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REVIEW ARTICLE

Special situations in inflammatory bowel disease: First Latin American consensus of the Pan American Crohn's and Colitis Organisation (PANCCO) (Second part)☆

J.K. Yamamoto-Furusho[a,*], F. Bosques-Padilla[b,c], P. Daffra[d], J.A. De Paula[d], J. Etchevers[d], M.T. Galiano[e], P. Ibañez[f], F. Juliao[g], P.G. Kotze[h], J.M. Marroquín de la Garza[b,c], R. Monreal Robles[b,c], J.L. Rocha[i], F. Steinwurz[j], R. Vázquez-Frías[k,1], G. Veitia[l], C. Zaltman[m]

[a] *Clínica de Enfermedad Inflamatoria Intestinal, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[b] *Servicio de Gastroenterología, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey, Mexico*
[c] *Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, Mexico*
[d] *Servicio de Gastroenterología, Hospital Italiano, Buenos Aires, Argentina*
[e] *Clínica de Enfermedad Inflamatoria Intestinal, Clínica Marly, Bogotá, Colombia*
[f] *Programa de Enfermedad Inflamatoria Intestinal, Departamento de Gastroenterología, Clínica Las Condes, Santiago, Chile*
[g] *Clínica de Enfermedad Inflamatoria Intestinal, Hospital Pablo Tobón Uribe, Medellín, Colombia*
[h] *Hospital Universitario Cajuru, Universidad Católica del Paraná (PUCPR), Curitiba, Brasil*
[i] *Grupo Académico y de Investigación en Crohn y Colitis Ulcerosa Crónica Idiopática de México, Mexico City, Mexico*
[j] *Hospital Israelita Albert Einstein, São Paulo, Brazil*
[k] *Departamento de Gastroenterología Pediátrica, Hospital Infantil de México Federico Gómez, Mexico City, Mexico*
[l] *Servicio de Gastroenterología, Hospital Vargas, Caracas, Venezuela*
[m] *Servicio de Gastroenterología, Hospital Clementino Fraga Filho, Departamento de Medicina Interna, Universidad Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*

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Abstract This is the first Latin American Consensus of the Pan American Crohn's and Colitis Organisation (PANCCO) regarding special situations in patients with inflammatory bowel disease (IBD). The aim of this consensus is to raise awareness in the medical community in all Latin

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* Corresponding author. Clínica de Enfermedad Inflamatoria Intestinal, Departamento de Gastroenterología, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Colonia Sección XVI, Tlalpan, C.P. 14000 Mexico City, Mexico.
Tel.: +52-55-55733418; Fax: +52-55-56550942.
E-mail address: kazuofurusho@hotmail.com (J.K. Yamamoto-Furusho).

[1] By the Gastroenterology Pediatrician Team Work.

Pregnancy;
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Infections;
Pediatrics

American countries with respect to pregnancy, vaccinations, infections, neoplasms, including colorectal cancer, and pediatric issues in patients with IBD.

PALABRAS CLAVE
Colitis ulcerosa crónica idiopática;
Enfermedad de Crohn;
Embarazo;
Cáncer;
Infecciones;
Pediatría

Situaciones especiales en la enfermedad inflamatoria intestinal: primer consenso latinoamericano de la *Pan American Crohn's and Colitis Organisation* (PANCCO) (Segunda parte)

Resumen Este es el primer Consenso Latinoamericano de la *Pan American Crohn's and Colitis Organisation* (PANCCO) que corresponde a situaciones especiales en pacientes con enfermedad inflamatoria intestinal (EII). El objetivo de este consenso es concientizar a la comunidad médica de todos los países de América Latina acerca del embarazo, la vacunación, las infecciones y las neoplasias, incluyendo el cáncer colorrectal, así como los aspectos pediátricos en pacientes con EII.

Pregnancy

Fertility and inflammatory bowel disease

1. *In patients with inflammatory bowel disease (IBD), fertility is not generally affected (Level of evidence: 3. Level of agreement: 100%), except in patients with active Crohn's disease (CD), women with a history of pelvic surgery (Level of evidence: 1. Level of agreement: 100%), or men receiving sulfasalazine treatment (Level of evidence: 3. Level of agreement: 100%).*

Although in general terms fertility rates in patients with IBD are similar to those of the general population, lower birth rates and smaller-sized families are common in this group of patients. A possible explanation for this is the decision of both male and female patients to remain childless, which underscores the impact this disease will have on family planning issues.[1,2]

In patients with CD, fertility is usually normal, although it may be decreased, especially in patients with active disease and/or multiple prior abdominal surgeries.[3]

In cases of ulcerative colitis (UC), fertility rates are normal, except in patients with total colectomy and ileoanal pouch (IAP) reconstruction. According to different reports,[4] there can be a 3-fold greater risk for infertility in those patients, as a result of pelvic adhesions after surgery and subsequent tubal obstruction. Two published studies evaluating the impact of proctocolectomy with IAP reconstruction on the pelvic anatomy indicated that 50% of patients presented with complete uni or bilateral Fallopian tube obstruction. This risk would appear to be somewhat less for laparoscopic procedures, although confirmatory studies are lacking.

Male patients may present with retrograde ejaculation or erectile dysfunction after IAP reconstruction, but different studies show no evidence of significant change in sexual function after surgery.[5]

With respect to medication for IBD and fertility, men taking sulfasalazine present with reversible changes in semen (oligospermia, decreased motility, and morphologic changes) and infertility in up to 60% of cases.[6] The mechanisms of these effects are not entirely clear, but sulfasalazine is thought to alter sperm maturation, an effect which disappears 2 months after discontinuing the drug or changing it for mesalazine.

Conversely, azathioprine does not appear to affect semen quality or produce infertility in men.[7] Infliximab does appear to affect fertility by decreasing sperm motility, a finding shown by a study on a small patient cohort. However, sperm counts rise after each infusion.[8] The mechanisms underlying the effects on male fertility remain unclear.

2. *Oral contraceptive use does not appear to worsen the course of IBD (Level of evidence: 3. Level of agreement: 100%). When additional risk factors are present, oral contraceptive use increases the risk for thromboembolic events (Level of evidence: 1. Level of agreement: 100%).*

Oral contraceptive use does not appear to affect the course of IBD, as was shown by several case series and a prospective study on 331 women with CD, in which contraceptive use had no influence on disease activity.[9] Both IBD and oral contraceptive use are risk factors for thrombotic events. Studies show that IBD patients have a three-fold greater risk for thrombotic episodes,[10–12] which is why oral contraceptive use in IBD patients should be prescribed on a case-by-case basis.

Low-molecular-weight-heparin (LMWH) has proven to be safe for use during pregnancy, as well as for IBD patients. LMWH prophylaxis is recommended for pregnant IBD patients with active disease or during hospitalization.[13]

Pregnancy and inflammatory bowel disease

3. *When pregnancy begins during disease remission, relapse risk is the same as for non-pregnant patients. On the other hand, when conception overlaps with active disease, the risk of persistent disease is higher. (Level of evidence: 3). Conception is therefore recommended during periods of remission. (Level of evidence: 3. Level of agreement: 91%).*

Pregnancy seems to have a beneficial effect on IBD symptoms, especially when it evolves during a period of disease remission. A minor, but nevertheless significant, decrease in Harvey-Bradshaw index levels has been observed in CD patients that become pregnant, in comparison with disease activity during the previous and/or subsequent year.[14] However, the underlying mechanism of this effect is not known, and it has also been linked to patients curtailing smoking during pregnancy.

Disease state at the time of conception is also an important factor affecting the course of the disease. Patients that conceive during periods of active disease will usually present with symptoms during pregnancy, whereas those that conceive during remission most likely will not present with disease symptoms during pregnancy.

In a cohort with a 10-year follow-up, conception during remission usually meant that the risk for relapse was similar to that of non-pregnant patients. In contrast, when conception occurred during an active phase of the disease, two thirds of the patients presented with relapses during pregnancy.[3]

Unfortunately, most relapses, especially those occurring during the first trimester, are often the result of inappropriate discontinuation of maintenance therapy.

4. *Most drugs can be considered safe for use during pregnancy, with the exception of thalidomide and methotrexate. (Level of evidence: 3. Level of agreement: 80%). Infliximab and adalimumab cross the placenta, and detectable levels in the fetus are seen after the second trimester. Fetal exposure should be limited as much as possible and therefore these drugs should be discontinued during the third trimester. Eventually, continuation of anti-TNF treatment should be established on an individualized basis (Level of evidence: 3. Level of agreement: 80%).*

Most drugs used for IBD treatment, except for methotrexate and thalidomide, are not linked to increased risk for congenital malformations or fetal adverse events and therefore are approved for use during pregnancy.

