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Abstract

Purpose of review: Clozapine has recently been described as a novel cause of secondary antibody deficiency (SAD), associated with long-term therapy. Here we critically review the evidence linking clozapine-use to an increased infection risk, describe immunological alterations, and discuss potential mechanisms.

Findings: Individuals with schizophrenia are at 2-5 times more likely to develop pneumonia than the general population, in particular when receiving clozapine. Delayed-onset distinguishes clozapine-associated hypogammaglobulinaemia from agranulocytosis or neutropenia that occur at lesser frequency. Biomarker searches in treatment-resistant schizophrenia highlight an immune signature associated with long-term clozapine use. This includes reduction in class-switched memory B-cells, echoing common variable immunodeficiency. Recent identification of a role for dopamine in T follicular helper – B cell interactions may inform future clinical studies.

Summary: The detrimental impact of the increased infection risk associated with clozapine necessitates a re-evaluation of the current monitoring strategies as well as further studies to better understand the underlying mechanisms of SAD in this setting. Based on available evidence, we suggest simple modifications to clozapine monitoring including integration of routine vaccination, smoking cessation, and assessment of humoral immunity. Further studies are required to understand the role of clozapine in neuroinflammation as well as potentially other autoantibody mediated diseases.

Keywords: Clozapine, Hypogammaglobulinaemia, Secondary Antibody Deficiency (SAD), Monitoring, Immunoglobulin Replacement Therapy (IgRT).

Abbreviations:

ANC	Absolute Neutrophil Count
CSMB	Class-Switched Memory B-cell
CVID	Common Variable Immunodeficiency
DRD	Dopamine Receptor
HBV	Hepatitis B Virus
IgRT	Immunoglobulin Replacement Therapy
NMDA-R	N-Methyl-d-Aspartate Receptor
REMS	Risk Evaluation and Mitigation Strategy
SAD	Secondary Antibody Deficiency
SMI	Severe Mental Illness
SMR	Standardised Mortality Ratio
TFH	T-Follicular Helper
TRS	Treatment Resistant Schizophrenia

Introduction

Major global causes of secondary immunodeficiency include malnutrition, HIV, and malaria. In this review we focus on secondary antibody deficiency (SAD) and in particular the novel association of clozapine with SAD. The field of SAD comprises a heterogeneous and expanding group of clinical conditions characterized by a persistent impairment of antibody production due to a wide range of diseases and drugs. The growth in SAD is to a large extent driven by improvements in the therapies and their wider use to treat autoimmunity, inflammation, transplant rejection and malignancy, especially by agents targeting B cells (1). The mechanism(s) of action of the majority of these drugs is immunosuppressive while in contrast clozapine, a dibenzodiazepine atypical antipsychotic, used in treatment resistant schizophrenia (TRS) does not at first glance fall into this category. Indeed, the association of clozapine with SAD was serendipitously discovered as part of population-based screening for antibody deficiency using calculated globulin (2-5).

Clozapine is an important global medication and is one of the World Health Organisation (WHO) essential medicines. It represents one of only two major therapeutic advances in the treatment of schizophrenia in over half a century (chlorpromazine in 1950 and clozapine in 1958) and remains the gold standard therapy for TRS (6). Schizophrenia affects around 1% of the population with 30% of cases being treatment resistant. It has superior efficacy over other antipsychotics in reducing both positive and negative symptoms and is effective in approximately 60% of previously treatment

refractive patients with a significant reduction in suicide risk (7, 8). Clozapine can cause serious adverse effects including agranulocytosis (cumulative incidence 0.8%) (9, 10); necessitating intensive centralised registry-based monitoring systems to support its safe use.

In 2015 in the United States, the Federal Drug Administration (FDA) merged and replaced the six existing clozapine registries combining data from over 50,000 prescribers, 28,000 pharmacies, and 90,000 patients records into a single shared registry for all clozapine products, the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (www.clozapinerems.com). Blood testing of the absolute neutrophil count (ANC) is initially required weekly in order to receive ongoing clozapine therapy. Patients with schizophrenia are a vulnerable group with a number of independent risk factors for infection in addition to the potential risk of neutropenia.

The recognition of SAD in this context is important not only because patients receiving long-term clozapine form a large and vulnerable group but also to prevent potential life-threatening infections and irreversible organ damage, such as bronchiectasis. Early detection allows potential changes in monitoring, further immunological assessment or the initiation of therapies to reduce the risks of infection such as vaccination, antibiotics or in selected cases immunoglobulin replacement therapy (IgRT) (11).

We will review the evidence supporting an increase in infections, in particular pneumonia, in patients taking clozapine, the association with SAD and potential mechanisms. In addition, we describe the immunological and clinical features and management of clozapine related antibody deficiency and propose an amendment to the current clozapine REMS monitoring schemes to include testing for SAD.

