SECOND EUROPEAN EVIDENCE-BASED CONSENSUS ON THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF OPPORTUNISTIC INFECTIONS IN INFLAMMATORY BOWEL DISEASE
3.1. Hepatitis C virus infection

3.1.1. Background

The hepatitis C virus (HCV) is a hepatotropic RNA virus that belongs to the family flaviviridae. In Europe it is estimated that 0.2–2% of the population is infected with HCV. In most cases transmission of hepatitis C virus occurs parenterally. Sexual, perinatal, and sporadic transmission are reported, but infrequent. Acute HCV infection is often asymptomatic without jaundice. Chronic HCV infection develops in about 85% of all cases. Among patients with chronic HCV infection, 20% develop liver cirrhosis within 20 years of disease duration, with a high rate of hepatocellular carcinoma (1–2% per year).

3.2. Hepatitis B virus (HBV) infection

3.2.1. Background

Hepatitis B (HBV) virus is a hepatotropic DNA virus belonging to the Hepadna virus family. HBV is transmitted parenterally, sexually, and perinatally. The rate of progression from acute to chronic hepatitis B depends largely on the age of infection. It is estimated at 90% for infection acquired perinatally, 20–50% at age 1–5 years and 5% for infection acquired during adulthood. [48, 49, 50, 51] The early phase of chronic HBV infection features high viral replication associated with active liver disease, while the later, low replicative phase is characterised by remission of overt liver disease. In contrast, patients with perinatal HBV infection exhibit another clinical course during their early decades, with active viral replication and the absence of hepatic injury, which is considered an immunotolerant phase of disease. It is important to note that even in patients who recover from acute hepatitis B, HBV DNA is still detectable in the hepatocytes of most patients. [52] In some of these patients traces of HBV DNA are detectable in peripheral blood many years after resolution of acute hepatitis B. [53, 54] A flare of HBV infection or reactivation refers to an abrupt increase of transaminases and reappearance of high levels of HBV DNA in patients with chronic hepatitis B. Reactivation reflect an increase in the immune response against HBV, which might explain why flares of disease may frequently appear after immunosuppressive therapy withdrawal (e.g. corticosteroids or cytotoxic agents). HBV reactivations in immunosuppressed patients have been associated with hepatic decompensation in a considerable proportion of cases.

3.3. Human immunodeficiency virus (HIV) infection

3.3.1. Background

The human immunodeficiency virus (HIV) belongs to the human retrovirus family. The hallmark of HIV is transcription of its genomic RNA to DNA by an enzyme called ‘reverse transcriptase’. Infection is mediated by binding of viral gp120 to the CD4 co-receptor that is expressed on the surface of CD4+ T helper cells, monocytes/macrophages and dendritic cells. Certain co-receptors such as CCR5 and CXCR4 are mandatory for viral entry. The consequence is a progressive quantitative and qualitative deficiency of T-helper cells and a subsequent impairment of T-cell mediated immune responses. If T-helper cell concentrations ultimately decline below a certain threshold, patients are at high risk of developing opportunistic diseases, including infections and malignancies that are AIDS defining illnesses. Transmission of HIV occurs by homo- or heterosexual contact, blood or blood products and by infected mothers to their infants, whether intrapartum, perinatally, or via breast
feeding. The clinical manifestations of HIV infection comprise a broad spectrum from an acute HIV syndrome associated with primary infection, to a prolonged phase of clinical latency, to the state of symptomatic advanced disease. Thanks to highly active anti-retroviral therapy (HAART), viral replication can be effectively suppressed, so that an almost normal immune status can be regained in HIV-infected patients.