Many pregnant IBD patients abandon treatment for fear of adverse effects on the fetus. This shows the importance of providing the patient with opportune and detailed information on the risks and benefits of treatment, prior to conception, as well as during pregnancy, and of promoting close communication between the treating physicians (obstetricians, neonatologists) to avoid inconsistencies.[15]

Aminosalicylates. Sulfasalazine and all aminosalicylates in general are considered safe (FDA category B). Case series, population cohorts, and two meta-analyses showed no increase in adverse events during early pregnancy (ectopic pregnancy or miscarriage). Some studies did find increased rates of preterm labor, stillbirths, and low birth weight. However, disease activity during pregnancy is a confounding factor.

Studies in both human and animal models showed no signs of teratogenic effects.[16] Only the meta-analysis by Cornish et al.[17] indicated a slight increase in the risk for congenital abnormalities, which was interpreted as a result of disease activity.

Because sulfasalazine alters folate absorption rates, supplements (2 mg/daily) or substitution with mesalazine, are recommended.

Steroids. All corticosteroids (FDA category C) cross the placenta, but undergo rapid conversion to less active metabolites through the action of the placental enzyme 11β-hydroxysteroid dehydrogenase. This occurs in such a way that concentration in fetal blood is low. Prednisone, prednisolone, and methylprednisolone are metabolized rapidly and fetal concentration is below that of dexamethasone or betamethasone, which makes them drugs of choice for use during pregnancy. Although an increased risk for orofacial malformations has been observed in mothers receiving corticosteroids during the first trimester,[18,19] the risk was small and has not been confirmed by all observational studies.[20]

Azathioprine (AZA) and 6-mercaptopurine (6-MP). Both AZA and its metabolite 6-MP remain in FDA category D, indicating risk for the fetus. This dates back to a study from 1960, in which teratogenic effects were observed in mice and rabbit offspring. However there have been many case-control and cohort studies in humans since then, indicating that this is not the case, which is why 9 out of 10 experts give AZA during pregnancy.[21]

The most commonly reported adverse events are increased rates of spontaneous abortion, premature delivery, and low birth weight, which appear to be due to greater disease activity, more than to the use of AZA or 6-MP.[22] Moreover, a recent retrospective, multicenter cohort study showed that thiopurines were not only not linked to an increased risk for complications during pregnancy, but that they could even have a protective effect.[23]

Preliminary data from IBD patients in the Prospective Registry of Pregnancy Outcomes (the PIANO study) exposed to anti-TNF and thiopurine treatment suggest no link between immunosuppressant therapy and congenital anomalies, or abnormal newborn growth and development.

Cyclosporine. Cyclosporine (FDA Category C) is a widely-used drug in post-transplant patients or those with graft-versus-host disease, with most available data coming from studies on this patient population. In a meta-analysis of 410 pregnant women, no increase in the risk for congenital anomalies was observed.[24] In the context of IBD, cyclosporine prescribed to treat refractory UC has proven to be both safe and effective. Although the use of this drug should be considered for cases of fulminant UC, some authors suggest that first-line use of biologics is safer in those cases (FDA Class B), now that more evidence on their use during pregnancy is available.[25]

Methotrexate (MTX) and thalidomide. Both drugs are teratogenic (FDA Category X) and are contraindicated during pregnancy. Patients of reproductive age receiving these medications need to be well informed and warned of the absolute need for effective contraception. Although reports of normal outcomes do exist in women receiving methotrexate during the first trimester, its use may induce miscarriage, intrauterine growth retardation, and congenital anomalies including cranioencephalic defects, failure of neural tube

closure, and central nervous system (CNS) anomalies.[26] Intracellular MTX metabolites have a very long half-life, and may take up to 6 weeks to clear, therefore both male and female patients trying to conceive are advised to discontinue dosing and wait 3 to 6 months before abandoning contraceptive use.

Thalidomide has been linked to major malformations affecting limbs, eyes, and ears, as well as causing neural tube defects. Neonatal mortality rates are as high as 40%, making its contraindication in pregnancy absolute.

Biologics: anti-tumor necrosis factor antibodies (anti-TNF). All currently available anti-TNF agents are classified by the FDA as category B for pregnancy, indicating that no teratogenic effect has been found in animals, but that there is a lack of controlled human safety data. TNF produced by the placenta plays an important role during pregnancy, intervening in fetal immune development during early stages and probably protecting the fetus against teratogenic agents.[20] In spite of this, anti-TNF therapy can be considered safe prior to and in the early stages of pregnancy, since IgG cannot cross the placenta during the first trimester. Placental transport occurs at the end of the second and during the third trimester, which is the same time the fetus acquires maternal immunity, until its own system becomes functional.[27]

Infliximab (IFX) and adalimumab (ADA) are IgG1 monoclonal antibodies actively transported across the placenta, whereas certolizumab is a Fab fragment of IgG1, which does not cross the placenta. Animal studies have confirmed these findings, but there are no studies in humans.

Anti-TNF antibody transfer to the fetus in the third trimester exposes the newborn to increased risk for infection, as well as to inadequate response to vaccination, especially with live-attenuated vaccines such as BCG, rotavirus, and varicella-zoster. IFX and ADA should therefore be discontinued in the third trimester, and vaccination postponed until 6 months after birth.[25] However, recent studies have shown the presence of IFX, as well as ADA, in cord blood from UC patients that had discontinued anti-TNF drug treatment at 30 weeks, making anti-TNF treatment duration and when it should be discontinued, subjects of continuing debate.[28]

Several observational studies, registries, and systematic reviews have shown their use to be safe during pregnancy.[29,30] The PIANO registry has not reported increased rates of congenital anomalies, abnormal growth and development, or other complications in the newborns of mothers receiving biologics.

For relapses during pregnancy, the use of mesalazine and corticosteroids seems to be the preferred treatment choice. Little data is available on starting anti-TNF treatment during pregnancy. In spite of this, increased maternal and fetal risks linked to active untreated disease need to be considered. The possibility of indicating anti-TNF therapy should be considered for both corticosteroid-refractory cases and cases of adverse events resulting from their use. Certolizumab should be contemplated in particular, because it has shown low placental transfer.

Antibiotics. Metronidazole (FDA Category B) and ciprofloxacin (FDA Category C) are antibiotics frequently employed to treat perianal CD.

Table 1 Risk linked to different drugs used to treat IBD during pregnancy and lactation.

Drug	Risk during pregnancy	Risk during lactation
Mesalazine/ sulfasalazine	Low	Low
Corticosteroids	Low	Low[a]
Thiopurines	Low	Low[a]
Anti-TNF	Low[b]	Probably low
Ciprofloxacin	Avoid during the first trimester	Avoid
Metronidazole	Avoid during the first trimester	Avoid
Methotrexate	Contraindicated	Contraindicated
Thalidomide	Contraindicated	Contraindicated

[a] Discard breast milk pumped up to 4 hours after dosing.
[b] Discontinue at week 24 in patients in remission.

Animal studies using metronidazole showed carcinogenic effects and orofacial malformations, although these studies have not been replicated in humans.

Use was not linked to premature delivery, low birth weight, or congenital anomalies in a study on 2,829 patients.[31]

A meta-analysis evaluating the use of ciprofloxacin during the first trimester revealed no increase in the risk for congenital anomalies, miscarriage, preterm labor, or low birth weight.[32] Nevertheless, due to the known effects of ciprofloxacin on bone and cartilage, its use should be avoided during pregnancy.[33]

Table 1 illustrates all medications used to treat pregnant IBD patients.

Delivery, postpartum, and lactation

5. *The choice of delivery route will mainly depend on obstetrical requirements (Level of evidence: 5). However, joint decisions should be made by obstetricians, gynecologists, and/or surgeons specializing in IBD. In cases of active perianal disease or rectal involvement, patients should undergo C-section delivery (Level of evidence: 5). The presence of an ileoanal pouch or ileorectal anastomosis is a relative indication for delivery by elective cesarean section (Level of evidence: 5. Level of agreement: 100%).*

Mode of delivery for mothers with IBD will depend on obstetrical requirements. Nevertheless, it is best that decisions be joint ones made by gastroenterologists and/or colorectal surgeons. Cesarean delivery is recommended for cases of active perianal or rectal involvement. Although C-section is often suggested in all patients with CD, it is reasonable to allow vaginal delivery in women with quiescent or mild disease.[34] Episiotomy should be avoided when possible, because of subsequent risk of perianal disease involvement.

