomosis itself (n = 6, 12%).

Median observation time post diagnosis was 40 [19–67] months. During this period, several options have been proposed to control the disease with an average of 3.2 therapeutic lines per patient (Fig. 3A). Responses to treatments were very heterogeneous from one patient to another making difficult to elaborate recommendations. Redo anastomosis was at least partially effective in 18/22 (82%) patients. Among the other frequently effective options are exclusive enteral nutrition (31/35, 88%) and alternate antibiotic treatment (37/64, 58%). At last visit, antibiotics and cholestyramine

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Data availability: the data underlying this article cannot be shared publicly because of the privacy of individuals who participated in the study.

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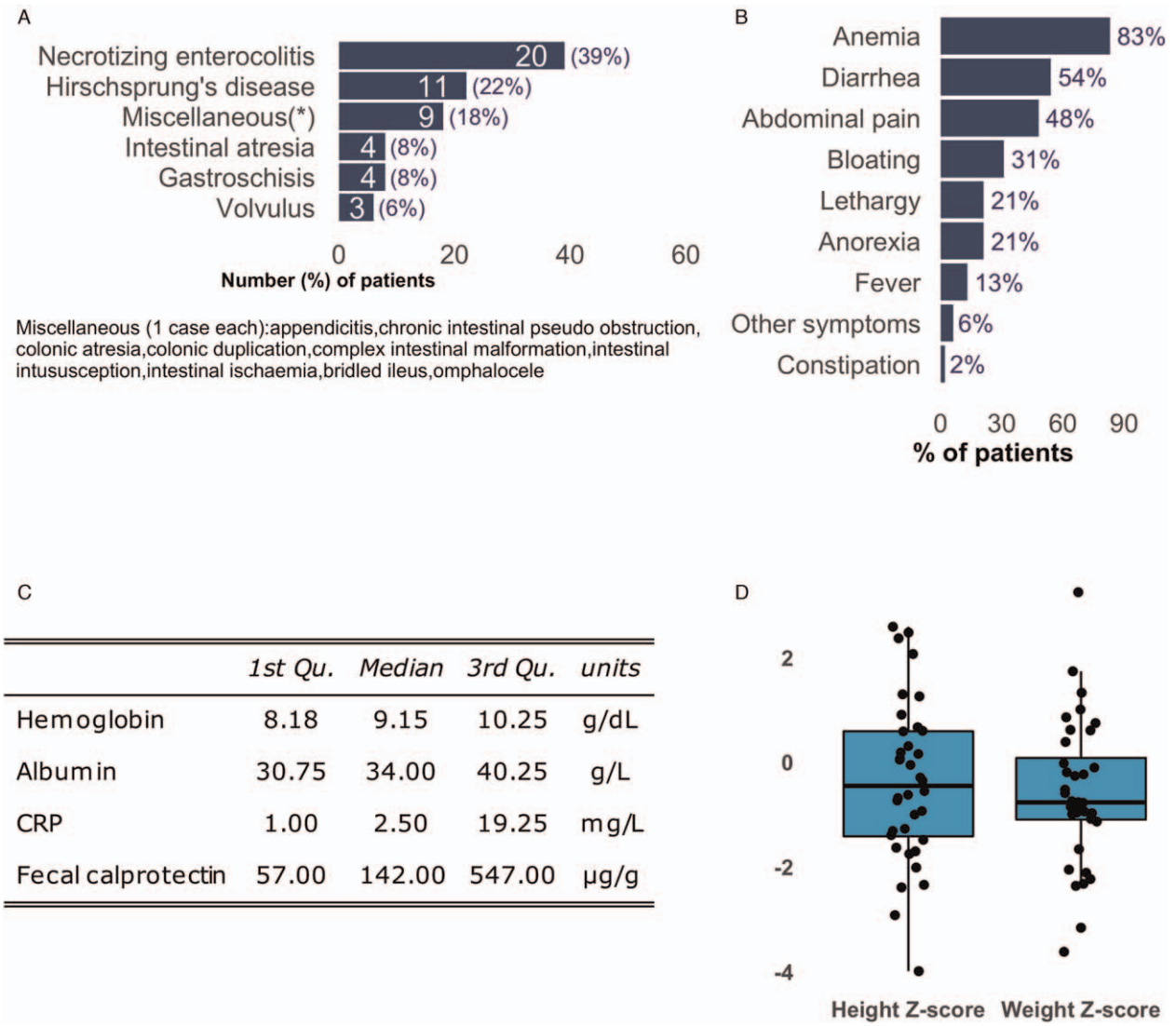