4. Herpesviruses (HSV, VZV, EBV, CMV), human papilloma virus, and influenza virus

4.1. Cytomegalovirus (CMV) infection

4.1.1. Background
The majority of primary infections with CMV are asymptomatic. Clinically apparent infections may present as a mononucleosis-like syndrome, but can affect virtually any organ. [90, 91] Although CMV may persist in a latent form after primary infection, development of severe CMV-related disease during or after immunosuppressive therapy is rare in IBD. In IBD colitis CMV remains in the colon after a severe flare-up despite remission suggesting that the virus might not be responsible for disease flare-up. [92] There is, however, a risk of hepatitis, colitis, oesophagitis, pneumonia, encephalitis or retinitis. [90, 93] Although CMV has a world-wide distribution, the prevalence of CMV is higher in developing countries, or areas with poor socioeconomic conditions. This is probably related to closer physical contact, since CMV is transmitted via close personal contact with affected persons excreting the virus in their body fluids, or shedding from throat or uterine cervix. [91] Ten to twenty % of children are infected with CMV before puberty and CMV seroprevalence increases after infancy to 40–100% in adults.[91, 94] In IBD patients prevalence rate of CMV ranged from 10% to 43% according to the diagnostic method [95, 96, 97] but in steroid-refractory patients studies have reported consistent detection of CMV by IHC in 20-67% of both endoscopic and colectomy species. [97, 98, 99, 100, 101, 102]

CMV colitis mimicking an acute exacerbation of ulcerative colitis (UC) or Crohn’s disease (CD) is associated with a poor outcome and a higher colectomy rate. [103, 104, 105] Determination of high levels of CMV DNA in the blood may help identify patients with CMV colitis.

4.2. Herpes simplex virus (HSV)

4.2.1. Background
Herpes simplex virus type 1 (HSV-1) is implicated in most cases of orofacial herpes and type 2 (HSV-2) still predominates in genital herpes. [115, 116] Both primary infection and subsequent reactivations are frequently subclinical, with viral shedding facilitating transmission to intimate contacts. [115] HSV can cause severe disease in immunocompetent individuals including keratitis, encephalitis and retinitis. [115] Following primary infection, HSV-specific IgG may not appear for many months and does not prevent recurrent disease. [116] Cell mediated immunity appears to be the dominant process for controlling viral replication. [117] The worldwide seroprevalence of HSV-1 by the fourth decade is 45–98%. [115] HSV-2 seroprevalence correlates with age and gender (higher in women), rising with initiation of sexual activity in adolescence and increasing through adulthood. [116]

4.3. Varicella zoster virus (VZV)
4.3.1. Background

Primary VZV infection is nearly always symptomatic causing chickenpox (varicella), characterised by fever and generalised vesiculopustular rash. [140] Chickenpox is not severe in most children, but may be life-threatening in adults, with the risk of potentially fatal pneumonitis especially in late pregnancy. [140, 141] Latent VZV persists lifelong in dorsal root ganglia with the potential for clinical reactivation, manifest as shingles (zoster). [140, 142] Shingles presents as a painful, unilateral, vesicular rash distributed in one or more contiguous dermatomes. [140, 142]

A negative history of chickenpox is unreliable; most individuals prove to be VZV IgG-positive on testing. In contrast, a history of chickenpox (or shingles) has a high positive predictive value for immunity in temperate countries, eg Belgium and Ireland, where the adult seroprevalence exceeds 90%. [143, 144] History is less reliable for individuals raised in tropical or subtropical climates (e.g. sub-Saharan Africa, South India, West Indies) with a mean age of infection in early adulthood. [145, 146]

4.4. Epstein–Barr virus (EBV)

4.4.1. Background

EBV is ubiquitous. Primary infection may be delayed, with as many as 40% early adolescents still susceptible in resource-rich settings, but ultimately over 90% of adults worldwide are infected. [171, 172] The spectrum of primary infection disease ranges from a clinically unapparent infection to a devastating, or even fatal, illness. The age of the patient is important: usually asymptomatic in young children, primary infection causes infectious mononucleosis or “kissing disease” in 57-75% susceptible adolescents/young adults. [171, 172] Typically infectious mononucleosis presents with sore throat, fever, and lymphadenopathy. Mild hepatitis is common and there may be jaundice, hepatomegaly and/or splenomegaly. Red maculopapular rash can occur without antibiotic therapy. Typically the lymphocyte and/or monocyte counts are increased with atypical lymphocytes on blood film. The acute features resolve over 3-4 weeks, but fatigue very often persists, lasting for a median of 8 weeks. [171] The vast majority of patients recover uneventfully without significant complications. Fatalities (<1:3000) cases are usually associated with an underlying immunological deficiency but may also be associated with splenic rupture, airway obstruction, haemophagocytic syndrome or neurological complications.

After primary infection, EBV persists lifelong in latently-infected circulating B-lymphocytes. [171, 172] Frequent asymptomatic reactivation with salivary shedding facilitates transmission to intimate contacts. Seropositive status, with detectable EBV IgG indicates prior infection.