Infectious Risk and antibody deficiency in Clozapine-treated patients

Patients with schizophrenia have a 10-20 year reduction of life expectancy compared to the general population (12) with a consistent contribution toward this reduction due to a high risk of respiratory infection (**Table 1**). Patients with chronic psychosis are known to be at greater risk of infection though factors such as elevated smoking rates, metabolic disorders, dental caries and poorer integration with community health providers (13-17). In a recent study, assessing mortality in people with severe mental illness (SMI), the standardised mortality ratio (SMR) was 2.6 higher compared to the general population. Schizophrenia patients had the highest SMR of all, with 3.8 times the number of deaths observed compared to that expected based on the age- and sex-specific rates for the general population (18). Interestingly, 17.8% of deaths were attributable to respiratory disease with mortality for pneumonia 3.8-fold higher compared to the general population, with a SMR of 10.7 in subjects younger than 45 years. Consistent with this and using a similar retrospective approach, the overall incidence of pleural empyema was found to be 2.44-fold greater in schizophrenia than the general population (19). Increasing evidence has highlighted clozapine as the antipsychotic drug most strongly associated with pneumonia risk (20-24). Current users of clozapine alone were twice as likely to develop pneumonia, and use of clozapine combined with other antipsychotics (olanzapine, quetiapine, zotepine, risperidone, or amisulpride) was associated with even greater risk (25). Moreover, although all of the antipsychotics with the exception of amisulpride were significantly associated with increased risk of pneumonia in the first 30 days of use, clozapine had the highest risk-increase both in this interval and long term (25). In keeping with this data, a higher use of antibiotics compared to clozapine-naïve schizophrenia control patients was described in a cohort study including clozapine-treated patients drawn from Danish Central Psychiatric Research Registry (26). It is important to consider the limitations of epidemiological studies to date; for instance, analysis of both the Danish (26) and Taiwanese Registries (19, 25) lacked information on smoking, drinking, nutrition, and social-deprivation status. Socio-economic drift is well-recognised in association with schizophrenia (8) and is plausibly exaggerated in treatment-resistant patients.

In testament to the efficacy of clozapine in the treatment of schizophrenia, a systematic review including 24 studies reported lower mortality rate ratios in patients continuously treated with clozapine compared

to other antipsychotics (27). This finding could reflect the effectiveness of clozapine in increasing the overall level of function, thus leading to the improvement in a number of risk factors linked to lifestyle, cardiovascular disease and reduction in suicide rates (27, 28). However, as this systematic review did not stratify mortality rate ratios based on the cause of death it was not possible to analyse data on the impact of respiratory infections in clozapine-treated patients. Overall, this suggests that reducing infection-related mortality could further enhance clozapine's efficacy.

The relationship between infection, clozapine use, and adverse events are likely to be complex and multi-factorial. Various mechanisms for the increase in infectious risk in clozapine-treated patients have been suggested including smoking, sedation, agranulocytosis, diabetes, alcohol intake, illicit drug use, poor diet and physical inactivity, sialorrhoea, aspiration and, most recently, antibody deficiency (29, 30). The impact of clozapine on antibody deficiency was investigated in a cross-sectional case-control study comparing immunological and clinical features of schizophrenia patients taking either clozapine or other antipsychotics (5). Clozapine-treated patients showed a significant reduction of all three immunoglobulin classes (IgG, IgA and IgM) compared to clozapine-naïve group. In particular, 8.5% of clozapine-treated patients versus 1% of controls had IgG serum levels below the lower limit of the reference range (6.0 g/l); 13.8% of clozapine-treated versus no controls had low IgA levels (<0.80 g/L); and 34% of clozapine-treated versus 15.3% of control group had low IgM levels (<0.50 g/L). Interestingly, a significant association was found between clozapine treatment duration and the degree of reduction in IgG serum levels, with an annual decline of serum IgG by 0.15 g/L, thus suggesting a cumulative effect of clozapine on antibody production (**Figure 1**). This was despite identification and exclusion of possible secondary causes of hypogammaglobulinaemia with additional linear regression analysis to control for possible effect of diagnoses (e.g. asthma or chronic obstructive pulmonary disorder) associated with use of medications with potential immunosuppressive effects (e.g. glucocorticoids) not documented in available psychiatric or electronic healthcare records. In addition, although no differences in levels of specific IgG against haemophilus influenzae B, pneumococcus, and tetanus were observed between the two study-groups, clozapine-treated patients had a significant reduction of pneumococcal-specific IgA and IgM, perhaps reflecting the observed greater relative

reductions in total IgA and IgM levels. Immunological abnormalities were mirrored by the clinical history: clozapine-receiving patients had higher antibiotic use, with 5.3% patients reporting more than five antibiotic courses per year versus 1% in clozapine-naïve group. Taken together the data suggest both a quantitative and qualitative impairment of antibody production associated with clozapine accompanied by an increase in infection susceptibility.

Immunological alterations and possible pathogenetic mechanisms

Disturbances of innate immunity associated with clozapine are well described and include transient fever and eosinophilia with a small proportion (<1%) developing neutropenia or agranulocytosis (31-35). Of note, clozapine-induced fever characteristically appears around 10-14 days following initiation, thus might erroneously contribute to the early spike in pneumonia detection rates discussed above (25). Here we focus on adaptive immune disturbances associated with clozapine therapy.

To date, only one study has been reported using multi-parameter flow cytometry to compare TRS patients with healthy volunteers (36). The observed differences include a shift towards naïve B-cell populations, with reduction in plasmablast ($CD3^{-}CD19^{+}IgD^{-}CD20^{+}CD38^{+}$) and class-switched memory B (CSMB; $CD3^{-}CD19^{+}IgD^{-}CD27^{+}$) populations. Importantly, 17 of the 18 TRS patients tested had received clozapine therapy with a mean duration of 18 years. Thus, this search for biomarkers of TRS potentially highlights a distinctive immunophenotype of long-term clozapine therapy. Reduced CSMB populations are predictive of immunoglobulin replacement requirement in secondary hypogammaglobulinemia (37). This is in keeping with our initial report (5), and we have independently noted marked a reduction in class-switched memory B-cell populations and plasmablast frequencies among clozapine-treated patients referred clinically based on calculated globulin screening (*manuscript in submission*). Within our cohort of patients requiring immunoglobulin replacement therapy (IgRT) for hypogammaglobulinemia and infection, 7 patients with a diagnosis of schizophrenia of which 6 have a history of clozapine therapy. This raises diagnostic challenges as the constellation of hypogammaglobulinemia, infection susceptibility, and low CSMB, are core defining and diagnostic features of common variable immunodeficiency (CVID) (38, 39). We are currently conducting a survey

of Immunodeficiency Centres to define immunological phenotype in clozapine-treated patients across the UK.