Continence in patients with ileoanal pouch reconstruction will depend on good sphincter function, therefore C-section delivery is recommended to protect the sphincter and preserve pelvic floor function as much as possible.[15]

6. *Most drugs are safe for use during lactation (Level of evidence: 2. Level of agreement: 100%).*

Recent studies indicate that nursing mothers have no major risk for disease relapse.[32]

Based on either physician indication or personal choice, many women choose not to nurse their infants out of fear that medication might affect the child.

Aminosalicylates. Concentration in breast milk is minimal, making risk of toxicity unlikely. This finding has been confirmed by prospective trials,[35] and the European Crohn's and Colitis Organisation (ECCO) considers aminosalicylate use safe during breastfeeding.[15]

Azathioprine (AZA) and 6-mercaptopurine (6-MP). Only small amounts of AZA and 6-MP metabolites are excreted into breast milk in the first 4 h after dosing. Therefore, some authors recommend pumping and discarding (''pump and dump'') breast milk during the 4 h after dosing.[25] In any case, studies have shown no increase in risk for infection in children nursed by mothers exposed to thiopurines.

Methotrexate. Methotrexate is excreted into breast milk and is contraindicated both during pregnancy and while breastfeeding because of its teratogenic effects.

Corticosteroids. Corticosteroids are excreted at low concentrations in breast milk, and like thiopurines, reach peak concentrations during the first 4 h after dosing. Thus, pumping and discarding breast milk during the 4 h after medication intake is also recommended.[25]

Antibiotics. Because both metronidazole and ciproflaxin are excreted into breast milk, neither is considered appropriate for use during lactation.[15]

Biologics. Studies on small numbers of patients taking IFX and ADA showed no increase in pediatric infection rates, given that only small amounts are excreted into breast milk. However, available data is insufficient to establish recommendations. Therefore, even though the most recent publications support their use during lactation,[25] careful consideration is required and drug and antibody level monitoring in both the milk and neonate, when feasible, should be contemplated.[15]

7. *Patients with IBD should be adequately informed on matters related to contraceptive use, as well as on eventual pregnancy, delivery, lactation, and newborn infant health in relation to IBD and its treatment (Level of evidence: 5. Level of agreement: 100%).*

Most IBD patients seeking pregnancy have little information about the drug safety of IBD treatments around the time of conception. In this regard, reproductive wishes can lead to a change in therapeutic strategy in up to one third of patients.[36]

Thus, the information conveyed to patients in this context should always be appropriate, accurate, and reassuring.

To obtain an adequate response, encompassing all aspects of the special circumstance pregnancy represents, multidisciplinary management should include gastroenterologists, obstetricians, and pediatricians specializing in IBD.[15,37–39]

8. *In newborns of mothers exposed to anti-TNF agents that cross the placental barrier (infliximab, adalimumab, golimumab), detectable levels can be found during the first 6 months of life. Therefore, the administration of vaccines with live attenuated germs (BCG, oral polio, rotavirus) should be avoided during that period (Level of evidence: 3. Level of agreement: 91%).*

The transfer of anti-TNF antibodies to the fetus exposes the neonate during the first months of life to an increased risk for infections and an inadequate response to vaccines, especially live germ vaccines such as BCG, rotavirus, and varicella-zoster. Therefore, it is recommended to delay live virus vaccination for at least 6 months after birth.[25] This is not the case with respect to dead virus vaccines.

9. *In case of relapse in pregnant women, mesalazine and corticosteroids are the preferred therapies, depending on disease phenotype and activity. Anti-TNF agents should be considered for the treatment of relapses in appropriate situations (Level of evidence: 5. Level of agreement: 91%).*

There are few data about the initiation of anti-TNF therapy during pregnancy, but despite the limited data, both the maternal and fetal risk for developing active disease during pregnancy should be taken into account. In cases of corticoid-refractoriness, as well as in cases of significant corticosteroid adverse events, anti-TNF initiation should be considered. This is particularly true for certolizumab, due to its limited passage through the placenta.

10. *Infliximab and adalimumab cross the placenta and their use beyond the second trimester results in detectable levels in the neonate. When both the physician and patient consider it appropriate, the recommendation is to limit exposure to the fetus by stopping anti-TNF administration in the third trimester of pregnancy. Its continuation should be individualized (Level of evidence: 3. Level of agreement: 80%).*

The transfer of anti-TNF antibodies to the fetus during the last trimester of pregnancy exposes the neonate during the first months of life to an increased risk for infections and an inadequate response to live germ vaccines. Therefore, it is recommended to discontinue infliximab and adalimumab early in the third trimester, and to administer the final dose of the anti-TNF agent in the second trimester, as late as possible (week 24-26), to maintain remission and limit transmission of the drug to the fetus.[37]

Vaccination and infections

Vaccinations

11. *All patients with IBD must be tested for hepatitis B virus (HBV) (HBsAg, anti-HBsAg, anti-HBcAb) upon diagnosis of IBD to determine the status of HBV. In patients with positive HBsAg, viremia (HBV DNA) should also be quantified (Level of evidence: 2. Level of agreement: 100%). HBV vaccination is recommended in all HBV anti-HBcAb seronegative patients with IBD (Level of evidence: 1. Level of agreement: 100%).*

The prevalence of chronic HBV infection in patients with IBD is similar to that of the general population,[40,41] but the former have a higher risk for reactivation[42] and fulminant presentation when on immunosuppressive therapy.[43,44] Based on the need for immunosuppressive therapy in patients with IBD, experts recommend that screening and vaccination begin at the time of diagnosis.[45,46] Serologic screening for hepatitis B should include AgHBs, anti-HBs, and anti-HBc. HBV DNA should be quantified in those patients

with positive AgHBs. HBV vaccination should be administered to negative anti-HBs and anti-HBc patients. The standard recommendation is a regimen at 0, 1, and 4 months.[47]

12. *At IBD diagnosis, patients must be examined for a history of susceptibility to primary varicella-zoster virus (VZV) infection. Those without a clear history of varicella, herpes zoster, or administration of two doses of the varicella vaccine should be tested for VZV IgG (Level of evidence: 2). Whenever possible, seronegative patients should complete the course of two doses of varicella vaccine at least 3 weeks before the start of the immunomodulatory therapy (Level of evidence: 5). Subsequent immunization can only be given after a 3 to 6-month cessation of all immunosuppressive therapy (Level of evidence: 4). Seronegative patients should receive timely prophylaxis after exposure (Level of evidence: 4. Level of agreement: 82%).*

Herpes virus infections are reported in some studies to be the most common immunosuppression-related viral infections in patients with IBD.[48,49] The incidence of disseminated disease in immunocompromised adults with VZV has been reported to be approximately 30%.[50] Reactivation can occur after a period of latency, resulting in herpes zoster or other less common complications.[50] Serologic testing is recommended to help guide vaccination practices in those patients with no clear history of chickenpox or vaccination, as soon as the diagnosis of IBD is made.[51] However, it is not certain if a history of varicella or herpes zoster is an actual seroprotection indicator.[49,52] It is unclear if confirming seroprotection (VZV IgG) is necessary and it may give rise to the dilemma of a seronegative patient that is already on immunosuppression and whether immunosuppression should be held to permit safe vaccination.

