



Appropriate management of special situations in Crohn's disease (upper gastro-intestinal; extra-intestinal manifestations; drug safety during pregnancy and breastfeeding): Results of a multidisciplinary international expert panel—EPACT II

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KEYWORDS

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Abstract

Introduction: High-grade evidence is lacking for most therapeutic decisions in Crohn's disease. Appropriateness criteria were developed for upper gastro-intestinal, extra-intestinal manifesta-

Abbreviations: AGA, American Gastroenterological Association; 5-ASA, 5-aminosalicylates (mesalamine and other aminosaliculates); AZA, azathioprine; 6MP, 6-mercaptopurine; CD, Crohn's disease; CysA, cyclosporin-A; ECCO, European Crohn's & Colitis Organization; EPACT, European Panel on the Appropriateness of Crohn's Disease Therapy; EIM, extra-intestinal manifestations; IBD, inflammatory bowel disease; MTX, methotrexate; PSC, primary sclerosing cholangitis; PPI, proton pump inhibitors; TNF- α , tumour necrosis factor- α .

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Upper gastro-intestinal CD;
Extra-intestinal
manifestations;
Appropriateness;
RAND Appropriateness
Method

tions and drug safety during conception, pregnancy and breastfeeding in patients with Crohn's disease, to assist the physician in clinical decision making.

Methods: The European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT II), a multidisciplinary international European expert panel, rated clinical scenarios based on evidence from the published literature and panelists' own clinical expertise. Median ratings (on a 9-point scale) were stratified into three categories: appropriate (7–9), uncertain (4–6 with or without disagreement) and inappropriate (1–3). Experts were also asked to rank appropriate medications by priority.

Results: Proton pump inhibitors, steroids, azathioprine/6-mercaptopurine and infliximab are appropriate for upper gastro-duodenal Crohn's disease; for stenosis, endoscopic balloon dilation is the first-line therapy, although surgery is also appropriate. Ursodeoxycholic acid is the only appropriate treatment for primary sclerosing cholangitis. Infliximab is appropriate for Pyoderma gangrenosum, ankylosing spondylitis and uveitis, steroids for Pyoderma gangrenosum and ankylosing spondylitis, adalimumab for Pyoderma gangrenosum and ankylosing spondylitis, cyclosporine-A/tacrolimus for Pyoderma gangrenosum. Mesalamine, sulfasalazine, prednisone, azathioprine/6-mercaptopurine, ciprofloxacin, and probiotics, may be administered safely during pregnancy or for patients wishing to conceive, with the exception that male patients considering conception should avoid sulfasalazine. Metronidazol is considered safe in the 2nd and 3rd trimesters whereas infliximab is rated safe in the 1st trimester but uncertain in the 2nd and 3rd trimesters. Methotrexate is always contraindicated at conception, during pregnancy or during breastfeeding, due to its known teratogenicity. Mesalamine, prednisone, probiotics and infliximab are considered safe during breastfeeding. **Conclusion:** EPACT II recommendations are freely available online (www.epact.ch). The validity of these criteria should now be tested by prospective evaluation.

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1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease that can involve any part of the digestive tract, while also being associated with extra-intestinal manifestations (EIM) and physicians may thus occasionally be confronted with special situations, such as upper gastro-duodenal CD, Pyoderma gangrenosum, ankylosing spondylitis, primary sclerosing cholangitis (PSC) and uveitis. Reports in the literature reveal that EIM are experienced by ~20% of patients in tertiary referral centres.^{1,2} whereas symptomatic upper gastro-intestinal CD affects ~4% of patients.³

CD frequently affects young adults of both sexes, in whom a desire for conception, management of pregnancy and breastfeeding are frequent and clinically relevant problems. A comprehensive literature review was recently prepared as a basis for the European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT II) dealing with the treatment of upper gastro-intestinal CD,⁴ extra-intestinal manifestations of CD⁵ as well as the safety of drug prescription during pregnancy and breastfeeding.⁶ High-grade evidence based on randomized controlled trials is often lacking, particularly in these special situations, and disease management recommendations are thus particularly helpful in daily clinical practice.