Immunophenotyping also revealed heightened expression of DRD3 on peripheral HLA-DR^{+} memory T- and regulatory T-cells in clozapine-treated patients (36). Interplay between neuronal and immune systems has long been recognised (40) and has led to novel therapeutic avenues (41-43). Recently, Papa et al have identified dopamine synthesis occurs within T-follicular helper cells (TFH) of the germinal centre (44). Dopamine release from TFH granule stores is triggered by cognate interaction with B-cells. This acts on the B-cell to stimulate rapid deployment of pre-formed ICOS-ligand to the cell surface, supporting rapid co-stimulation and resulting in CD40L upregulation on the TFH cell (44). Thus, dopamine signalling contributes to a feedforward co-stimulatory loop facilitating T-B cell interactions (**Figure 2**). Dopamine synthesis is not detectable within murine T-cells, suggesting this mechanism has arisen later in evolution. Therefore, computational modelling, instead of conventional murine studies, have been used to predict this mechanism significantly enhances germinal centre output but has little impact on affinity maturation (44).

Could antagonism of germinal centre dopaminergic signalling by antipsychotics underlie clozapine-associated hypogammaglobulinaemia? Whilst certainly an attractive explanation, Papa et al found DRD1 to be the dominant receptor type expressed by human tonsillar B-cells. Based on receptor binding affinities (45), this would predict a class effect for antipsychotics over a clozapine-specific mechanism. Indeed, both haloperidol and a DRD1-specific antagonist were able to block ICOS-L upregulation *in vitro* (44). Nevertheless, previous studies of human B cells have reported frequent expression of both DRD1 and DRD2 (46), and differences between B-cells within blood, lymphoid, and tonsillar tissue are well recognised (47). Extrapolation from these insights is also complicated by changing patterns of dopamine receptor expression following antipsychotic exposure (48). Despite such limitations, this work directly raises clinically relevant questions. Do individuals receiving antipsychotics differ in their ability to mount and sustain a response to vaccination from antipsychotic-naïve individuals? How do different antipsychotics vary in their impact?

We previously demonstrated reduction in serum IgM levels relative to the normal adult range level, and low concentrations of specific IgG to frequently encountered vaccinations, are common across anti-psychotic treated individuals with schizophrenia (5). These results are difficult to interpret in isolation however, as access and uptake of vaccinations is often lower than for those with serious mental illness (49). Remarkably, despite intense interest in the role of early-life infection in the aetiology of psychosis, and convergent evidence indicating an elevated risk of pneumococcal disease (19), few large-scale studies have considered this issue to date. An Ovid Medline Search conducted 28th June 2019 using the terms "vaccine OR vaccination" AND "schizophrenia OR psychosis" identified only one major case series in which 175 institutionalised psychiatric patients received Hepatitis B virus (HBV) vaccination. This concluded vaccine response rates were significantly lower than expected for healthy individuals (50). A subsequent case-control study of 415 Chinese schizophrenia patients also found a greater rate of HBV infection in those receiving clozapine, even in those who had received routine immunization (51). Historical studies containing small numbers of patients showed mixed results for vaccination responses (52, 53).

Neuroinflammation and immunosuppressive effects of clozapine: two sides of the same coin?

Recognition of anti-neuronal antibodies underlying acute psychosis provides the clearest evidence for the role of autoimmunity in psychiatric disease (54). Antibodies to N-methyl-d-aspartate receptor (NMDA-R) are detectable in approximately 3% of patients with first-episode psychosis, when tested within 6 weeks of commencing antipsychotics (54). Early diagnosis directs treatments to remove autoantibodies and halt production to induce remission (55). It has been suggested TRS may represent an enriched patient cohort with respect to the presence of anti-neuronal antibodies (56). A smaller study identified anti-NMDA-R antibodies in 3 of 43 patients (7%) with chronic treatment-resistance psychosis (57). Intriguingly, in 2 cases, treatment with clozapine resulted in both symptomatic remission and resolution or reduction of autoantibody-titres, whilst the 3rd patient elected to remain on quetiapine with persistence of symptoms (57). Recent insights suggest ongoing germinal centre reactions are essential for anti-NMDA-R autoantibody production (58). Further studies to assess the ability of clozapine to influence this are suggested, for instance utilising recently developed murine models (59).

Based on current auto-antibody prevalence information however, it seems unlikely that an effect targeting anti-neuronal antibodies alone underlies clozapine's superior efficacy.

Evidence of neuroinflammation in the pathophysiology of schizophrenia is growing. Microglial activation is observed in patients with schizophrenia and those at ultra-high risk of psychosis (60). Similarly, induction of neuro-inflammation by administration of a viral mimetic (polyI:C) leads to microglial activation and progressive cognitive impairment in rodents – an effect reversed by clozapine (61). Wider models of neuroinflammation support clozapine's efficacy in amyloid-plaque related neuroinflammation (62) and highlight its superiority to other antipsychotics in ameliorating experimentally induced encephalitis (63). These illuminate potential mechanisms including AMPK-activation (62) and induction of autophagy (64, 65). Autophagy is a key homeostatic process balancing synthesis, degradation/detoxification, and recycling of cellular components (66). Whilst a universal cellular process, autophagy plays a non-redundant role in B-cell development and homeostasis (65, 67), inflammasome activity (68), and appears dysregulated in schizophrenia (69): highlighting it as an important avenue for future research linking clozapine's therapeutic and adverse effects.

