# Seroprevalence of functional antibodies and response to vaccination in a cohort of patients with secondary immunodeficiency following haematological malignancy

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## Introduction

Secondary immunodeficiency (SID) has emerged as a major cause of morbidity in patients with haematological malignancies. There has been a 20% increase in the use of immunoglobulin replacement therapy (IRT) for SID in 2017-18 primarily driven by increased survival in haemato-oncology patients following chemotherapy and/or bone marrow transplantation. Vaccination can be used to prevent infections but also to interrogate immune function in SID; the UK *Clinical Guidelines on Immunoglobulin Use* mandates a documented failure to respond to test vaccination prior to the consideration of immunoglobulin replacement therapy (IRT) in patients with SID. The clinical performance of test vaccination in this cohort is undefined.

## Methodology

A single-centre retrospective study of patients with haematological malignancy, referred for investigation of SID was undertaken

**1.** Between 2014 and 2019, 77 patients with haematological malignancy were evaluated for SID at QEHB

**2.** Clinical evaluation included: review of antibiotic use, infection history vaccination history

**3.** Laboratory evaluation included: immunoglobulins, pre/post vaccine functional antibiotics, lymphocyte subset enumeration.

**4.** B cell phenotyping using a EUROClass panel was also undertaken (excl. CLL patients)

| Patients (n) | Abx | IVIG | p |
|---|---|---|---|
| No. | 46 | 31 | |
| Female (%) | 47.8 | 38.7 | NS |
| Age (yrs) | 55.2 | 58.9 | NS |
| % BMT<br>-Allograft | 52.1<br>79% | 41.9<br>77% | NS |
| Time to referral to immunologist (months) | 103 | 116 | NS |
| Time under immunology care (months) | 24 | 32 | 0.04 |

## Critical Findings

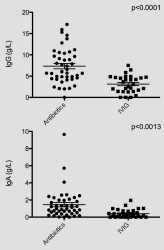
### 1 8.8 years

Average time from diagnosis of haematological malignancy to initial referral to immunologist for investigation and management of SID

### 2 Infections

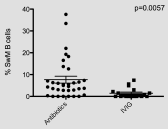
51% of patients have at least one radiological or microbiological proven pneumonia prior to immunology referral. 22% have CT proven bronchiectasis

### 3 IgG and IgA




Patients ultimately requiring IVIG have significantly lower IgG and IgA at initial referral to Clinical Immunology

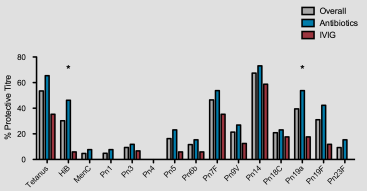
### 4 Switched Memory B cells ($CD19^+$, $CD27^+$ $IgD^-$)




Patients requiring IRT have fewer switched memory B cells (1.46% vs. 7.68%)

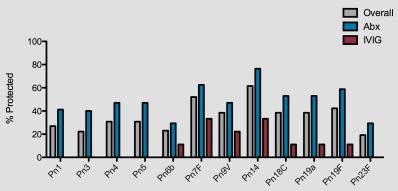
Routine flow cytometry (T/B/NK cell enumeration) was unable to discriminate between the two groups of patients.

### 5 Baseline FnAb



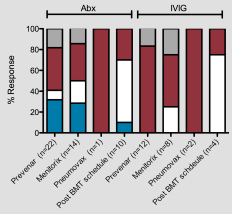

The percentage of individuals demonstrating protective titres of antibodies directed against *H. influenza B* (p=0.0063) *and S. pneumoniae* serotype 19a (p=0.0261) at baseline were significantly lower in patients ultimately requiring IVIG. Even in patients requiring IVIG, the prevalence of protective titres of antibodies against certain pneumococcal serotypes is high (e.g. Pn14 – 58.8%)

### 6 Response to PCV13



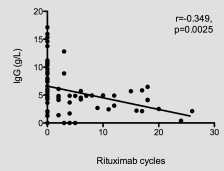

Failure to respond to test vaccination with a single dose of PCV13 is a sensitive but non specific test, in discriminating patients requiring future IVIG treatment. Overall, 55.8% of patients with SID do not achieve protective titres in >8 pneumococcal serotypes following mandated vaccination. Immunologists should consider additional booster vaccinations to optimise protection.

### 7 Overall response to vaccination




Response to test vaccination was poor; less than 50% on long term Abx mounted a partial or complete response to Prevenar or Menitorix. The positive predictive value of test vaccination failure was 52.6% (Prevenar) and 44.4% (Menitorix) in predicting need for immunoglobulin replacement.

### 8 Rituximab




Increasing number of cycles of rituximab (anti-CD20 monoclonal antibody) in haemato-oncology patients negatively correlate with total serum IgG. Any prior exposure to rituximab is associated with an odds ratio of 4.90 (CI 1.80-13.37, p=0.0019) of requiring future immunoglobulin replacement therapy.

## Take home

- There is diagnostic delay in recognising SID in haemato-oncology patients - this is associated with long-term damage from infections
- Patients requiring IVIG have, on average, lower mean IgG and IgA and % switched memory B cells
- HiB and Pn19A are useful predictors of future IVIG use. Test vaccination has poor PPV.
- Rituximab exposure is a significant risk for hypogammaglobulinaemia and future IVIG use.

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