The EPACT II panel convened in Geneva, Switzerland on November 30th and December 1st 2007, and brought together 12 experts (8 gastroenterologists, 1 general practitioner and 3 surgeons), from 9 European countries (Croatia, France, Germany, Ireland, Italy, Spain, Sweden, Switzerland, The Netherlands). This panel aimed to update the results of the first panel EPACT I which took place in Lausanne, Switzerland in 2004,⁷ given the current rapidly evolving published literature.

This article focuses on appropriate therapy for upper gastro-intestinal CD and extra-intestinal manifestations of CD as well as on *safety* of therapy for CD during conception, pregnancy and breastfeeding.

2. Methods

2.1. RAND Appropriateness Method

The RAND Appropriateness Method is a well-recognized means of standardising expert opinion based on an evidence-based literature review, discussion at a panel meeting and a voting process. Methodological details of the various steps that took place during the RAND panel process (recruitment of experts, literature review, first rating round, second rating round, expert panel meeting) are described in detail in earlier articles on EPACT.^{7,8} A few specific changes in the methodology that occurred during the current update are described here.

2.2. List of scenarios and treatment options with definitions

Factors which contributed to the appropriateness of various types of treatment for differing presentations of CD were identified, based on the literature review. Clinical scenarios were created, describing patients corresponding to clinical indications in daily practice. For upper gastro-duodenal CD, the scenarios encompassed the presence or absence of stenosis. The panel voted on symptomatic gastro-duodenal stenotic and non-stenotic CD with endoscopic and histological findings compatible with this diagnosis; in all cases,

Helicobacter pylori infection should be ruled out and treated if present. The following extra-intestinal manifestations were assessed: Pyoderma gangrenosum, ankylosing spondylitis, uveitis and primary sclerosing cholangitis (PSC); the panel rated the treatment options for each extra-intestinal manifestation independently of the underlying CD activity. Extra-intestinal side-effects of CD therapy had to be excluded for each scenario. The safety, and not the appropriateness, of drugs was rated according to the time-point of prescription i.e. for male and female patients considering conception, during early pregnancy (1st trimester), late pregnancy (2nd and 3rd trimesters, rated separately) as well as during breastfeeding. Treatment options were previously described in detail in an article which appeared in 2007 on the occasion of the first EPACT panel.⁹

2.3. Definition of appropriateness and disagreement

For upper gastro-intestinal CD and extra-intestinal manifestations of CD, a treatment is defined as being appropriate in a situation where the benefit to the patient exceeds the potential risks by a sufficiently wide margin that the treatment is worth giving.¹⁰ The rate of appropriateness of each clinical indication was calculated using the median of the twelve experts' votes (1=extremely inappropriate, 9 extremely appropriate). According to the value obtained, each scenario was classified as "appropriate" (7–9), "uncertain" (4–6) or "inappropriate" (1–3).

Treatment options, at time of conception or during pregnancy and breastfeeding, were rated according to their safety for the embryo, the foetus or the newborn. The safety of each clinical indication was calculated using the median

of the twelve experts' votes between 1 and 9 (1=extremely unsafe, 9=extremely safe). According to the value obtained, each scenario was classified as "unsafe" (1–3), "uncertain" (4–6) or "safe" (7–9).

The IPRAS (Interpercentile Range Adjusted for Symmetry) method of analysis¹¹ was used to identify the presence of "disagreement" between the experts' votes; "disagreement" was automatically considered "uncertain", irrespective of the median panel score.