Management of Clozapine associated antibody deficiency

The nature, timing, and incidence of neutropenia and agranulocytosis have shaped clozapine risk monitoring programmes internationally. Within the first 6 months of clozapine's introduction to Finland, 17 patients developed blood dyscrasias including 8 fatal cases of agranulocytosis due delayed recognition and secondary infection. Now almost 3 decades since its re-introduction, the "no blood, no drug" policy is well established with emphasis on the initiation period (70). Recent changes to the US clozapine REMS programme support widening access and reduced monitoring intensity requirement for clozapine. Currently, requirements are for a *weekly* absolute neutrophil count assessment from initiation to 6 months, every 2 weeks from 6 to 12 months, then monthly after the first 12 months-reflecting a 10-fold decrease in agranulocytosis risk after this point (33, 71). Studies modelling safety and cost have not considered clozapine-associated hypogammaglobulinemia (72, 73). Evidence suggests the magnitude of reduction in immunoglobulins is comparable, if not greater, than that described following long-term combination therapy with rituximab and methotrexate for rheumatoid

arthritis (based on pooled data from the rituximab clinical trials programme) (74). Post-rituximab immunoglobulin reduction is associated with increased risk of recurrent infection (75, 76). Based on these observations, we propose the incorporation of antibody testing within a clozapine risk assessment matrix as infrequent (vs rare) but with moderate (vs high) risk of adverse outcome (compared to agranulocytosis). In general for SAD, the likelihood of requiring IgRT is inverse to IgG levels (11). We therefore suggest changes to clinical monitoring (**Figure 3**). This would begin with documentation of a clinical infection history (including e.g. antibiotic course requirements over past 6 months) and establishing a baseline for humoral immunity *early* after psychosis onset. Serum sampling at this time also allows exclusion of treatable autoimmune causes (54). An integrative approach to mental and physical health should also include measures to improve rates of smoking cessation and vaccination to reduce pneumonia and chronic lung disease risk. We suggest seasonal influenza and pneumococcal vaccination protocols as per national guidance for "at risk" populations (77, 78). Given an increased risk of vaccine preventable hepatitis in this often institutionalized population group (50, 51), we also suggest HBV vaccination with subsequent response evaluation. Our experience of clozapine-associated hypogammaglobulinemia patients supports a stepwise approach to management including consideration of standby antibiotics and regular prophylaxis depending on the frequency and severity of infections. If a significant infection burden remains despite prophylactic antibiotics on a background of hypogammaglobulinaemia and impaired vaccine responses, IgRT should be considered.

Following clozapine withdrawal, we have observed a slow recovery of immunoglobulin levels but rapid return of schizophrenic symptoms - suggesting a separation of mechanism. In practice, close liaison with the patient, psychiatry and immunology teams supports individualised therapy. Immunoglobulin replacement therapy to reduce infection frequency is feasible in this patient population (*manuscript in submission*). Future studies are required to define the health economic impact of extending current monitoring to include total and vaccine-specific immunoglobulin assessment, enabling cost consequence analysis of the excess infection-related healthcare burden attributable to clozapine-associated hypogammaglobulinaemia.

Conclusions

Premature mortality is a feature of this schizophrenia and undermines clozapine's unique therapeutic efficacy. Clozapine-associated secondary antibody deficiency has only recently been described. Humoral dysfunction may contribute the observed sinopulmonary infection related morbidity and mortality. Our understanding of mechanism remains limited. Early recognition and treatment are likely to improve long-term outcome and quality of life of schizophrenia patients by enabling monitoring and interventions to reduce infection susceptibility. We therefore suggest a structured approach to assessment and risk mitigation, including introduction of routine vaccination and antibody testing to routine clinical care. Larger studies are needed to evaluate the impact of dose, concomitant medications and duration and their interaction with genetic and environmental factors (e.g. smoking) on development of antibody deficiency and the overall risk of sinopulmonary and other infection. Mechanistic insights to clozapine's unique therapeutic efficacy promise to reveal new approaches to combating neuroinflammation and potentially inflammation in a wider context.

Key Points:

- Clozapine treatment is associated with a 2-5 fold increase in pneumonia risk for patients with schizophrenia relative to the general population or alternative antipsychotic users.
- Clozapine associated hypogammaglobulinaemia has been recently described as a treatable cause of sinopulmonary infection susceptibility.
- Dopamine signalling contributes to T follicular helper and B-cell interactions within the germinal centre suggesting antipsychotics may impair the adaptive humoral response.
- An integrated approach improving access to healthcare including smoking cessation, access to vaccination, and evaluation of immune functionality beyond neutrophil testing is suggested.