EBV is implicated in the pathogenesis of various non-Hodgkins and Hodgkins lymphomas and carcinomas, especially in the immunocompromised. [172, 173]

4.5. Human papilloma virus (HPV)

4.5.1. Background

Human papillomavirus (HPV) is the most common sexually transmitted infection in the world. [193] The distribution varies widely, depending on gender (higher in women than in men), geographical region (higher in
poor countries), age, sexual behavior and viral type, as well as the methods and site of detection. [194, 195] About 40 types of HPV are sexually transmitted. They are classified into low-risk types, associated with anogenital warts or mild dysplasia, and high-risk types associated with high-grade dysplasia and anal neoplasia (cervical and anal carcinoma). [196, 197] Cutaneous warts are also caused by HPV.

4.6. Influenza virus

4.6.1. Background

There are two types of influenza virus that cause human epidemics: type A and type B. Influenza virus A is divided into subtypes, of which H1N1 and H3N2 are circulating globally. [223] Infection with influenza is associated with mortality, depending on risk stratification. [224]

5. Parasitic and fungal infection

5.1. Background and impact of immunomodulator therapy on natural history of the disease

Safety data from 6 global clinical trials studying the effect of adalimumab on CD resulted in 3402 patient-years of exposure [243] two opportunistic infections per 100 patient-years occurred (1.8% prevalence), mainly localized fungal infection with Candida sp and only one case of Coccidioidomycosis. Case-reports describe fatal outcomes of invasive fungal infections in IBD patients under immunosuppressive therapy. [244, 245, 246, 247] A recent retrospective cohort study of more than 100,000 IBD patients in the USA resulted in an increased risk of P. jiroveci pneumonia in IBD patients with an overall hazard risk of 2.96 and even 4.01 for Crohn’s disease patients, the majority (53%) taking corticosteroids alone or in combination with other immunosuppressants. [248]

Fungi are found in soil or farm dust. Some appear ubiquitous (Aspergillus spp., Candida spp.), while others are associated with animals (C. neoformans in pigeon droppings) and some, such as H. capsulatum and Coccidioides, are geographically distributed, known as endemic mycosis, the first in the southern United States or Central Africa and the second on parts of United States of America, Mexico and Central and South America. Parasites are more commonly associated with endemic areas and gastroenterologists should be aware of travel to, or from, the tropics and the sub-tropics, where for example S. stercoralis is patchily endemic. There are, however, no vaccines for fungal or parasitic infections, so preventive measures depend on making immunocompromised individuals aware of the risks. General advice includes avoiding farms, pigeon lofts, or an extended duration of stay.

6. Mycobacterium tuberculosis infection

6.1. Background

The incidence of tuberculosis (TB) is a concern at the start of the third millennium, particularly with the increase of multiresistant (MDR-TB) and extended resistant (XDR-TB) Mycobacterium tuberculosis. More than 80% of tuberculosis diagnosis in the United States is due to reactivated latent infection. [257, 258] The infection
is more prevalent in developing countries, but migration, together with the HIV pandemic (an important reservoir for TB) have increased concerns of TB in economically-developed areas. [259, 260] In the pre-biologic era patients with IBD appeared to be at higher risk of TB than the general population due to immunomodulators. [261] Anti-TNF therapy further increases the risk of TB infection. When TB occurs in patients on anti-TNF therapy it is more commonly atypical, extrapulmonary and disseminated, making the diagnosis more difficult. Mortality in patients with TB during anti-TNF therapy has been reported to be up to 13% [262, 263, 264, 265, 266] but in a recent case-control cohort was similar to background population.

7. Bacterial infection

7.1. Streptococcus pneumonia infection

IBD patients on immunomodulators are considered to be at high risk for pneumococcal infections. [227, 243] In cohort studies bacterial pneumonia is one of the most prevalent infections in IBD patients on immunomodulators. [293, 294] Invasive infection with S. pneumoniae related to immunomodulators in IBD has been reported. [295]

7.2. Legionella pneumophila infection

Immunomodulator therapy is considered a high-risk condition for infection with L. pneumophila. [312] Concomitant treatment of immunosuppressives and anti-TNF agents is a major risk factor for the development of L. pneumophila infection, which should be ruled out in all cases of pneumonia. [313] Invasive L. pneumophila infections, some with fatal outcome, in patients on immunomodulators for IBD or rheumatological patients have been reported. [314, 315, 316, 317, 318] Fulminant legionellosis [319] and L. pneumophila pneumonia in pregnancy treated with anti-TNF-α antibodies for CD was also reported. [320] In the majority of those case series infection occurred early within the first months of immunomodulator/anti-TNF-α treatment.