	1st Qu.	Median	3rd Qu.	units
Hemoglobin	8.18	9.15	10.25	g/dL
Albumin	30.75	34.00	40.25	g/L
CRP	1.00	2.50	19.25	mg/L
Fecal calprotectin	57.00	142.00	547.00	µg/g

FIGURE 1. Findings at diagnosis. (A) Disease underlying the gut resection(s). (B) Frequencies of clinical symptoms. (C) Values of major biological parameters. (D) Height and weight values expressed as *z* scores.

were the most used suggesting that these 2 drugs could have beneficial effects (Fig. 3B).

Unfortunately, response to treatment was generally incomplete as shown by the persistence of symptoms (Fig. 3C) and abnormal laboratory tests (Fig. 3D) at last visit. Thirty-one control endoscopies were reported. Mucosal healing was found in 6 while ulcerations and/or stenoses (n = 7) were present in the other cases. Failure to thrive worsened in comparison to the time of diagnosis (Fig. 3E, $P < 0.005$ for weight and height, paired t test). The underlying disease and/or insufficient parenteral nutrition supply may contribute to growth difficulties and/or pubertal delay together with anemia. These poor results, however, also suggest that control of the disease was the exception rather than the rule at the date of the survey.

DISCUSSION

DPAU are rare but often unrecognized long-term complications of infantile digestive surgery with anastomoses. They are most often complications of anastomoses between SB and LB (including Duhamel procedures) suggesting (without proving it) that the anatomical pattern participates in the development of DPAU. They are usually discovered many years after the initial surgical procedure. They often manifest by serious conditions including anemia, various digestive symptoms, failure to thrive, and loss of general well-being. Of note, these symptoms may also be explained by the underlying disease but their co-occurrence with ulcers and their resolution in case of ulcer healing strongly suggests that they are also related to DPAU. We thus suggest that children with ileocecal resections would be followed by a pediatric gastroenterologist at least once a year to detect DPAU in due course. A prospective evaluation of patients will also have the advantage to provide additional information on the natural history of DPAU.

In respect to the published reports, DPAU is difficult to treat. Many therapeutic options have been tried but no recommendations have been made to date. The present study was built to document the medical practices within a large consortium of expert pediatric