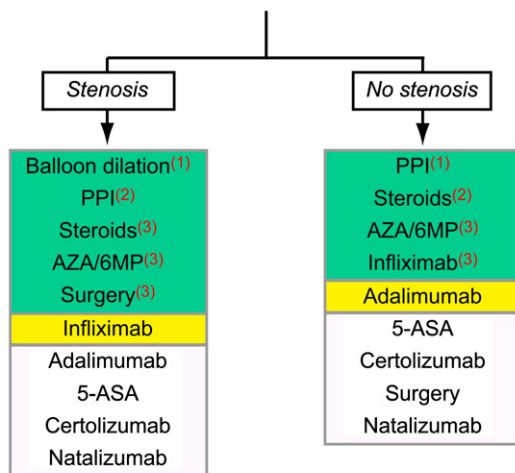
2.4. Ranking

When several treatment options were deemed appropriate in a given clinical scenario, the experts were asked to rank the treatments as first- (A), second- (B) or third- (C) choice and a ranking was obtained by attribution of points: A=2 points; B=1 point, C=0 points.

3. Results

3.1. Upper gastro-intestinal CD

Upper gastro-intestinal CD was rated for stenotic and non-stenotic disease. Fig. 1 summarises appropriateness and ranking of the following treatment options: proton pump inhibitors (PPI), 5-aminosalicylate compounds (5-ASA), corticosteroids, azathioprine/6-MP, infliximab, adalimumab, certolizumab, natalizumab, surgery and balloon dilation. Certolizumab, natalizumab and 5-ASA were considered inappropriate for the treatment of upper gastro-intestinal CD. In the absence of stenosis, PPI, corticosteroids, azathioprine/6-MP and infliximab



AZA/6MP = Azathioprine / 6-Mercaptopurine; 5-ASA = 5-aminosalicylic Acid; PPI = Proton pump inhibitor

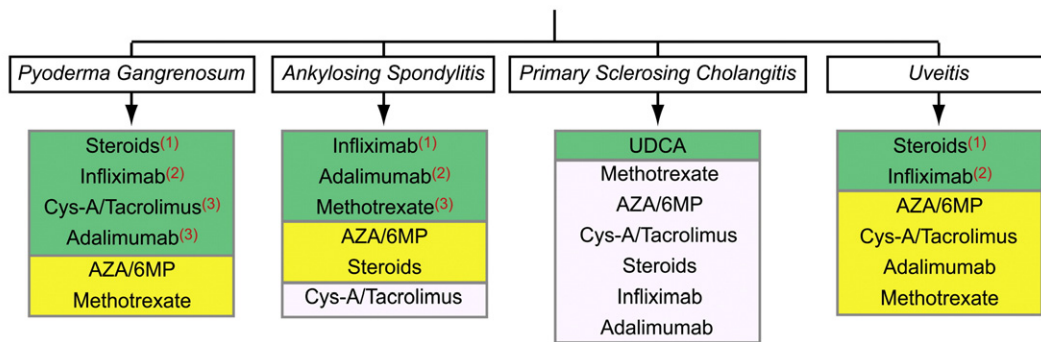
THERAPY RANK:

(1): 1st line therapy - (2): 2nd line therapy - (3): 3rd line therapy



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Figure 1 Appropriateness and ranking of treatment options for upper gastro-intestinal CD.



AZA/6MP = Azathioprine / 6 Mercaptopurine; Cys-A = cyclosporine; UDCA = Ursodeoxycholic Acid

THE THERAPY RANK:

