**Scottish Guidance on the use of Immunoglobulin replacement therapy in Hypogammaglobulinaemia secondary to Haematological Malignancies**

Secondary antibody deficiency (SAD) is found in a wide range of circumstances. Hypogammaglobulinaemia may be secondary to certain drug therapies (eg. Steroids / DMARDs / Immunosuppressants / anti-convulsant drugs), acute sepsis (consumption of IgG), in protein losing states (eg. nephrotic syndrome) and in many B- lymphoprolferative disorders.

Symptomatic antibody deficiency is associated with frequent and / or severe bacterial sino-pulmonary infections.

Immunoglobulin replacement therapy (IGRT) has been shown to reduce encapsulated bacterial infection in patients with antibody deficiency secondary to B cell malignancies, who have had persistent infections despite prophylactic antibiotic therapy and their hypogammaglobulinaemia cannot be reversed or reversal is contraindicated.

This guidance note reflects the output from a meeting held on the 3rd December 2018 with representations from Scottish Haematology, Immunology and Microbiology. The purpose was to review evidence for using Immunoglobulin replacement therapy in SAD and to clarify guidance for initiation of therapy.

The DoH Clinical Guidelines for Immunoglobulin therapy state that treatment with Immunoglobulins may have a part to play in SAD when:

- The underlying cause of hypogammaglobulinaemia cannot be reversed or reversal is contraindicated

**OR**

- The hypogammaglobulinaemia is associated with NHL/CLL/MM or other relevant B cell malignancy

**AND**

- Recurrent or severe bacterial infections despite 3 months of continuous oral antibiotics

**AND**

- IgG<5g/L

**AND**

- Documented failure of serum antibody response to unconjugated pneumo**c**occal vaccine (or other polysaccharide vaccine) challenge

**Selection of Patients for Immunoglobulin therapy**

1. **Clinical Assessment** – this must include a history of the pattern and severity of infection including associated pathology which may make the patient particularly susceptible (eg. bronchiectasis ). Any other causes of hypogammaglobulinaemia ie drug therapy (eg. rituximab). Microbiology results for encapsulated infections +/- radiologically proven pneumonia.

2. **Laboratory assessment** – the total levels of IgG / A / M should be measured. Subtypes of IgG are of no value in such patients. Evaluating for cellular defects ie. T / B / NK cell enumeration can be helpful both to further ascertain infection risk and guide choice of anti-microbial prophylaxis therapy in some patients.

3. **Determination of response to vaccination** – in particular to polysaccharide pneumococcal vaccine – Pneumovax II. A prevaccination level of specific IgG to pneumococcus is taken before administration of Pneumovax II and the level repeated at 4 weeks post immunisation. Measures of non response include testing for the total Pneumococcal IgG test. Protective levels are sought with a 2-4 fold rise in pneumococcal IgG level post immunisation or Serotype specific Pneumococcal IgG (13 serotypes measured). An 'adequate' response maybe defined as 66% response- so most of the measured 13 serotypes specific IgGs antibodies are protective ( > 0.35) units. If total IgG is <1 g/L / very low – there is no point in vaccination studies and in the presence of repeated infections these patients should move to a trial of IvIgG therapy.

If the patient has had repeated /severe bacterial infections and reduced response to Pneumovax II then a risk assessment should be carried out to determine if antibiotics or Immunoglobulin is recommended.

The risk assessment should include

a) Frequency of / Number of infections (despite antibiotic prophylaxis)

b) Severity of infections - requiring hospital / ITU admission (radiologically proven pneumonia/Sputum /blood culture positivity)

c) End organ damage – presence of bronchiectasis or evidence of progression of bronchiectasis

d) Total IgG level very low (<4 g/L)

In most patients prophylactic antibiotics should be trialled in the first instance.

Microbiological results from sputum samples taken at the time of infections may be helpful in guiding the choice of antibiotic used for prophylaxis / treatment. Guidance for the potential uses of antibiotic prophylaxis is shown below

**Graded antibiotic regimens**

| Antibiotic regimen | Dosing schedule | Additional options | Emergency plan | Example |
|---|---|---|---|---|
| Intermittent antibiotics | None | | Attend GP with symptoms | n.a. |
| | None | | Early use of home back-up antibiotics | Co-amoxyclav 625 mg tds for 2 weeks held at home |
| | Prophylactic antibiotics during the winter months with home rescue during the summer | Low-dose and full-dose options, eg. Azithromycin 250–500 mg 3 days / week | Early use of home back-up antibiotics | Azithromycin 3 days/week plus back-up<br>Co-amoxyclav for 2 weeks held at home |
| Ongoing prophylaxis | Prophylactic antibiotics | Low-dose and full-dose options, eg. Azithromycin 250–500 mg 3 days / week | Early use of home back-up antibiotics | Azithromycin 3 days / week plus back-up<br>Co-amoxyclav for 2 weeks held at home |
| | Rotating prophylactic antibiotics | | Early use of home back-up antibiotics | |
| | Prophylactic antibiotics | Nebulized antibiotics | Early use of home back-up antibiotics | Azithromycin 3 days /week plus back-up<br>Co-amoxyclav for 2 weeks held at home |
| | Prophylactic antibiotics | Intermittent planned IVAB | Early use of home back-up antibiotics | Azithromycin 3 days / week plus back-up |

| Antibiotic regimen | Dosing schedule | Additional options | Emergency plan | Example |
|---|---|---|---|---|
| | | | | Co-amoxyclav for 2 weeks held at home |

The flow chart below delineates the steps in the treatment pathway for Hypogammaglobulinaemic patients with infections. This shows that Immunoglobulin therapy (IGRT) should only be instigated when there are recurrent bacterial infections despite at least 3 months of antibiotic prophylaxis and limited response to Pneumovax.

For patients already on Immunoglobulin therapy vaccine challenge testing can only be undertaken when immunoglobulin replacement therapy has been stopped for a minimum of 6 months – perhaps during a drug holiday / trial off therapy. Trials off immunoglobulin therapy may be useful to determine if the patient may benefit clinically from antibiotic prophylaxis alone, rather than the continued requirement for IGRT.

Immunoglobulin dosing should be started at 0.4G/Kg /month and levels of trough IgG should achieve at least the lower limit of IgG. Informed written consent should be obtained at the point of initiating IGRT. The patient should be reviewed at least 6 monthly to ensure that therapy is preventing infection and that the dose is adequate. Patients on IgG replacement should be monitored for any side effects / reactions to treatment.

## Immunoglobulin replacement therapy (IGRT) initiation assessment pathway