BSPGHAN
working for children with digestive and liver disorders
British Society of Paediatric Gastroenterology Hepatology and Nutrition

Infection screening and vaccination guidance in PIBD

Screening for common and or serious infections is an essential part of PIBD care. The increased infection risk for PIBD patients is explained by the underlying immune dysregulation and other factors such as malnutrition which contribute to a perturbed immune response. The use of immunomodulatory medicines however constitutes the main cause of immunocompromise in children with IBD. Immunomodulators used in IBD are corticosteroids, thiopurines (Azathioprine or 6-mercaptopurine), methotrexate, calcineurin inhibitors (e.g. tacrolimus), anti-tumor necrosis factor agents (infliximab or adalimumab), or other biologics. The risk for infection is higher for patients on combination therapy. Patients with early-onset IBD may suffer from primary immune deficiencies with IBD-like phenotype and should be identified and treated accordingly (see separate PIBD Working Group BSPGHAN Statement).

Infections discussed in this statement:

No	Microbe	Routine serological screening available	Vaccine available	Type of vaccine
1	Varicella-Zoster virus	yes	yes	Live-attenuated
2	Mumps/Measles/Rubella virus	yes	yes	Live-attenuated
3	Mycobacterium tuberculosis	yes	yes	Live-attenuated
4	Influenza virus	no	yes	Non-live (injection)/Live-attenuated (nasal)
5	Hepatitis B virus	yes	yes	Non-live
6	Human papilloma virus	no	yes	Non-live
7	Streptococcus pneumoniae	no	yes	Non-live
8	Hepatitis C virus	yes	no	N/a
9	Herpes Simplex virus	no	no	N/a
10	Epstein-Baar virus	yes	no	N/a
11	Cytomegalovirus	yes	no	N/a
12	Human immunodeficiency virus	yes	no	N/a
13	Pneumocystis jiroveci	no	no	N/a

Vaccination in PIBD

In general, children with IBD should be vaccinated according to the latest UK vaccination schedule (www.dh.gov.uk/greenbook). It is common practice for PIBD centres across the UK not to give live-attenuated vaccines once a patient started on immunosuppressive therapy in line with previous European and UK IBD guidance. Children are more likely to present with extensive disease requiring early treatment escalation compared to adults with IBD which means that the window of opportunity for live-attenuated vaccination is small.

According to latest guidance published in The Green Book, Part 1, Chapter 6 however, live-attenuated vaccinations can be safely given to patients on immunosuppressive therapy providing the following criteria are fulfilled:

Green Book, Part 1, Chapter 6

(www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6)

Long term stable low dose corticosteroid therapy (definition: up to 1mg/kg/day in children under 20kg body weight or up to 20mg/day in children above 20kg body weight for more than 14 days), either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. MTX up to 15mg/m^2 per week, azathioprine up to 3mg/kg/day or 6-mercaptopurine up to 1.5mg/kg/day) are not considered sufficiently immunosuppressive and these patients can receive live vaccines.

The BSPGHAN IBD working group appreciates that this new approach to live-attenuated vaccination will be implemented inconsistently across the UK and it ultimately remains at the physicians' discretion whether to follow the recommendations outlined above (Green Book, Part 1, Chapter 6). We advocate that, if clinically feasible, newly diagnosed patients with IBD complete live-attenuated vaccine schedule four weeks prior to initiating immunosuppressive therapy. Physicians can still consider live vaccines for patients on immunomodulation providing the criteria above are fulfilled (Green Book, Part 1, Chapter 6).

Infections:

1. Varicella zoster virus (Screening: VZV IgG):

Patients without a clear history of chickenpox/shingles should be tested for VZV IgG. The working group advocates a low threshold for screening if in doubt. Receipt of two doses of varicella vaccine is considered sufficient. VZV IgG testing to confirm vaccine response is not predictive of immunity (www.dh.gov.uk/greenbook).

2. Mumps/Measles/Rubella virus (Screening M/M/R Virus IgG):

Patients who have not received MMR vaccination should be offered vaccination. The working group advocates a low threshold for screening if in doubt. Receipt of two doses of MMR vaccine is considered sufficient (www.dh.gov.uk/greenbook).

3. Mycobacterium Tuberculosis (Screening: IGRA/TST):

Bacillus Calmette Guerin (BCG) vaccination is not recommended in the routine work up for patients with IBD. International guidelines recommend TB risk evaluation before immunomodulation/anti-TNF therapy (see separate statement in process).