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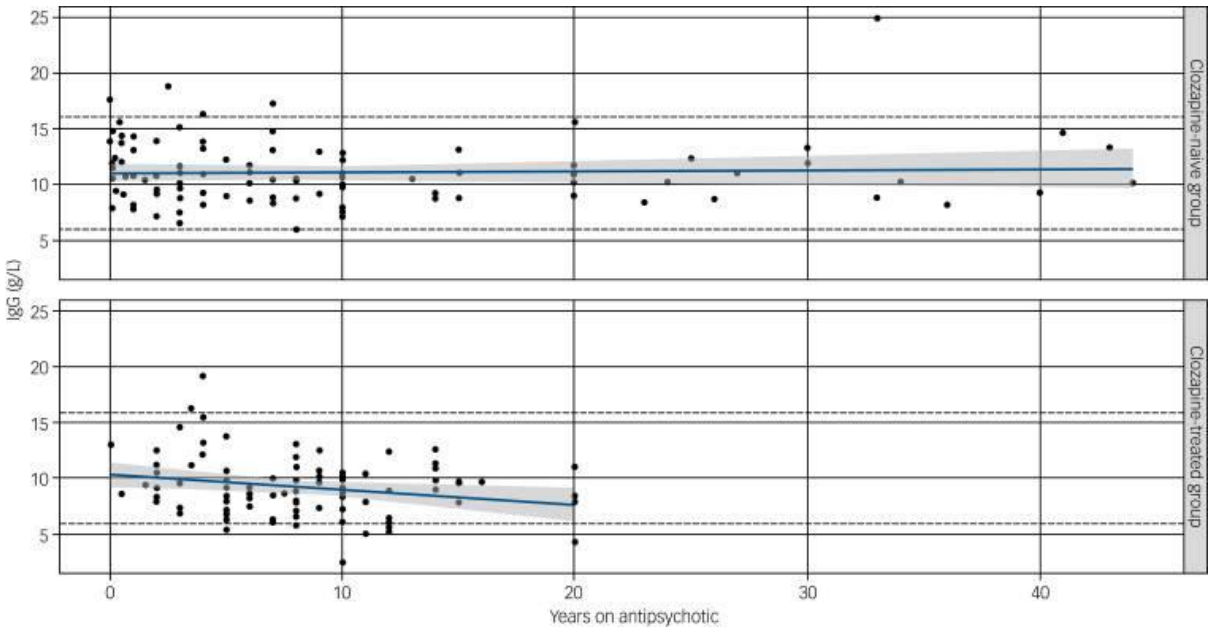
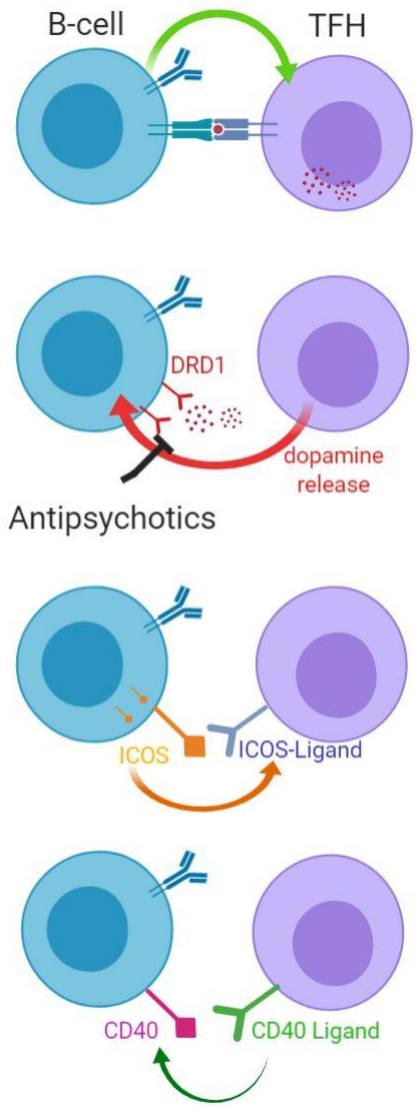
Figure 1: Effect of duration of non-clozapine antipsychotic (upper) or clozapine (lower) treatment on immunoglobulin IgG levels.



No correlation was seen with serum IgG level and non-clozapine antipsychotic medications ($P = 0.14$) despite a longer duration on therapy. A significant negative correlation of duration of clozapine use (years) was observed with an annual reduction in IgG levels of 0.15 g/L ($P = 0.03$). Straight lines show predicted IgG at different durations of treatment (in years), based on fitted linear models. Shaded regions display pointwise 95% confidence intervals. Dotted lines indicate normal range for IgG 6.0-16g/L. Reproduced with permission from (5).

Figure 2: Dopamine's actions within the germinal centre (based on (44))



1: Antigen presentation by B-cell stimulates dopamine release from T-follicular helper cell

2: Dopamine acts via cell-surface receptors, triggers ICOS trafficking from intracellular stores to the B-cell surface

3: ICOS ligand - ICOS interaction provides co-stimulatory signal for the TFH cell

4: CD40L- CD40 interaction stimulates B-cell survival and differentiation

Image created by MP using Biorender tool.

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Figure 3: Suggested flowchart for monitoring of humoral immunity during clozapine therapy