(1): 1st line therapy - (2): 2nd line therapy - (3): 3rd line therapy

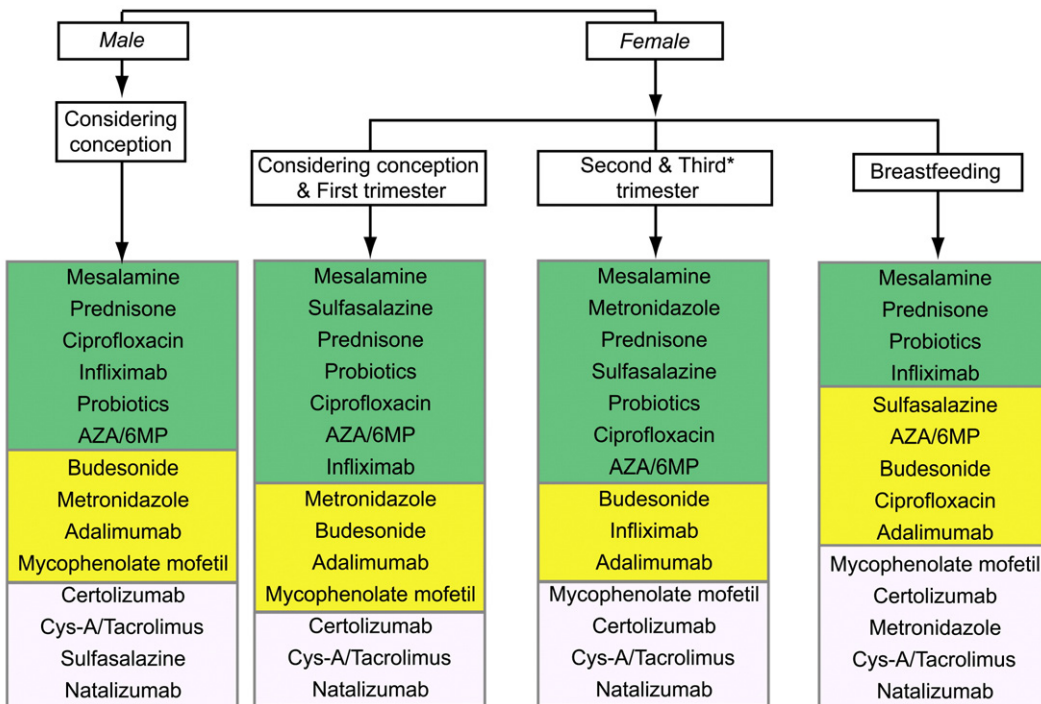


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Figure 2 Appropriateness and ranking of treatment options for extra-intestinal manifestations of CD.

were rated appropriate. PPI were ranked as first-line therapy, corticosteroids as second-line therapy, and azathioprine and infliximab as third-line therapy. Adalimumab was deemed uncertain and surgery inappropriate. In the presence of stenosis, the treatments considered appropriate were balloon

dilation, PPI, corticosteroids, azathioprine/6-MP and surgery; balloon dilation being the first-line therapy, PPI the second-line therapy, corticosteroids, azathioprine/6-MP and surgery the third-line therapy. Infliximab was judged uncertain with disagreement and adalimumab was inappropriate.



* were voted separately but as the voting result are the same they are presented together
 NB Metotrexate were not subject to vote as considered teratogenic and absolutely contraindicated.

AZA/6MP = Azathioprine / 6-Mercaptopurine; 5-ASA = 5-aminosalicylic Acid; Cys-A = cyclosporine A



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Figure 3 Conception, pregnancy and breastfeeding: safety of drugs.

3.2. Extra-intestinal manifestations of CD

For EIM of CD, the following conditions were assessed: Pyoderma gangrenosum, ankylosing spondylitis, primary sclerosing cholangitis (PSC) and uveitis. The panel voted on the appropriateness of treatment independently of the underlying CD activity. In all cases, extra-intestinal side-effects of CD therapy were deemed to have been ruled out. Fig. 2 summarizes the results of the panel's voting. For Pyoderma gangrenosum, appropriate treatments were corticosteroids (first-line), infliximab (second-line), adalimumab and cyclosporine-A/tacrolimus (either, third-line); the immunomodulators methotrexate and azathioprine/6-MP were rated uncertain. For ankylosing spondylitis, infliximab was the first-line treatment, adalimumab the second-line treatment and methotrexate the third-line treatment, whereas azathioprine/6-MP and corticosteroids were rated uncertain and cyclosporine-A/tacrolimus inappropriate. In the presence of PSC, the only appropriate option was ursodesoxycholic acid. For uveitis, only steroids (first-line) and infliximab (second-line) were judged to be appropriate treatments, while the immunomodulators (methotrexate, azathioprine/6-MP and cyclosporine-A/tacrolimus), as well as adalimumab, were uncertain.