7.3. Salmonella species infection

S. enteritidis and S. typhimurium are the most common serotypes. [325, 326] Invasive Salmonella spp infection, some with fatal outcome related to immunomodulator therapy for IBD or rheumatologic patients have been reported. [315, 317, 327, 328, 329, 330, 331, 332] Early infection starts within the gastrointestinal tract, but patients may present with symptoms of disseminated infection such as sepsis, meningitis, urinary tract infection, or reactive arthritis. [325] Prevention consists of food hygiene: advise immunocompromised patients to avoid the consumption of raw eggs (fresh mayonnaise), unpasteurised milk and undercooked or raw meat (including carpaccio). Extra caution when visiting farms and contacting farm animals, including animals at petting zoos should be taken. Definitive diagnosis of enteric fever is made by isolating S. typhi or other Salmonella sp. from blood, stool, or urine.
7.4. Listeria monocytogenes

Immunomodulator therapy is considered a high-risk predisposing condition for infections with L. monocytogenes. [336] In particular, anti-TNFα treatment appears to carry a particular risk for serious infection compared to other immunomodulators. [315, 337, 338, 339, 340, 341, 342, 343] Prevention consists of food hygiene: avoid soft or unpasteurized cheese, unpasteurised milk, undercooked meat and raw vegetables, especially during pregnancy. [336, 343] Diagnosis is made by appropriate microbiological culture. Early infection starts within the gastrointestinal tract. A high index of suspicion in patients on immunomodulator therapy who present with signs of meningitis or other neurological symptoms is appropriate, with intensive investigation including lumbar puncture as soon as such symptoms develop. [343] When patients have meningoencephalitis without initial proof of Listeriosis, the pathogen should still be covered by the antibiotic regimen.

7.5. Nocardia species

Nocardia species are aerobic Gram-positive, weakly acid-fast actinomycetes. They are ubiquitous soil organisms, responsible for local skin infections through direct contact, or necroising pulmonary infections through inhalation. Haematogenous dissemination to the brain occurs in up to one third of all cases, most of which occur in immunocompromised host. [344] Nocardia species infection is increasingly found in the immunocompromised patient. IBD or rheumatologic patients on immunomodulator therapy are considered at risk. Cutaneous, hepatic, pulmonary, or neurologic infections in patients on corticosteroids or anti-TNFα treatment have been reported. [315, 327, 345, 346, 347, 348, 349, 350, 351, 352] The prevention of cutaneous Nocardia sp. infections consists of skin hygiene, avoiding soil-infected skin lesions and avoiding inhalation of soil-contaminated dust. [344] Nocardia sp. can be diagnosed rapidly by examination of sputum, pleural, or bronchial lavage fluid by Gram stain and a modified acid-fast stain. Long-term culture up to six weeks is necessary to grow the pathogen.

7.6. Clostridium difficile infection

C. difficile is a Gram-positive anaerobic spore-forming bacterium whose effects range from asymptomatic carriage to fulminant colitis. [353, 354] C. difficile spores are transmitted by fecal-oral route. The pathogenicity is dependent on toxin production: toxin A (enterotoxin) and B (cytotoxin). Other emergent hypervirulent pathogenic strains, producing an ADP-ribosylated binary toxin (toxin C) and characterized by high-level fluoroquinolone resistance, may play a role in the changing epidemiology of the infection. [355, 356] C. difficile -associated disease (CDAD) typically presents with watery diarrhoea, malaise, abdominal pain, fever, or leukocytosis. [357, 358] The increasing incidence of CDAD is well recognized both in the general population and in patients with active and non-active IBD. [353, 359, 360, 361, 362, 363, 364] A study reported a significant rise of C. difficile infection in IBD patients, from 1.8% in 2004 to 4.6% in 2005. [365] The adjusted odds ratio for the development of CDAD was 2.1 for CD (95% CI 1.3–3.4), 4.0 for UC (95% CI 2.4–6.6) and the diagnosis of IBD was an independent risk factor for CDAD. [366] Significant and temporal rises in hospitalization for IBD complicated by CDAD have also been reported, including prolongation of hospital stay,
increase in colectomy and mortality risks. [367, 368] The prevalence of C. difficile infection among hospitalized IBD patients between 1998 and 2004 was in UC 3.7%, in CD 1%. [369, 370] In patients with IBD relapse, the incidence of CDAD was 3-7% for UC and 7-9% for CD, while in children was 26%.