To establish evidence of immunity to varicella in adults, documentation of 2 doses of varicella vaccine at least 4 weeks apart, a history of varicella or herpes zoster based on diagnosis or verification of varicella disease by a healthcare provider, laboratory evidence of immunity or laboratory confirmation of disease must be confirmed.[53]

Expert consensus recommends vaccinating IBD patients (they should receive 2 doses of single-antigen varicella vaccine) that do not have a reliable history of disease or vaccination and have not begun therapy with immunosuppressive medications.[51,54–56]

For immunocompromised patients, live-virus varicella vaccine is contraindicated until immunosuppressive therapy has been discontinued for at least 3 months.[51,57]

Passive immunization may be required for immunosuppressed, seronegative patients that have high-risk exposure to VZV (i.e., close contact with a person with chickenpox or shingles). VZV immunoglobulin G (VZIG) should be given within 96 h of exposure at a dose of 125 units per 10 kg of body weight to a maximum of 625 units.[58]

13. *Routine prophylactic vaccination against the human papillomavirus (HPV) is recommended for women and men, according to national guidelines (EL2). Current or past HPV infection is not a contraindication for immunomodulatory therapy (Level of evidence: 2. Level of agreement: 91%).*

HPV is the most common sexually transmitted infection in the world.[59] HPV (mainly HPV-16 and 18) is known to cause cervical and anogenital cancers. A higher prevalence of cytologic abnormalities, high-grade dysplasias, and cervical cancer has been described in women with IBD taking immunomodulators.[60–63]

HPV immunization is recommended in IBD patients, even in those on immunosuppressive therapy, because it is based on an inactivated virus.[54] The bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4) are licensed for use in women, and the HPV4 vaccine is licensed for use in men. A complete series of either HPV4 or HPV2 consists of 3 doses at 0, 1-2, and 6 months. Both vaccines are efficacious, safe, and protective against HPV infection in immunocompetent patients.[64,65] We recommend administering HPV4 to all men and nonpregnant women with IBD between the ages of 9 and 26.

Current or previous HPV infection is not a contraindication for vaccination. Recent studies have demonstrated that patients with previous or active infection benefit from HVP vaccine administration, with high protective rate percentages (> 90%).[66,67]

14. *Immunomodulatory therapy patients have a higher risk for developing severe influenza infection (Level of evidence: 5). Annual vaccination with trivalent-inactivated-influenza vaccine is an effective strategy for preventing influenza (Level of evidence: 1. Level of agreement: 82%).*

The incidence of influenza infection does not appear to be higher in IBD patients, but they may develop a severe infection if they are under immunomodulation treatment.[55]

Annual immunization with trivalent-inactivated-influenza vaccine is an effective strategy to prevent influenza.[55] The Advisory Committee on Immunization Practices and the Centers for Disease Control and Prevention (CDC) recommend annual influenza vaccination for all immunosuppressed patients.[68] Trivalent-inactivated-influenza vaccine (influenza A H1N1, H3N2 and one influenza B strain) was shown to be safe in patients with chronic diseases.[69]

Immune response after influenza vaccine is reduced in patients receiving immunosuppressive therapy, particularly when on combination therapy.[70] Anti-TNF monotherapy may also reduce immune response to vaccination. Despite this, annual vaccination against influenza is recommended for all adult IBD patients because the immune response remains sufficient to warrant vaccination.[55]

15. Pneumocystis jiroveci *pneumonia prevention is recommended in patients with triple immunomodulatory therapy (a calcineurin inhibitor or anti-TNF therapy) (Level of evidence: 4). Prophylactic cotrimoxazole should be considered for those patients on a dual immunomodulator regimen, especially if one of them is a calcineurin inhibitor (Level of evidence: 4. Level of agreement: 91%).*

In addition to patients with human immunodeficiency virus (HIV), patients on immunosuppressive medications are increasingly being reported to develop *Pneumocystis jiroveci* pneumonia (PJP).[71] IBD patients on immunomodulatory therapies are at risk for developing PJP, especially those receiving combination immunosuppression that includes calcineurin inhibitors.[72] A recent meta-analysis showed a 91% reduction of PJP occurrence in hematologic cancer or transplant patients treated prophylactically with cotrimoxazole.[73]

Based on expert opinion, several groups (ECCO, British Society of Gastroenterology [BSG], American College of Gastroenterology [ACG]) recommend PJP prophylaxis in

patients on multiple immunosuppression agents that include a calcineurin inhibitor.[74–76] A double-strength tablet of 160-800 mg of trimethoprim-sulfamethoxazole (TMP-SMX) 3 times a week is the recommended standard prophylaxis.[54]

There is currently no consensus on the use of prophylactic cotrimoxazole for the prevention of PJP in IBD patients. The indication for PJP prophylaxis in patients that may benefit from it should be carried out on a case-by-case basis.

16. *Patients with IBD that are taking immunomodulators are considered at risk for pneumococcal infections (Level of evidence: 4. Level of agreement: 100%). Anti-pneumococcal vaccination should be given prior to immunomodulator administration (Level of evidence: 5. Level of agreement: 100%).*

Patients with IBD have an increased risk for severe pneumococcal infection.[29–40,77–79] Bacterial pneumonia is one of the most prevalent infections in patients undergoing prolonged immunosuppressive therapy.[80]

Currently there are two types of pneumococcal vaccines available: pneumococcal polysaccharide (PPSV23) vaccine and pneumococcal conjugate 13-valent (PCV13) vaccine. PPSV23 is the most commonly used and recommended vaccine for all adults. The use of PCV13 has recently been approved for adults above 50 years of age.[81,82]

PPSV23 contains up to 98% of the pneumococcal serotypes that cause pneumonia.[83] It reduces the morbidity associated with invasive pneumococcal disease in adults, especially those with a chronic medical condition that receive immunosuppressive medications.[84]

There is evidence that neither IBD itself nor monotherapy with immunomodulators impairs vaccine response.[85,86] However, the combined use of anti-TNF agents and immunomodulators has demonstrated a reduced response to PPSV23.[86,87] Therefore, pneumococcal vaccination is recommended for all patients with IBD at the time of diagnosis.[54]

17. *IBD should not be a reason for restricting patients from taking trips abroad. Patients travelling to developing regions should have a pre-travel consultation. Special consideration should be given to patients under treatment with immunomodulators (Level of evidence: 5. Level of agreement: 100%).*

IBD should not restrict foreign travel, but travel to areas where certain infectious diseases are common should be avoided. Patients travelling to developing regions should have a pre-travel consultation. An international vaccination unit should be visited to assess the patient's immunocompetence status, as well as the travel destination.

Immunizations should be indicated according to immunocompetence status, type of trip, and destination. Three types of vaccination groups are described in guidelines for travelers: routine vaccinations (tetanus-diphtheria-pertussis, hepatitis B, measles-mumps-rubella); recommended vaccination for endemic areas (cholera, typhoid fever, hepatitis A, Japanese encephalitis); and required vaccination for endemic areas (meningococcal infection and yellow fever).

Salmonella infection has been reported to be present in patients with UC in 2% of cases.[88] Even though it is not a highly prevalent infection among IBD patients, those on immunosuppressive therapy are at risk for a fatal presentation.[89–92] Furthermore, the occurrence of *Salmonella* infection in patients with UC may increase the severity of IBD.[93]

There are currently no preventive strategies for active immunization. The general recommendations to particularly avoid contaminated raw eggs, unpasteurized milk, and undercooked meat are advisable when travelling to endemic areas. It is important to explain to patients travelling to endemic areas that *Salmonella* is transmitted by the ingestion of contaminated food that is derived from traditional, identifiable sources and sold by street vendors.[94,95] These facts emphasize the important role of advice concerning hygiene in patients undergoing anti-TNF therapy.

Those on immunosuppressive therapy with documented infection due to *Salmonella* spp. are advised to discontinue immunosuppressive therapy. Immunosuppressive therapy should be delayed until the active infection is resolved, waiting at least 6 to 8 weeks after antibiotic completion.[95]

18. *A standardized checklist, as well as the detection of opportunistic infection risk adapted to local conditions, are recommended and should be completed at the time of IBD diagnosis (Level of evidence: 5). Vaccination history at the time of diagnosis should be documented and immunization status should be regularly updated (Level of evidence: 5). It is preferable to administer the vaccine before immunomodulatory therapy (Level of evidence: 3. Level of agreement: 91%).*

Before a vaccination program is initiated in patients with IBD, the patient's immunocompetence status should be determined, because it is an important factor that potentially influences the immunologic response, not only against infections, but also in response to vaccination.

In the IBD setting, an immunocompromised patient is defined as one undergoing immunomodulatory therapy or in whom malnutrition is present. A patient taking $\geq$ 20 mg of prednisolone (for $\geq$ 2 weeks), thiopurines, methotrexate, anti-TNF agents, or other biologic agents is considered to be receiving immunosuppressive therapy. This status also includes the 3 months after drug discontinuation.[56]

Immunization after immunosuppressive therapy is begun has been shown to impair the immune response to vaccination in patients with IBD.[87,96–98] Tables 2 and 3 show the considerations to be taken into account before starting vaccination in patients with IBD.