3.3. Drug safety during conception, pregnancy and breastfeeding

For this category, treatment options are rated at time of conception as well as during pregnancy (first, second and third trimester separately) and breastfeeding, according to their safety for the embryo, the foetus or the newborn. The panel also specifically voted on the safety of drugs prescribed to male CD patients considering conception. Methotrexate was not subjected to a vote as it is considered to be teratogenic and absolutely contraindicated. The results of the panel vote are summarized in Fig. 3. The following treatments were considered unsafe in all scenarios: certolizumab, cyclosporine-A/tacrolimus, natalizumab. Unsafe treatments were furthermore mycophenolate mofetil during 2nd and 3rd trimester and during breastfeeding, metronidazole during breastfeeding and sulfasalazine for men wishing to conceive. Budesonide and adalimumab were uncertain for all scenarios.

For male and female patients wishing to conceive, as well as for female patients in the 1st trimester of pregnancy, the panel considered the following treatment options safe: mesalamine, prednisone, infliximab, azathioprine/6-MP, ciprofloxacin and probiotics; whereas metronidazole, budesonide, adalimumab and mycophenolate mofetil were considered uncertain.

In late pregnancy, i.e. in the 2nd and 3rd trimester (rated separately by the panel but demonstrating a perfect concordance in votes), sulfasalazine, mesalamine, prednisone and azathioprine/6-MP, as well as the antibiotics ciprofloxacin and metronidazole, and probiotics were rated safe, whereas infliximab, adalimumab and budesonide were deemed uncertain.

During the breastfeeding period, the following drugs were considered safe: mesalamine, prednisone, probiotics and infliximab. Sulfasalazine, azathioprine/6-MP, budesonide ciprofloxacin and adalimumab were considered uncertain.

4. Discussion

High-level scientific evidence is lacking for many treatment decisions in CD. In particular, special situations such as upper gastro-intestinal CD,⁴ usually associated with a worse prognosis,¹² and extra-intestinal manifestations⁵ are rarely subjected to randomised clinical trials. The question of drug safety during pregnancy or breastfeeding in CD patients is also poorly documented.⁶ For all these situations, appropriateness criteria for use of drugs are particularly valuable. The RAND process combines a systematic review of the literature with expert clinical opinion without any need for a consensus and is a well-validated method of providing valid evidence on the use of therapeutic options according to current knowledge.¹³

The results of the EPACT II panel presented in this paper are in general agreement with published trials, consensus conferences^{14–17} and guidelines¹⁸; any divergent recommendations will be discussed later in this article.

At the beginning of the panel, all panelists unanimously acknowledged that smoking cessation in CD patients was beneficial for all scenarios.

For CD patients with upper gastro-intestinal involvement, therapy is in general similar to that for ileal CD, with the addition of PPI treatment. Furthermore, in the discussion preceding the vote, it was accepted by the panel that *H. pylori* infection, if present, should be eradicated. In the presence of an intolerance to azathioprine/6-MP, the ECCO consensus recommends methotrexate, but this was not voted on by the EPACT panel. EPACT rated infliximab appropriate in the absence of stenosis, as did the AGA consensus on biologics in IBD,¹⁵ and in concordance with the ECCO consensus¹⁷ which rated infliximab as an alternative for refractory upper gastro-intestinal disease. The "uncertain" rating of adalimumab and the rating as "inappropriate" of certolizumab reflect the scarce data in this particular clinical setting. In the presence of an upper gastro-intestinal stenosis, use of anti-TNF- α antibodies is controversial (infliximab) or not recommended (adalimumab and certolizumab), once again reflecting uncertainty, whereas endoscopic balloon dilation, the efficacy and safety of which has been confirmed in a systematic review,¹⁹ as well as surgery and medical treatments such as PPI, steroids and azathioprine/6-MP, were considered appropriate by the panel.