8. Special situations

8.2.1. Background

Traveller's diarrhoea, which may be severe and incapacitating, is the most common health problem reported during travel to developing countries. [421] The duration is usually 1 to 5 days, but 5–10% of travellers report diarrhea that lasts for 2 weeks or longer, and 1–3% report diarrhea that lasts four weeks or longer. [422] Two case-control studies, reviewed above in section 8.1.3, did not reveal a higher rate of traveler diarrhea among IBD patients compared to healthy controls. However, this common disease, particularly if prolonged, may lead the traveller or the clinician to a wrong diagnosis of an exacerbation of IBD and to unnecessary self-treatment with IBD medication. Nevertheless, infection with enteropathogens may provoke a relapse of quiescent IBD. Furthermore, travellers being treated with immunomodulators are at greater risk for acquiring food- and water-borne Salmonella sp., Cryptosporidium parvum, Isospora belli, Microsporidia, or Cyclospora sp. infection. For these reasons, patients with IBD should pay greater attention to precautions regarding food and water. Cryptosporidium is resistant to chlorination or iodination and prevention requires use of either boiled or filtered water or commercially bottled beverages. Travellers are also best advised to avoid swallowing water while swimming in water that may be contaminated.

8.2.2. Treatment and self-treatment

Travellers to developing countries are often advised to carry a fluoroquinolone for empirical self-treatment of traveller's diarrhoea. Azithromycin, which was found to be comparable to quinolones [423] should be considered for self-treatment of traveller's diarrhoea in the following situations:

(i) patients who take a fluoroquinolone as part of their treatment for IBD
(ii) Travellers to countries where endemic bacteria are known to have high levels of fluoroquinolone resistance (e.g. Thailand and India)
(iii) Patients who have no response to a quinolone within 36–48 h
(iv) Pregnant women and children <16 years (for whom a fluoroquinolone is contraindicated).

Rifaximin, an oral, nonabsorbed rifamycin antibiotic, was approved for the treatment of traveller's diarrhoea caused by non-invasive strains of E. coli. Rifaximin should not be used in patients with bloody diarrhoea or fever suspected of having traveller's diarrhoea due to pathogens other than E. coli since rifaximin lacks efficacy against invasive pathogens (e.g. Shigella, Salmonella, and Campylobacter sp.). Since IBD travelers may have more difficulty in distinguishing by symptoms invasive from non-invasive enteric pathogens, empirical selftherapy with rifaximin cannot be advocated at this stage. The immunocompromised traveller should have a lower threshold than immune competent travellers for initiating self-therapy for traveller's diarrhoea. If diarrhoea persists despite antimicrobial treatment efforts should be made to obtain a stool examination for ova and parasites.
8.4. Malaria

Unless pregnant, asplenic, or concomitant HIV infection, patients with IBD appear not to be at higher risk for acquiring malaria or the more severe complications of malaria compared to travellers without IBD, even when taking immunomodulators. Recommendations for malaria prevention, including prevention of mosquito bites and chemoprophylaxis, should be followed according to the existing guidelines. Interactions between antimalarial drugs and drugs for the treatment of IBD, particularly those that are new, should be taken into consideration. Metoclopramide decreases absorption of atovaquone (one of the demi-drug components of the anti-malarial drug Malarone) and may decrease the prophylactic efficacy.

8.5. Prevention of insect bites

Immunocompromised IBD travellers should take extra precautions to prevent bites of insects that are known to transmit diseases that are particularly severe in immunocompromised patients. Examples include reduviid bugs in rural Brazil and sandflies on beaches and rivers in exotic locations, which are the vectors of Chagas’ disease and visceral leishmaniasis respectively. Patients taking immunomodulators should also be aware that infestation with scabies may lead to a severe variant (Norwegian, or crusted scabies) that is often complicated by secondary bacterial infection.
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