19. *Patients with IBD are at an increased risk for suffering from opportunistic infections. There is a significant increase in those patients that take more than one drug, especially when corticosteroid use is added. Precautions should be taken in this regard, particularly screening for tuberculosis, hepatitis B, HIV, and parasites (according to local epidemiology) and vaccination prior to the use of immunomodulators and/or biologic agents (Level of evidence: 2. Level of agreement: 91%).*

Patients with IBD are at an increased risk for suffering from opportunistic infections.[99,100] The predisposing factors include IBD itself, advanced age, chronic comorbidities, and malnutrition.[54] Due to the use of immunosuppressants, and more recently, to biologic agents and the trend to employ combination therapy for achieving greater therapeutic efficacy, patients with IBD have a higher risk for suffering from opportunistic infections.[99–101]

The immunosuppression resulting from these therapeutic agents requires us to take precautions by screening for

Table 2 Vaccination considerations in patients with inflammatory bowel disease.

Recommendations
Find the maximum benefit with minimum risk
Do not make assumptions about susceptibility or protection of the patient in regard to preventable infectious diseases
Titers to check at first office visit: MMR, VZV, HAV, and HBV
Perform immunization when the immune response is optimal
Two weeks before immunosuppressive therapy
After 3 months of having stopped immunosuppressive therapy
During low dose treatment
Adjust the prescription (special vaccination guidelines)
Avoid live-virus vaccines
When on immunosuppressive therapy
Within 3 months after cessation of therapy
Seroconversion should be assessed after vaccination
Annual anti-HBs levels should be measured
IBD control is always a priority over a vaccination program

MMR: measles, mumps, rubella; VZV: varicella zoster virus; HAV: hepatitis A virus; HBV: hepatitis B virus; anti-HBs: hepatitis B surface antibody.

various infectious diseases, such as tuberculosis, hepatitis B, HIV, and parasitic diseases.[32,33]

Based on the need for immunosuppressive therapy in IBD patients, experts recommend screening and vaccination at diagnosis.[45,46]

Tuberculosis

Screening must be carried out for both tuberculosis (TB) and latent TB, mainly before initiating treatment with anti-TNF-α agents.[55] Screening should be conducted based on epidemiologic factors, physical examination, chest radiography, and tuberculin skin tests or interferon-γ release assays (IGRA). Latent TB must be considered in the presence of a positive skin test or IGRA and no radiologic evidence of active disease. In cases of suspected latent TB, prophylactic treatment with isoniazid should be started to prevent an active infection, especially in those patients in whom infliximab is planned to be started.[102–104] The chemoprophylaxis regimen consists of isoniazid prescribed for a period of 6-9 months.[103–107] When active TB is suspected, treatment with infliximab must be discontinued until the diagnosis is ruled out or the infection has been treated with anti-tuberculosis agents. Treatment with anti-TNF-α agents should be delayed for at least 2 months after antituberculosis agent therapy has begun or ideally until full antituberculosis treatment is completed.[108,109]

Hepatitis B

All patients should be evaluated for HBV infection. The prevalence of HBV infection in patients with IBD is similar to that of the general population.[40,41,110] Serologic screening for hepatitis B should include HBsAg, anti-HBs, and anti-HBc. HBV-DNA quantification by PCR should be performed on patients with positive HBsAg. The HBV vaccine should be administered to all patients that are seronegative (anti-Hbs $-$, anti-HBc $-$). Current evidence has led to the consensus that IBD patients, including those with immunosuppressive therapy, benefit from vaccination, mainly at diagnosis.[51,54,111]

For those patients that are HBsAg positive, antiviral prophylaxis should ideally be started 2 weeks before the start of immunomodulatory treatment and it must be continued for 12 months after stopping treatment. It is well demonstrated that antiviral treatment started before the administration of immunosuppressive therapy reduces the risk for HBV reactivation.[112–114] Entecavir and tenofovir are the preferred antiviral agents because of their rapid onset of action, high antiviral potency, and low resistance rate.[115] Pegylated interferon α-2a has been associated with the exacerbation of CD and the risk for myelosuppression.[116]

Human immunodeficiency virus

Screening for HIV is recommended in patients with IBD prior to the start of immunosuppressive treatment by detecting p24 antigen and HIV antibodies, due to the consequences of immunosuppressive therapy in HIV-positive patients. Susceptibility to opportunistic infections in patients with IBD and HIV is higher in those with low CD4 counts.[117] Nonetheless, the use of these therapeutic agents is contraindicated in patients with HIV.[118–120]

Currently, there is no information on the effect of immune reconstitution after starting treatment with highly active antiretroviral therapy (HAART) in patients with IBD and HIV. Also, the possible interactions between HAART and immunosuppressive therapy in IBD are unknown.[121]

Parasites

In the IBD scenario, there is no evidence that the performance of a screening study in search of parasitic infection prior to the start of immunosuppressive treatment is necessary. However, in patients with a history of parasitic infections or those that have traveled to endemic areas, a screening study could be performed. Treatment with ivermectin or albendazole should thus be considered for patients with compatible symptomatology and positive serology in whom steroid administration is planned.[55]

20. *Specific anti-integrin molecules for the gastrointestinal tract (vedolizumab) have not shown an increased risk for opportunistic infections. The use of these molecules has not been associated with an increased risk for developing neoplasia (Level of evidence: 1. Level of agreement: 100%).*

Approved by the FDA in 2014, vedolizumab is the first humanized monoclonal antibody selectively directed against $\alpha 4\beta 7$ integrin, present only in the gastrointestinal tract T cells. Its main role is in the treatment of UC and CD refractory to standard treatment or anti-TNF therapy. It has shown efficacy in both the induction and maintenance of remission in IBD.[122–124]

Currently, the effectiveness and safety of this biologic agent has been demonstrated. Vedolizumab has not been

Table 3 Inflammatory Bowel Disease. Check list for the prevention of infections through vaccination.

Patient's name:_____ ID number: _____

1. Past medical history	YES	NO	Date (mm/yyyy)
HAV	☐	☐	
HBV	☐	☐	
HSV (cold sores, genital)	☐	☐	
VZV (chickenpox and/or shingles)	☐	☐	

2. Serology screening at first visit	YES	NO	Date (mm/yyyy)
MMR	☐	☐	
VZV (VZV IgG)	☐	☐	
HAV (HAV IgG/depends on area seroprevalence)	☐	☐	
HBV			
• AgHBs	☐	☐	
• Anti-HBs	☐	☐	
• Anti-HBc	☐	☐	

3. Vaccination scheme	YES	NO	Date (mm/yyyy)
Routine vaccination			
• Tetanus and diphtheria (Td)	☐	☐	
• Pertussis (Tdap)	☐	☐	
• Human papillomavirus	☐	☐	
Ideally at diagnosis (non-immunocompromised patients)			
• HBV vaccine (negative anti-HBs/anti-HBc patients)	☐	☐	
• VZV vaccine (seronegative patients)	☐	☐	
• MMR (seronegative patients; 6 weeks prior to immunomodulation therapy)	☐	☐	
• Influenza vaccine (annually)	☐	☐	
• Pneumococcal vaccine (based on patient age)			
< 50 years: PPSV23	☐	☐	
≥ 50 years: PCV13 followed by PPSV23 8 weeks later	☐	☐	

Table 3 (*Continued*)

If immunocompromised		
• Meningococcal vaccine (MCV4)	☐	☐
• H. influenzae type b vaccine (Hib)	☐	☐
Boosters		
Pneumococcal vaccine PPSV23 (single booster 5 years later)	☐	☐
HBV annual booster (if anti-HBs levels < 10 mIU/mL)	☐	☐
Meningococcal vaccine (MCV4 every 5 years)	☐	☐
4. Seroconversion after vaccination (mm/yyyy)	YES	NO Date
Quantitative anti-HBs (anti-HBs levels > 10 mIU/mL)	☐	☐
5. Additional considerations		
Cervical cancer screening		
• Refer the patient to gynecologist for cervical smear.		
Travel		
• Refer the patient to an international vaccination unit before traveling for adequate evaluation of health measures and state of immunocompetence. Specific vaccination recommendations should be in accordance with immunocompetence status, journey type, and destination.		
• Live attenuated vaccines (MMR and yellow fever) should be avoided in patients on immunosuppressive therapy.		
For further information go to:		
• http://wwwnc.cdc.gov/travel/yello wbook/2016/advising-travelers-with-specific-needs/immunocompromised-travelers		