Extra-intestinal manifestations (EMI) of CD (Pyoderma gangrenosum, spondylarthropathy, PSC, uveitis) mostly evolve independently of disease activity. Infliximab is considered appropriate for EMI (except for PSC), as was recommended by the AGA consensus on biologics in IBD¹⁵ and the ECCO consensus.¹⁷ Adalimumab, appropriate for Pyoderma gangrenosum and spondylarthropathy, was rated uncertain for uveitis. Certolizumab was not rated at all, reflecting the lack of data available for EMI. In refractory uveitis, case reports have described the success of peri- or intra-ocular steroid injections²⁰; this option was, however, not subjected to vote by the EPACT II panel. Among the immunomodulators, methotrexate was only appropriate in spondylarthropathy and cyclosporine-A/tacrolimus in pyoderma gangrenosum, whereas azathioprine/6-MP were inappropriate or uncertain. Although not subjected to vote by the panel, sulfasalazine and physiotherapy have been shown to ameliorate peripheral or axial skeletal pain.¹⁴ Other EMI of CD, such as peripheral arthritis, erythema nodosum, aphthous ulcers or episcleritis,

generally related to underlying disease activity,²¹ extraintestinal associated diseases (gallstones, nephrolithiasis), and non-disease-specific complications (amyloidosis, osteoporosis, thromboembolic complication) were not subjected to vote.

An important aspect of EPACT II deliberations was drug safety during pregnancy in CD patients. EPACT II especially considered azathioprine/6-MP safe throughout pregnancy. This reflects an evolution towards a more liberal approach since EPACT I, potentially in the light of the BSG guidelines,¹⁸ the ECCO consensus¹⁴ and new published studies.⁶ One study using national Danish registries and databases²² reported that out of 20 pregnancies exposed to azathioprine and 6-MP (9 of them exposed to smoking) the rate of preterm birth, low birth-weight and congenital abnormalities was greater compared to the reference group; it should be stressed, however, that a confounder such as disease activity might not have been adequately assessed in this study. Prednisone was considered safe throughout pregnancy, although a marginally increased risk (OR of 3 with 95% CI of 1.08 to 8.54) of mostly oral cleft malformation has been shown in a meta-analysis after exposure to corticosteroids during pregnancy.²³ Sulfasalazine is rated as unsafe for men considering conception. This reflects the fact that reduced sperm motility and count (oligospermia) have been reported in males undergoing sulfasalazine treatment, although it remains unknown as to whether sulfasalazine per se could provoke spermatozooids' DNA damage in humans in the same way as in rats.²⁴ Mesalamine was however considered safe for female and male patients considering conception and throughout pregnancy and breastfeeding.

EPACT II also considered infliximab safe at time of conception or during the first trimester in view of the fact that increasingly data support this stance, but still considered it uncertain during late pregnancy (2nd and 3rd trimesters). This is supported by the fact that infliximab, an IgG1 antibody, is actively transferred through the placenta to the fetus in late pregnancy.²⁵ The EPACT panel voted conservatively as it considered not only the 3rd but also the 2nd trimester as uncertain whereas the ECCO guidelines would consider infliximab safe in the 2nd trimester but "treatment may best be avoided in the last trimester of pregnancy if circulating infliximab in the neonate is to be avoided".¹⁴

The EPACT II panel also differed from the ECCO consensus concerning breastfeeding, in so far that a slightly more cautious approach is recommended concerning azathioprine/6-MP and sulfasalazine. These attitudes were considered probably safe and safe respectively, by the ECCO consensus, but these compounds were rated uncertain by EPACT II.

5. Conclusion

In conclusion, the EPACT II panel was able to produce recommendations for the treatment of upper gastro-intestinal CD, extra-intestinal manifestations of CD and drug safety in case of conception, pregnancy and breastfeeding. All these recommendations are freely available online (www.epact.ch). Prospective evaluation should now test these appropriateness criteria, with particular emphasis on controversial or uncertain situations.

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