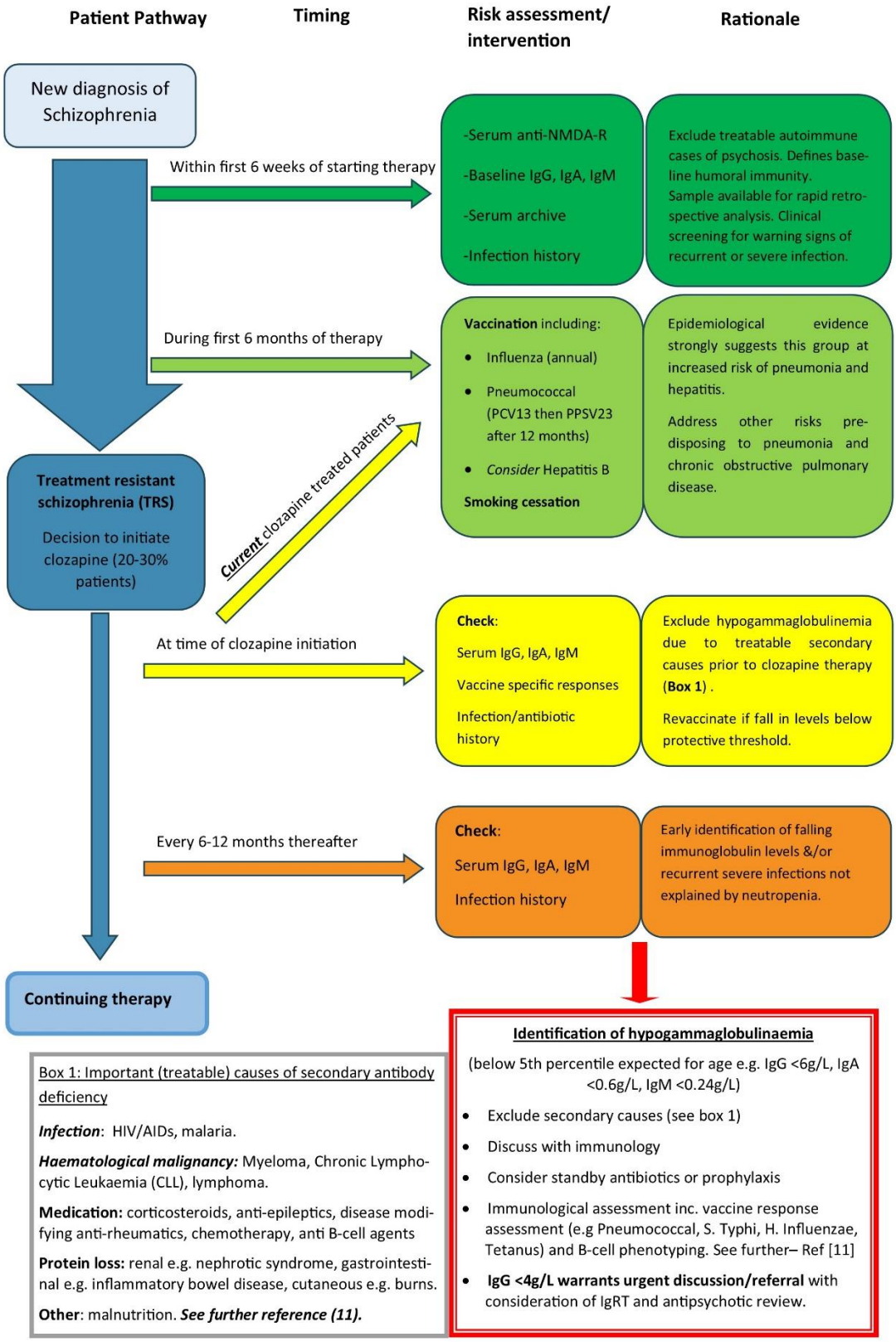

Table 1: Mortality and risk of pneumonia in schizophrenia.

Selected cohort studies investigating overall mortality, pneumonia-related mortality, and risk of pneumonia across schizophrenia and specifically clozapine-treated patients. Studies concerning other indications for antipsychotic prescription were excluded. Note studies differ in study design, population analysed, outcome considered and statistical methods, thus limiting comparison of results. SMR = standardized mortality rate; MRR = mortality rate ratio; AHR = adjusted hazard ratio; HR = hazard ratio; OR = odds ratio; RR = relative risk; ARR = adjusted risk ratio.

Study	**Year**	**Outcome**	**S i**
Overall Mortality in Schizophrenia			
John et al. (18)	2018	Overall mortality in schizophrenia compared to general population	
Hayes et al. (17)	2017	Overall mortality in schizophrenia compared to general population	
Pneumonia Risk and Mortality in Schizophrenia			
John et al. (18)	2018	Mortality for pneumonia in schizophrenia compared to general population	
Shen et al (79)	2017	Risk of pleural empyema in patients with Taiwanese patients with schizophrenia relative to matched control group from general population.	
Seminog et al (19)	2013	Rates of pneumococcal pneumonia in England based on linked hospital episode statistics	
Chou et al. (16)	2013	Risk of pneumonia in schizophrenia compared to general population	
		Mortality for pneumonia in schizophrenia compared to general population	
Overall Mortality in Clozapine-treated Schizophrenia			
Vermeulen et al. (27)	2018	Overall mortality in clozapine-treated compared to clozapine-naïve schizophrenia patients	

Tiihonen et al. (28)	2009	Overall mortality in clozapine-treated compared to clozapine-naïve schizophrenia patients	
Risk of Pneumonia in Clozapine-treated Schizophrenia			
Stoecker et al. (20)	2017	Risk of pneumonia in clozapine-treated compared to general population	
Kuo et al. (25)	2013	Risk of pneumonia in clozapine-treated compared to clozapine-naïve schizophrenia patients	
		Risk of pneumonia in patients treated with clozapine + any other antipsychotic compared to clozapine-naïve schizophrenia patients	
Haddad et al. (24)	2013	Risk of pneumonia in clozapine-treated compared to no-drug-use controls	

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Response to reviewers: ACI190611

Thank you for the reviewer's kind and helpful comments

We have adjusted the text to reflect the limitations of epidemiological studies to date, highlighting social drift as a potential confounding variable accompanying clozapine therapy.

I look forward to reading the manuscript in press on the immunologic flow cytometry changes in the B cell compartment among clozapine-treated patients.

-Thank you, this is currently with reviewers.

The data discussed showed low IgG levels in clozapine treated patients, are there data associating these IgG levels with infection? Do the authors anticipate similar effects to what is noted in antiseizure medications and hypogammaglobulinemia? Is there data correlating IgG levels and infection risk in this population?

We have added some additional detail concerning this study to stir the reader's interest: Within our cohort of patients requiring immunoglobulin replacement therapy (IgRT) for hypogammaglobulinemia and infection, 7 patients with a diagnosis of schizophrenia of which 6 have a history of clozapine therapy.