HSV: herpes simplex virus; MMR: measles, mumps, rubella; VZV: varicella zoster virus; HAV: hepatitis A virus; HBV: hepatitis B virus; AgHBs: hepatitis B Surface Antigen; Anti-HBs: hepatitis B surface antibody; Anti-HBc: hepatitis B core antibody; PPSV23: pneumococcal polysaccharide vaccine; PCV13: pneumococcal conjugate vaccine.

shown to increase the risk for opportunistic infections or malignancies. However, long-term prospective studies are required to assess the possibility of increased prevalence of gastrointestinal infections and neoplasia related to its mechanism of action.[125,126]

21. *The use of type 5 aminosalicylates has not been associated with an increased risk for opportunistic infections (Level of evidence: 1. Level of agreement: 91%).*

Studies that have evaluated the effectiveness and safety of these drugs in IBD have not reported the occurrence of opportunistic infections.[127] A case-control study that analyzed the association between opportunistic infections and the use of specific immunosuppressants in IBD did not find any significant association between the use of 5-aminosalicylate drugs and the occurrence of opportunistic infections (OR: 1.0; 95% CI: 0.6-1.6; p = 0.94).[99]

Neoplasias

Skin cancer, lymphoma, and cervical cancer

22. *Thiopurine drugs increase the risk for skin cancer (non-melanoma) and the anti-TNF drugs have shown an increased risk for melanoma. Sunscreen and the (annual) monitoring*

of the skin by a dermatologist in all patients exposed to these drugs are recommended (Level of evidence: 2. Level of agreement: 100%).

In recent years, an increased risk for melanoma and non-melanoma skin cancer (NMSC) has been reported in patients with IBD, regardless of immunomodulatory therapy.[128]

Several studies have shown an increased incidence of NMSC in patients with IBD immunomodulatory treatment with thiopurines (azathioprine and 6-mercaptopurine), with an almost six times higher risk, compared with controls.[2–5] Recently, a meta-analysis concluded that patients with IBD and thiopurine therapy are at increased risk for developing NMSC (OR: 2.28; 95% CI: 1.50-3.45).[129]

It has been shown that patients with IBD (mainly CD) are at increased risk for developing melanoma, regardless of treatment with immunomodulatory agents.[130] Similarly, biologic agents, specifically anti-TNF-α, significantly increased the risk for melanoma.[131]

Based on the above, the implementation of a program of permanent sunscreen protection against ultraviolet radiation and dermatologic monitoring (by a gastroenterologist or a dermatologist) on a yearly basis, particularly in patients treated with thiopurine and biologic agents, is recommended. If possible, self-examination at home is recommended every 2-3 months.[132]

23. *The risk of lymphoma in patients that use thiopurine drugs is increasing (3-5/10,000). The risk in patients receiving anti-TNF monotherapy is at an intermediate range between the general population and those using thiopurine drugs (1-3/10,000). Combination therapy appears to increase the risk reported for thiopurine drugs alone (Level of evidence: 2. Level of agreement: 100%).*

Information from two of the largest studies, The UK General Practice Research Database Study[133] and The Swedish Study,[134] has shown that IBD alone does not increase the risk for developing lymphoma. In addition, multiple studies have shown an increased risk for developing lymphoma in the IBD patient population treated with thiopurines,[135–139] observing a relation to both drug dose and drug exposure time.[133,140] Reports describe a 4 to 6-fold increase in relative risk, as well as an absolute risk of 1 in 4,000-5,000 in patients between 20-29 years of age and of 1 in 300-400 in those 70 years of age and older.[141] A prospective study with 3 years of follow-up reported that older age, male sex, and further IBD progression are factors associated with an increased risk for lymphoproliferative disorders in patients treated with thiopurines.[135]

In patients treated with anti-TNF-α agents, the risk appears to be less clear.[142] However, it seems that the risk is lower compared with those treated with thiopurines. In fact, several reports show that isolated treatment with anti-TNF does not increase the risk for developing lymphoma.[143,144]

Regarding combination therapy, higher incidence was observed.[145,146] In a study of 16,023 patients with a mean follow-up of 5.8 years, 43 cases with development of lymphoma were reported. There was an increased risk in those with the combined use of anti-TNF-α and thiopurines, with an incidence of 113.8/100,000 patients/year.[146]

24. *Hepatosplenic T-cell lymphoma is a rare disease. On an individual basis, one might consider avoiding combination therapy (thiopurine and anti-TNF drugs) for periods over 2 years in male patients under 35 years of age (Level of evidence: 3. Level of agreement: 100%).*

Hepatosplenic T-cell lymphoma (HSTCL) is a rare form of lymphoma associated with a poor prognosis and often with a fatal outcome.[147] An increased risk for developing HSTCL has been reported in IBD patients that receive immunosuppressive therapy, especially those under combined treatment with thiopurine and anti-TNF-α agents for at least 2 years.[148–150] Up to 10% of all cases of HSTCL have been reported to have a causal association with the combined use of thiopurine and anti-TNF-α.[148]

Because of these findings and observations made on this population, in which younger male patients and those with CD have a higher risk,[148–151] combination therapy with thiopurine and anti-TNF-α (especially for prolonged periods, > 2 years) should be considered in this IBD patient subgroup only if a clear benefit is expected from this therapy.

25. *The use of immunomodulators might increase the risk for cancer of the uterine cervix (CUC) associated with human papillomavirus (HPV) infection. HPV vaccination in IBD patients (before the start of immunosuppressive therapy) and monitoring for CUC more regularly (at least every 12 months) is recommended (Level of evidence: 3. Level of agreement: 81%).*

HPV is the most common sexually transmitted infection worldwide.[59] It is known that HPV (mainly HPV-16 and 18) is significantly involved in the development of cervical and anogenital cancer. In women diagnosed with IBD receiving immunosuppressive therapy, a high prevalence of cytologic abnormalities, high-grade dysplasia, and cervical cancer has been described.[60–63]

For this reason, the administration of the HPV vaccine is recommended in patients with IBD, regardless of their sexual history.[54] Currently, there are two licensed vaccines for HPV prevention. The two inactivated virus vaccines for use in women are the bivalent (VPH2) and quadrivalent (VPH4) HPV vaccines, and one (HPV4) for use in men.

A complete series of either HPV4 or HPV2 consists of 3 doses at 0, 1-2, and 6 months. Both vaccines have proven to be effective and safe against HPV infection in immunocompetent patients.[64,65] We recommend administering HPV4 to all men and nonpregnant women with IBD between 9 and 26 years of age.[152,153]

The recommendations for the screening of CUC in immunocompromised women are the same as those for the general population,[154,155] but it is advisable that screening be done twice in the first year after IBD diagnosis.[156] Closer monitoring is recommended in women with abnormal Pap smear or cervical cytology findings.

Dysplasia and colorectal cancer

26. *There is an increased risk for colorectal cancer in patients with IBD, but not as great as previously reported. The risk is very similar in ulcerative colitis and CD of comparable duration and extension. In Latin America, there are no overall figures of incidence and prevalence (Level of evidence: 2 b. Level of agreement: 100%).*

In recent years, a progressive decrease in the increased risk for colorectal cancer in patients with IBD has been detected.[157–159] A retrospective study in 2006 revealed a

significant decrease in the incidence of cancer. This was replicated in other studies, and it has been suggested that it could be related to better inflammation control through the use of chemopreventive agents, such as aminosalicylates, and the effect of adherence to colonoscopy screening programs that offer colectomy to patients with dysplasia. Several studies have shown that the degree of colonic inflammation at the time of conducting the research is an important determining factor in the risk for colorectal neoplasia.[160]

27. *Colorectal cancer risk factors in IBD are: extent and duration of the disease, severity of inflammation, pseudopolyps, a family history of sporadic cancer, primary sclerosing cholangitis, and a history of colonic dysplasia (Level of evidence: 1 b. Level of agreement: 90%).*

Patients with pancolitis or colitis that extends proximally to the splenic flexure are at increased risk for developing colorectal carcinoma, and those with left-sided colitis have an intermediate risk.[159,161,162] The latter does not increase in patients with UC limited to the rectum. Histologic extension, even without visible endoscopic abnormalities, might also be an important determining factor for cancer.[163] The most consistently reported factors include primary sclerosing cholangitis, with a risk of up to 31%,[164,165] and histologic or clinical activity.[166] Post-inflammatory polyps can be markers of previous inflammatory severity and they may also be considered risk factors.[167] However, it is possible that this is related to dysplastic lesions misinterpreted as post-inflammatory polyps. Disease onset before 20-25 years of age might also be a contributing factor.[166,167]