4. Inactivated influenza virus (No routine screening available)

Patients on immunomodulators have a higher risk of developing severe influenza infection. Annual vaccination with quadrivalent/trivalent inactivated influenza vaccine is an effective strategy to prevent influenza for any person older than 6 months (www.dh.gov.uk/greenbook). For the live-attenuated vaccine see statement above (Green Book, Part 1, Chapter 6).

5. Hepatitis B virus (Screening: HBV surface antigen, HBV surface antibody and HBV core antibody)

HBV screening and vaccination is recommended in all HBV core antibody seronegative patients with IBD. Efficacy of hepatitis B vaccination is impaired in IBD (by the disease itself and by anti-TNF drugs). HBV surface antibody response should be measured after vaccination and higher doses of the immunizing antigen may be required to provide protection (e.g. accelerated double dosing at 0-1-2 months). Maintenance of HBV surface antibody should be monitored in patients at risk (www.dh.gov.uk/greenbook).

6. Human papilloma virus (No routine screening available)

Routine prophylactic HPV vaccination is recommended for all children according to national guidelines. Current or past infection with HPV is not a contraindication for immunomodulator therapy (www.dh.gov.uk/greenbook).

7. Streptococcus pneumonia (No routine screening available)

Pneumococcal vaccination should ideally be administered at least two weeks before the start of immunomodulator therapy, since immunomodulators may reduce the antibody response. Children who have not been vaccinated with the pneumococcal conjugated vaccine (13-valent PCV) should receive at least one dose. In patients with IBD (high-risk population) the pneumococcal polysaccharide vaccine (23-valent PPV) should be considered for those over 2 years of age (www.dh.gov.uk/greenbook).

8. Hepatitis C virus (Screening: HCV IgG):

HCV screening is advised in all IBD patients. General measures to prevent HCV infection are appropriate since vaccination is not available.

9. Herpes Simplex Virus (No routine screening available):

A history of oro-labial, genital or ophthalmic HSV infection should be ascertained prior to initiating immunosuppressive therapy. Routine prophylaxis to suppress virus replication may be considered for patients with recurrent attacks and/or who are already taking intermittent suppressive antiviral therapy (consult local microbiology guidance).

10. Epstein Baar Virus (Screening: EBV IgG):

EBV screening should be considered before initiation of immunomodulator therapy. The EBV status may influence the choice of immunomodulation (e.g. controversy regarding increased risk of developing EBV-driven HLH/lymphoma in EBV sero-negative patients on azathioprine) although

robust evidence/guidance is not available. Preference regarding therapy remains at the clinician's discretion.

11. Cytomegalovirus (Screening: CMV IgG):

CMV screening is not recommended routinely. Detection of CMV IgG is indicative of latent infection and does not reliably predict clinical scenarios that would require prophylaxis or change of therapy.

12. Human Immunodeficiency Virus (Screening: HIV antigen/antibody):

HIV screening is recommended particularly in adolescent and high-risk patients (consult local microbiology guidance).

13. Pneumocystis jiroveci (No routine screening available):

For patients on triple immunomodulators with one of these being either a calcineurin inhibitor or anti-TNF therapy, standard prophylaxis with cotrimoxazole is recommended if tolerated. For those on double immunomodulators, prophylactic cotrimoxazole should be considered especially if one of these is a calcineurin inhibitor (consult local microbiology guidance).

Key statements supported by the IBD Working Group (BSPGHAN):

- Vaccination status for live-attenuated vaccines (i.e. VZV, MMR) should be ascertained (patients' red book and if in doubt titre measurement) in all patients with newly diagnosed IBD.
- If clinically feasible, newly diagnosed patients with IBD complete live-attenuated vaccine schedule four weeks prior to initiating immunosuppressive therapy. Physicians can still consider live vaccines for patients on immunomodulation providing the criteria above are fulfilled (Green Book, Part 1, Chapter 6).
- Serological screening should be performed for HBV and HCV and considered for EBV and HIV.
- Annual quadrivalent/trivalent inactivated influenza vaccination is recommended.
- HBV, HPV and pneumococcal vaccinations as per national guidance are recommended (www.dh.gov.uk/greenbook).

By Elena Cernat and Jochen Kammermeier on behalf of BSPGHAN IBD working group

Core References:

1. Rahier et al. JCC 2014: 'Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease'
2. The Green Book, www.dh.gov.uk/greenbook
3. Veereman-Wouters et al. JCC 2012: 'Risk of Infection and Prevention in Pediatric Patients With IBD: ESPGHAN IBD Porto Group Commentary'
4. Long et al. IBD 2015: 'Immunizations in Pediatric and Adult Patients with Inflammatory Bowel Disease: A Practical Case-based Approach.'