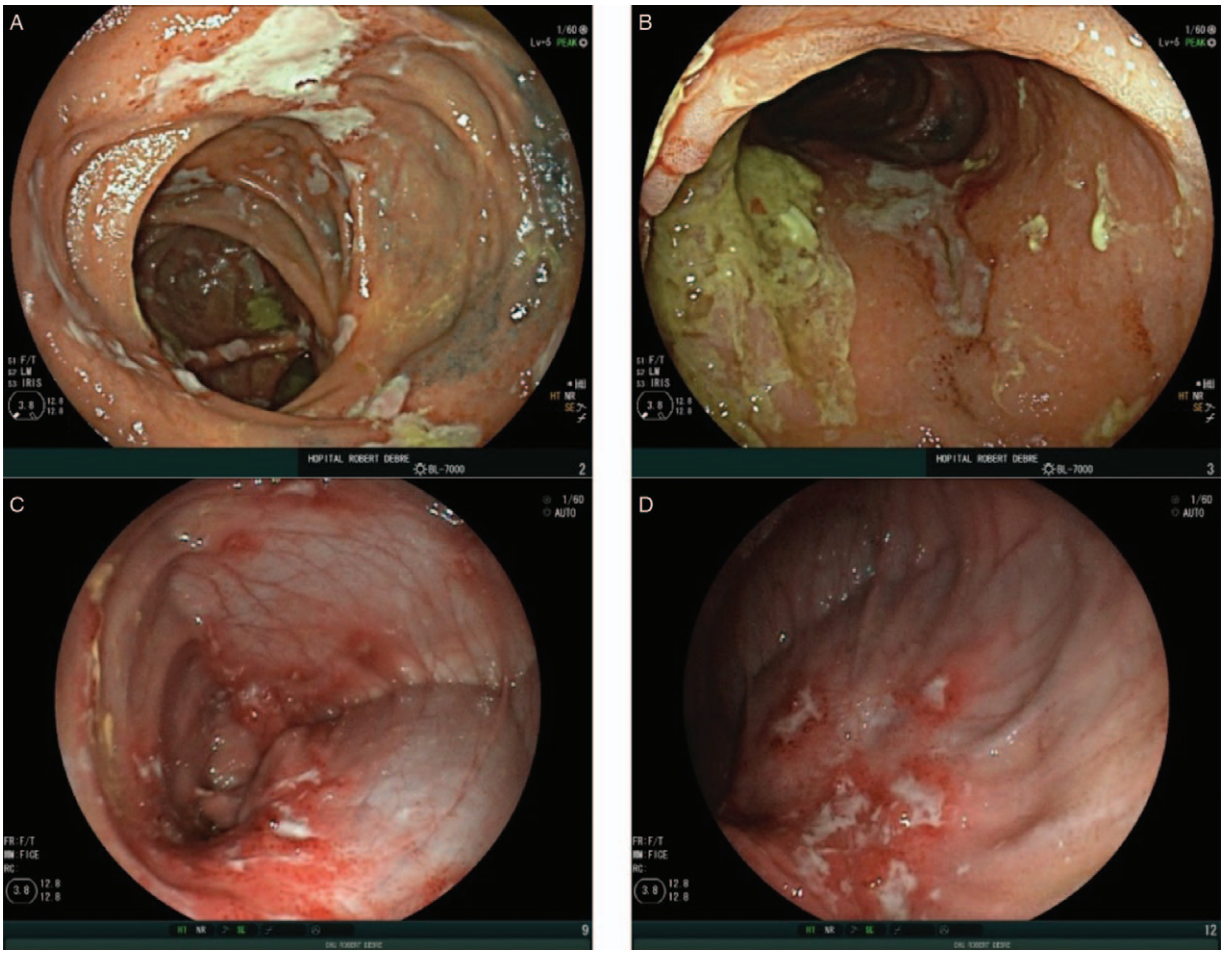

FIGURE 2. Examples of deep ulcerations above ileocolonic anastomoses. (A and B) Young adult with a short bowel syndrome after laparoschisis. (C and D) Child with a limited resection of the ileocaecal region related to an intussusception.

gastroenterologists. Indeed, our series is the largest one published to date and it includes patients from several European countries. It appears that no specific treatment can be generally recommended, and diverse therapeutic options are in use. Exclusive enteral nutrition may be seen as an option in the light of common malnutrition, its good tolerance, and its reported efficacy (at least in some patients). Alternate antibiotic treatment and cholestyramine are the most often applied options but they are not always effective. Good results have been reported by some groups with surgical redo of the anastomosis, especially in case of severe bleeding and/or when the ulceration is located on the anastomosis itself. Ulcerations, however, are often multiple and located on a large portion of the SB proximally to the anastomosis hampering their resection. This is especially true in the case of short bowel syndrome, a situation frequently encountered in DPAU. Of note, fecal microbiota transplantation has been performed in 8 patients refractory to other treatments but partial responses were observed only in 2.

The relationship between DPAU and CD has been discussed previously (9). Indeed, the presence of scattered ulcerations on the SB is reminiscent to CD lesions, especially in case of recurrence after ileocecal resection. The association between DPAU and NOD2 mutations (like for CD) further supported the idea that DPAU could be an ''experimental CD'' situation (9). Of note, we failed to confirm this association in a subgroup of 10 patients genotyped for the 3 main CD-associated NOD2 mutations (data not shown). According to the histopathological reports available, granulomas were found in 3 cases and most inflammatory lesions were not specific. Lack of response to classic CD treatments including immunosuppressors and anti-TNF antibodies was the rule but exclusive enteral nutrition was efficient in some patients. Altogether, the question of common mechanisms between CD and DPAU remains open.

Several ideas may be raised to explain DPAU. An increased inflammatory reaction of Peyer patches located in the distal ileum may be discussed. Indeed, Peyer patches are more developed in children and young adults, and they could be involved in disease mechanisms. The loss of the ileocecal valve may also induce small intestinal bacterial overgrow and/or bile salt malabsorption, which could contribute to the inflammation. The efficacy of exclusive enteral nutrition, cholestyramine, or antibiotics may argue in favor of these explanations. Impaired postsurgical vascular/blood supply has also been proposed. In fact, no definitive explanation can be retained and further understanding of the pathophysiological mechanism is warranted to guide improvement in management of this severe and difficult-to-treat condition.