The proposal for Igs/ specific vaccination titers testing in Clozapine treated patients seems reasonable. Would the authors dare discuss the potential opportunity of a cost analysis? Would be a study in and of itself….

This is in fact part of an active submission. We have amended the text to: include total and vaccine-specific immunoglobulin assessment, enabling cost consequence analysis of the excess infection-related healthcare burden attributable to clozapine-associated hypogammaglobulinaemia.

Minor changes:

Table 1:
Remove underlined section: " Risk of pleural empyema in patients with Taiwanese patients with schizophrenia relative to matched control group from general population"

We regret we could not identify an underlined section but would be happy to edit this if it still appears within revised version.

Figure 2:
Numbers 1, 2, 3 and 4 are missing from the figure

Thank you, we have updated this in the revised version

Figure 3:
Is S. Typhi antibody titers a routine analysis recommended for adults with hypogammaglobulinemia? Similarly HIB titers are commonly collected in children, should they also be collected in adults?

Our centre's practice is to make use of a combination of vaccination responses (including Hib and S typhi), however in light of recent surveys (e.g. UKPIN) we recognise variation in practice exists. This is beyond the scope of this review, and we have amended the Figure to reference Jolles et al: "When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: a practical approach. Clin Exp Immunol. 2017;188(3):333-41" which provides a more complete discussion.

Figure 1

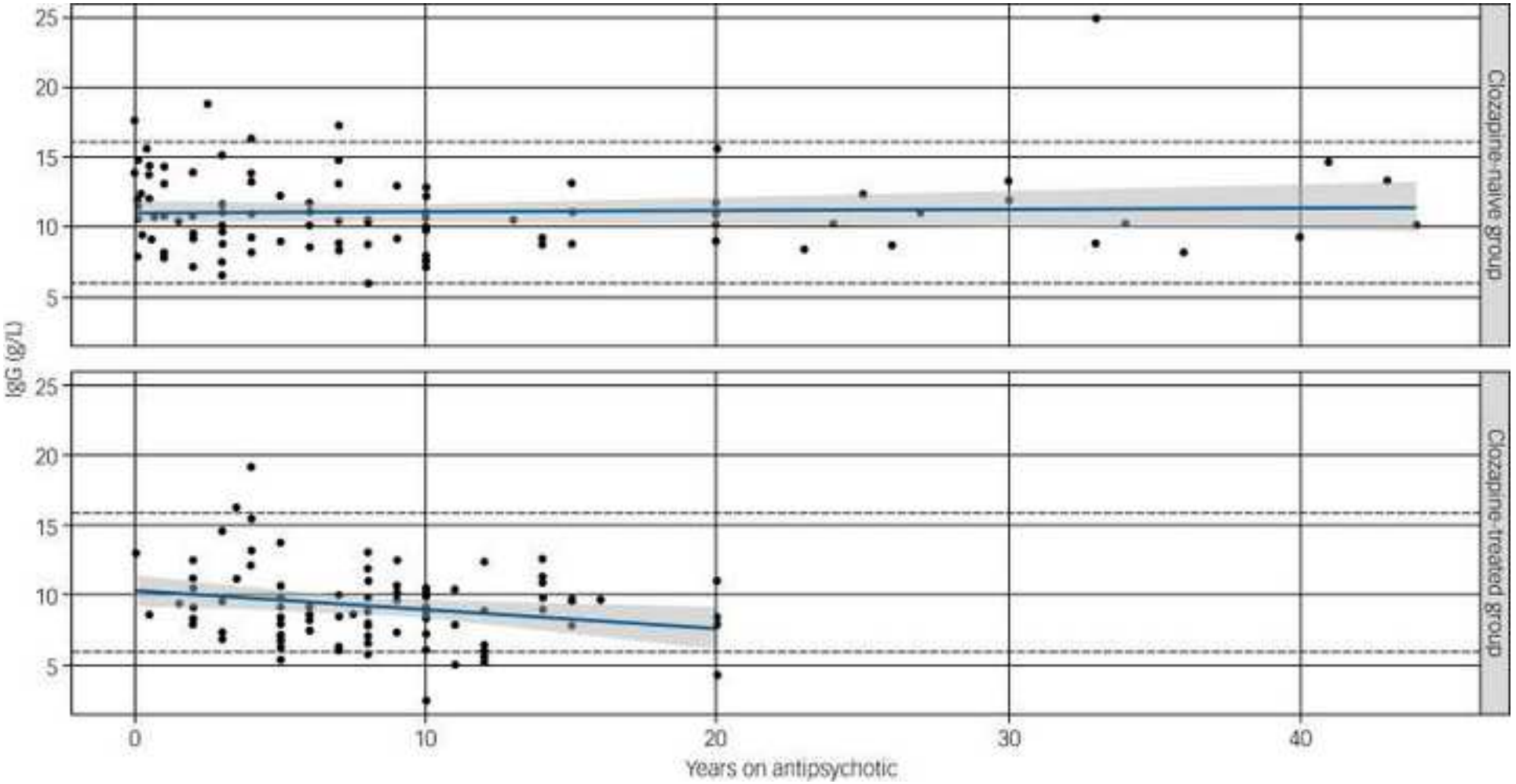
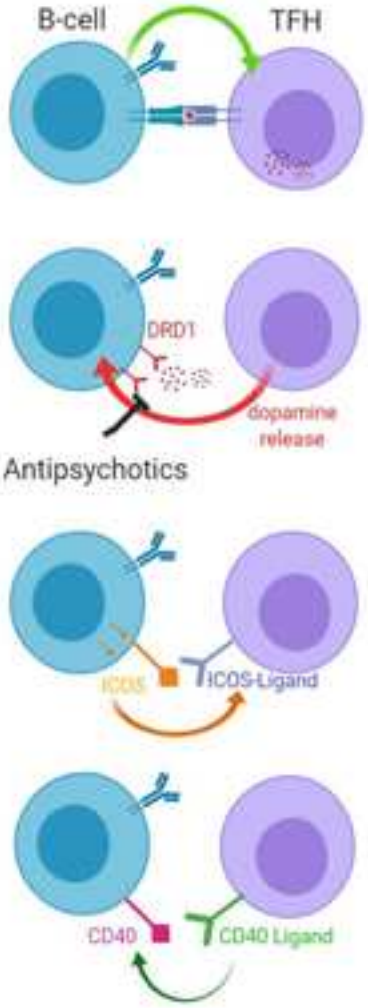