28. *Colonoscopy screening allows for the detection of dysplasia and early colorectal cancer, which leads to a better prognosis. It should be performed 8-10 years after the onset of symptoms for all patients with extensive ulcerative colitis, and 12 years after left-sided colitis. In primary sclerosing cholangitis it should be performed from the time of diagnosis (Level of evidence: 5. Level of agreement: 91%).*

Colonoscopic surveillance in colitis is widely accepted in the attempt to prevent disease development and ensure early detection of cancer associated with colitis.[168,169] Surveillance is required in both ulcerative colitis and CD, since both represent a higher risk. The previous BSG guidelines recommend short surveillance intervals based on the duration of the disease, because risk is thought to increase exponentially, up to 18% at 30 years of age.[162] However, more recent data from London's St. Mark's Hospital suggest that risk may be linear or related to specific and more important factors. This has led to stratifying the risk for surveillance, and monitoring should be performed every year in higher-risk patients, such as those with primary sclerosing cholangitis or prior dysplasia, whereas low-risk patients, such as those with left-sided colitis and no swelling, can have 5-year monitoring intervals. Risk stratification is used in the BSG and ECCO guidelines. The combination of surveillance according to stratified risk and chromoendoscopy without stepped biopsies may be cost-effective.[170]

29. *The use of high definition endoscopy equipment for optimal detection of neoplasia is generally preferred. Pancolonic chromoendoscopy, preferably with indigo carmine, should be performed during colonoscopy screening, with targeted biopsies of a lesion (Level of evidence: 4. Level of agreement: 100%).*

Endoscopy equipment, preparation of the patient, and other diagnostic techniques have advanced considerably. High definition equipment provides better image quality and it may improve the dysplasia detection rate. In 2012, a surveillance study on colitis showed that high definition colonoscopy improved the detection of dysplasia compared with standard resolution.[168,171,172] In addition, a longer withdrawal period may be associated with an increase in dysplasia detection.[173]

30. *Other advanced imaging techniques, such as narrow band imaging or autofluorescence, have not proven to be superior to white light endoscopy or chromoendoscopy in detecting neoplastic lesions, and so are not routinely recommended for surveillance (Level of evidence: 2. Level of agreement: 100%).*

Narrow band imaging (NBI) is a type of technology that highlights the architecture of the crypts and vessels, but no randomized study using first[168,174] or second generation[175,176] endoscopes, including those of high definition, identifies any benefits in NBI for detecting dysplasia associated with colitis or for differentiating neoplastic from non-neoplastic mucosa,[177,178] compared with white light endoscopy.[174–176]

31. *For patients with flat unifocal low-grade dysplasia, the decision to perform colectomy or continue intensive monitoring should be an individualized one, involving the patient, the gastroenterologist, and the colorectal surgeon. Multifocal low-grade dysplasia (LGD) and multifocal high-grade dysplasia (HGD) confirmed by two expert pathologists are indicative of colectomy (Level of evidence: 2a. Level of agreement: 91%).*

High dysplastic lesions in a patient with colitis (formerly called a dysplasia-associated lesion or mass [DALM]) have been considered an indication for colectomy. In the context of surveillance, the term ''flat lesion'' has traditionally been used for endoscopically visible dysplastic lesions diagnosed through biopsies taken at random.

Both terms are confusing and should be abandoned, especially the term ''flat'', which now has a different endoscopic definition (Paris endoscopic classification).[179] It is preferable to use the description *endoscopically visible and macroscopically invisible lesions*, upon recognizing that the well-circumscribed visible lesions can be completely resected by endoscopy,[180,181] regardless of their location in areas with or without documented UC or the presence of LGD or HGD. This also applies to sporadic adenomas in the context of colitis.[182] If complete polypectomy is confirmed by histology and biopsies of the flat mucosa immediately adjacent to the site of the polypectomy and no dysplasia is found there, or anywhere in the colon, a colonoscopy follow-up should preferably be performed with chromoendoscopy 3 months before the annual recommended follow-up, because at least half of such patients can develop further lesions. However, a high cancer risk has not been detected during close surveillance,[183] as confirmed by a meta-analysis in 2013.[184] If the lesion is unresectable or is associated with dysplasia in the adjacent mucosa, colectomy is indicated due to the high risk for concomitant colorectal cancer.[185]

32. *Endoscopic resection and continuous monitoring are an appropriate management strategy for patients with sporadic adenoma and for those with a high-grade dysplastic lesion with no evidence of flat dysplasia around the lesion*

or elsewhere in the colon (Level of evidence: 2. Level of agreement: 91%).

Once detected, the subsequent management of dysplastic lesions depends on their origin in the flat or elevated mucosa. It is widely accepted that the detection of HGD in flat mucosa is an indication for emergency colectomy. The management of patients with LGD is controversial. Several studies have shown a variable rate of progression to HGD or colorectal cancer, ranging from 0 to 55% over a period of 5-10 years.[166,186]

Management options include increased surveillance or prophylactic colectomy, since 20% of patients will already have an unrecognized cancer. The decision to proceed with intense surveillance or colectomy must be made with the full commitment of the patient, the gastroenterologist, and the colorectal surgeon. Surgery should especially be considered for those patients with multifocal, LGD, or HGD identified on more than one occasion.

Pediatrics and inflammatory bowel disease

IBD has an incidence of 5 to 10 of every 100,000 children. There are racial/ethnic variations in the prevalence of the disease, mostly in Europe and North America, most likely due to globalization and industrialization.[187–189] IBD diagnosis is established in 10 to 25% of patients under 18 years of age. It may occur early in children (before 5 years of age) or late (6-18 years of age), but the most common age for onset is during adolescence.[190,191] IBD with onset at the pediatric stage has a different pattern and a more aggressive disease progression, compared with disease that begins in adulthood.[192]

Diagnosis

33. *The diagnosis of IBD in pediatric patients should be based on a combination of findings obtained through patient interrogation, physical examination, laboratory tests, imaging studies of the small bowel, endoscopy, esophagogastroduodenoscopy, and ileocolonoscopy, as well as histologic findings (Level of evidence: 1. Level of agreement: 100%).*

The cardinal symptoms of IBD are bloody diarrhea and abdominal pain. Systemic symptoms, such as fever or weight loss, fecal urgency, anorexia, anemia, and hypoalbuminemia may also appear. Symptoms can be ominous and even without apparent gastrointestinal involvement. The effect on the growth rate may be present before the abdominal symptoms, even up to 5 years prior, and this may be the only sign of disease in about 5% of patients.[193] There may be a delay of 6 to 24 months in the diagnosis of IBD in pediatric patients.[190]

34. *When IBD is suspected in children, both bacterial intestinal infections, including* Salmonella, Shigella, Yersinia, Campylobacter, *and* Clostridium difficile, *and parasitic infections must be ruled out (Level of evidence: 1. Level of agreement: 100%).*

Differential diagnosis must be performed with other diseases that show similar clinical and laboratory findings, such as infections, allergies, and neoplasia. The most frequent differential diagnoses are those for viral, bacterial, and parasitic infections.[194] Allergic colitis can mimic UC, particularly in infants and preschoolers. Eosinophilic gastroenteritis can mimic CD with ulceration.[195]

Laboratory studies that should be ordered as part of the approach include a complete blood count with platelet count, erythrocyte sedimentation rate, C-reactive protein (CRP), total protein, serum albumin and globulins, immunoglobulins, stool analysis, ova and parasite exam with 3 samples, *Salmonella*, *Shigella*, *Yersinia*, and *Campylobacter* cultures, and determination of toxins and culture for *C. difficile*.[194,196,197] ASCA, ANCA and pANCA serologic studies can support the diagnosis, but if they are negative that does not rule out the disease.[194]

35. *Candidates for endoscopic procedures to confirm IBD diagnosis in pediatric patients can be determined through fecal calprotectin levels as a non-invasive biomarker (Level of evidence: 2. Level of agreement: 100%).*

Fecal calprotectin is a surrogate marker of neutrophil flow in the intestinal lumen, as well as a noninvasive IBD diagnostic test. Its measurement may identify which patients are candidates for an endoscopic evaluation, with values equal to or greater than 212 μg/g.[198,199] In addition, measurement of the levels of fecal calprotectin is a useful indicator of disease activity in pediatric patients already diagnosed with IBD.[192]