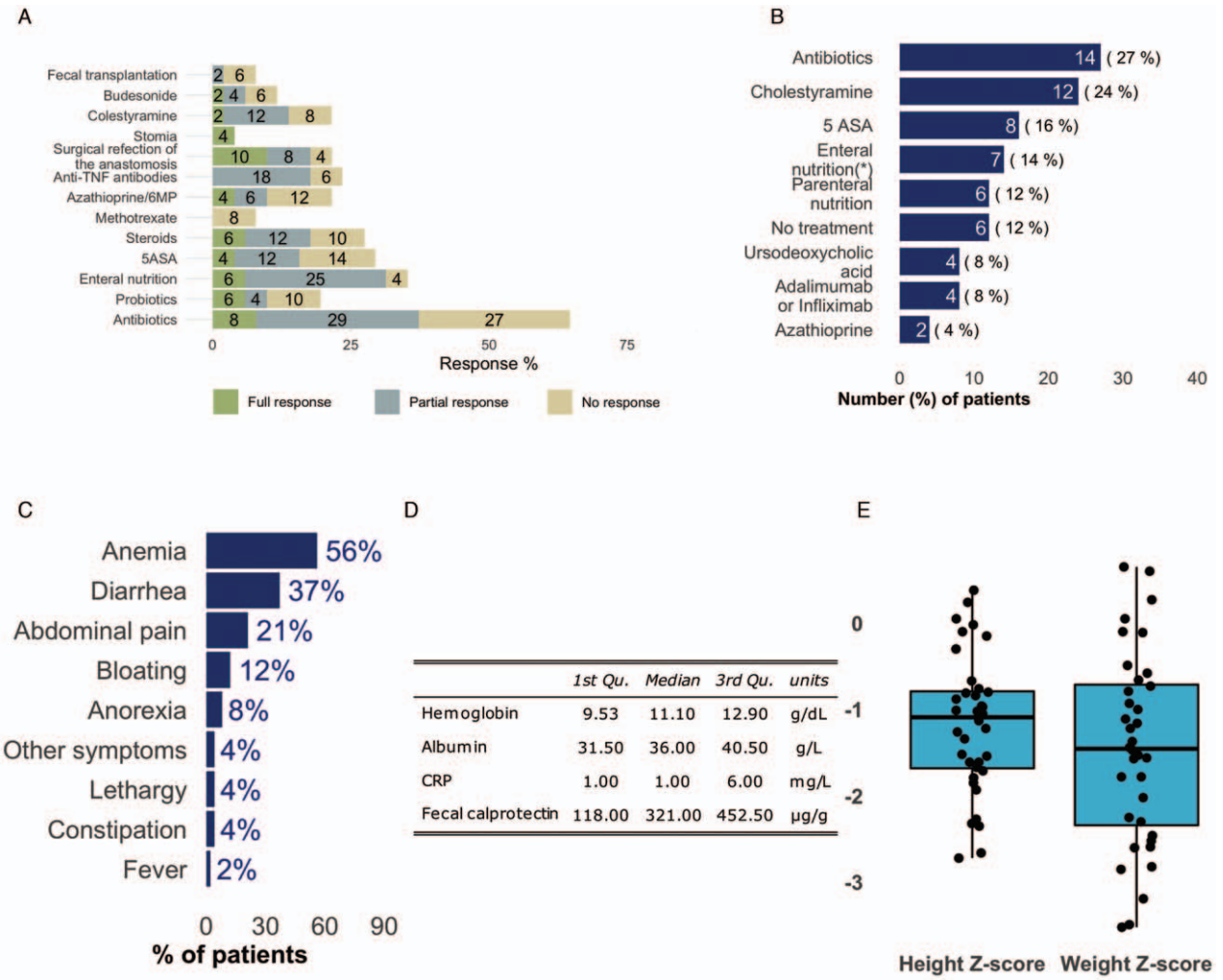

FIGURE 3. Findings at last visit. (A) Responses to various treatments proposed by the European centres. (B) Therapeutic options still used at the end of follow-up. (C) Persistent symptoms. (D) Values of the biological parameters. (E) Height and weight values expressed as *z* scores. *Exclusive and nonexclusive.

CONCLUSIONS

In conclusion, DPAU are rare but severe conditions which justify a follow-up of children with anastomosis between the small and large intestines. Re-do anastomosis, exclusive enteral nutrition and antibiotics may be proposed but they rarely control the disease for a long period.

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