36. *To establish the severity of UC in pediatric patients, the Pediatric Ulcerative Colitis Activity Index (PUCAI) should be used at the beginning of the evaluation, as well as at the follow-up. In the case of CD in pediatric patients, the Pediatric Crohn's Disease Activity Index (PCDAI), or its abbreviated version, should be used at both the baseline and follow-up evaluation (Level of evidence: 2. Level of agreement: 100%).*

The pediatric ulcerative colitis activity index (PUCAI) is a validated clinical outcome measure developed to standardize the reporting of disease activity in UC in the pediatric population.[200,201] The pediatric Crohn's disease activity index (PCDAI) was developed for use in the development and standardization of new therapies in pediatric populations. However, its usefulness in this field has recently been questioned and consequently is now unclear in relation to the assessment of disease severity and response to treatment in the clinical setting.[202–204]

Perianal complications of CD in children are common, and they occur in up to 38% of pediatric cases with CD, which may result in significant morbidity when not precisely characterized before surgery. The successful assessment of perianal fistula images is essential in the evaluation and management of perianal disease. Magnetic resonance imaging is the technique of choice for children because of the lack of ionizing radiation, for addressing the perianal complications, as well as for the general management of patients with IBD.[205,206]

Treatment

Just as with adults, the response to management in children is variable.[182] The selection of treatment management for inducing remission and maintenance depends on disease activity. The ''step-up'' treatment schedule is generally well-accepted. Many patients will require escalation in early treatment due to a more severe form of the disease.[192]

Management includes both drugs and nutritional treatment. The drugs used are divided into six categories: aminosalicylates, corticosteroids, immunomodulators, antibiotics, probiotics, and biologic agents.

37. *Exclusive enteral nutrition may be considered a first-line treatment for inducing remission in pediatric patients with CD, given its similar effectiveness to that of steroids, but without the adverse events in relation to growth (Level of evidence: 2. Level of agreement: 83%).*

In children with CD, exclusive enteral nutrition (EEN), meaning exclusive administration of either an elemental or polymeric nutritional formula (with the elimination of the current diet), is considered a first-line therapy for inducing remission. This is due to success rates: they are similar to those obtained with the use of steroids, but with numerous advantages, since EEN reduces steroid use and prevents adverse effects.[194,207–211] However, the effect is not lasting and maintaining remission with drug treatment must be considered.

On the other hand, EEN has a positive impact on mucosal cytokine profiles. It actively reduces intestinal inflammation and enhances recovery of bone metabolism.[211,212] As for the type of formula to be chosen, there are no significant differences between the effects of elemental versus non-elemental (peptide and polymer) formulas. The semi-elemental and elemental formulas are generally not recommended.[213] Enteral nutrition may also have a beneficial effect on patients with stenosis of the small intestine, and those with perianal fistulas. In addition, it may be used as adjunctive therapy to immunomodulators and biologic agents in patients with refractory CD. In different studies, the duration of EEN therapy used for inducing remission varies from 6 to 10 weeks.[211]

38. *The treatment of choice for induction of remission in pediatric patients with mild-to-moderate UC is with aminosalicylates or prednisolone (Level of evidence: 2. Level of agreement: 100%). The treatment of choice for induction of remission in pediatric patients with serious UC is intravenous corticosteroids (Level of evidence: 2. Level of agreement: 100%).*

To induce remission in pediatric patients with moderate-to-severe CD, the use of oral prednisone/prednisolone as monotherapy may be considered, if exclusive enteral feeding is not an option.

Regarding drug therapy in remission induction, aminosalicylates, such as 5-ASA, are the first line of treatment for mild-to-moderate UC. Higher doses may be considered in more prolonged or more severe disease. The use of topical therapy is not usual because proctitis is uncommon in UC in the pediatric population.[192] Glucocorticoid use is indicated in patients with severe UC, and has been shown to be initially effective in 70 to 90% of cases; 50% will be steroid-dependent with consequent deleterious effects on growth, so that, ideally, this treatment should not be maintained and immunosuppressive therapy or biologic drugs should be used.

39. *The treatment of choice for the induction of remission in pediatric patients with mild-to-moderate UC is low-dose aminosalicylates or azathioprine (Level of evidence: 2. Level of agreement: 100%). The treatment of choice for maintaining remission in pediatric patients with severe UC is with thiopurines, such as azathioprine or 6-mercaptopurine (Level of evidence: 2. Level of agreement: 100%). The treatment of choice for maintaining remission in pediatric patients with severe UC is with thiopurines (azathioprine or mercaptopurine) and free from steroids. Thiopurines are not indicated for the induction of remission (Level of evidence: 2. Level of agreement: 100%).*

In UC and CD remission maintenance, aminosalicylates are the first-line therapy. However, a large number of patients will require immunomodulators, such as azathioprine or mercaptopurine, as a maintenance therapy, especially for patients that are steroid-dependent, intolerant to aminosalicylates, or those that have frequent relapses.[192] The evaluation of thiopurine metabolites enables toxicity monitoring and treatment optimization in non-responders in pediatric patients with IBD.

40. *Treatment with anti-TNF agents in patients with UC should be considered for refractory or steroid-dependent patients. Step-down management may be considered with anti-TNF in thiopurine-naïve patients (Level of evidence: 1. Level of agreement: 100%). Management with anti-TNF agents may be considered for induction therapy in pediatric patients with CD, regardless of whether they have previously received immunomodulatory therapy, as well as in steroid-refractory disease (Level of evidence: 1. Level of agreement: 100%).*

The use of anti-tumoral necrosis factor alpha (anti-TNF-α) biologic drugs is usually indicated for patients that are refractory to steroids or for steroid-dependent patients. Infliximab's effectiveness is confirmed for the treatment of moderate-to-severe disease in the pediatric population with or without the combination of immunosuppressive therapy.[214–218] Adalimumab has been shown to be efficacious in pediatric CD patients and non-responders to infliximab and may also be used in pediatric patients that have never received treatment with infliximab to induce remission.[219–222] There is some evidence that the combination of adalimumab with an immunomodulator for at least 6 months of treatment has the effect of reducing both the failure rate for adalimumab and the need for dose escalation.[223,224]

Given the more common characteristics of severity in the pediatric population, the step-down scheme is increasingly used and probably with better results if pediatric CD patients are initially treated with anti-TNF-α, although there is still little evidence to recommend its widespread use.[192,225]

41. *Surgical treatment during UC should be considered in pediatric patients when the disease is limited to the distal ileum and they show impaired growth despite optimal treatment or in cases of refractory disease (Level of evidence: 2. Level of agreement: 100%).*

Surgical treatment must be considered during the course of severe UC in pediatric patients when they do not tolerate or accept treatment with corticosteroids, or when there is no improvement after 72 hours from treatment commencement.[192]

42. *There is insufficient evidence for recommending the use of probiotics in the management of pediatric patients with IBD (Level of evidence: 1. Level of agreement: 100%).*

Several studies show the benefits of certain probiotics against pouchitis and UC, but they do not show efficacy in the management of CD.[226,227]

There is evidence from randomized controlled trials that the *E. coli* Nissle 1917 (EcN) strain has similar effectiveness to mesalazine in maintaining remission in adult patients with mild-to-moderate UC.[228] The usefulness of the probiotic product, VSL#3, for the induction of remission and maintenance in UC has also been confirmed in pediatric patients.[229]

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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José Antonio Chávez Barrera, Head of the Department of Pediatric Gastroenterology of the *UMAE Hospital General Centro Medico La Raza, IMSS*.

Jorge Chávez Sáenz, Head of the Pediatric Gastroenterology and Nutrition Service of the *Hospital General de Occidente, Secretaría de Salud*.

Sergio Javier Fernández Ortiz, Pediatric Gastroenterologist and Nutritionist, Coordinator of the Pediatric Service of the *ISSSTELEON*.

Erick Toro Monjaraz, Staff Physician of the Department of Gastroenterology and Nutrition of the *Instituto Nacional de Pediatría*.

Alejandra Consuelo Sánchez, Staff Physician at the Department of Gastroenterology and Nutrition of the *Hospital Infantil de México Federico Gómez*.

José Antonio Chávez Barrera, Head of the Department of Pediatric Gastroenterology of the *UMAE Hospital General Centro Medico La Raza, IMSS*.

Jorge Chávez-Sáenz, Head of the Department of Pediatric Gastroenterology and Nutrition of the *Hospital General de Occidente, Secretaría de Salud*.

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