IgG (g/L)
25
20
15
10
5
Clozapine-naive group
Clozapine-treated group
0
10
20
30
40
Years on antipsychotic

Figure 2 - v0.8



1: Antigen presentation by B-cell stimulates dopamine release from T-follicular helper cell

2: Dopamine acts via cell-surface receptors, triggers ICOS trafficking from intracellular stores to the B-cell surface

3: ICOS ligand - ICOS interaction provides co-stimulatory signal for the TFH cell

4: CD40L- CD40 interaction stimulates B-cell survival and differentiation

Image created by MP using Biorender tool.

Figure 3 - v0.8

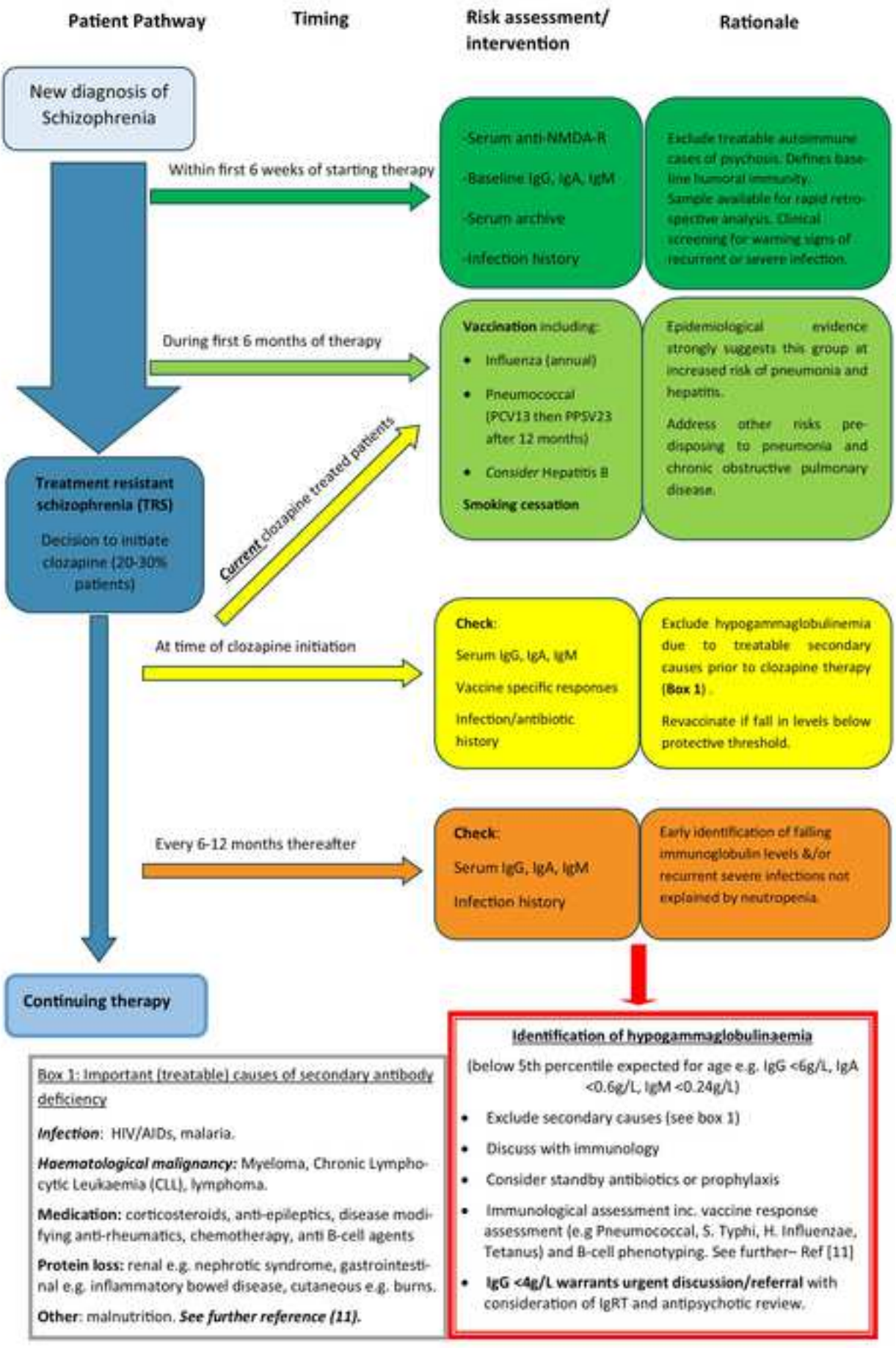

Patient Pathway
Timing
Risk assessment/ intervention
Rationale
New diagnosis of Schizophrenia
Within first 6 weeks of starting therapy
-Serum anti-NMDA-R
-Baseline IgG, IgA, IgM
-Serum archive
-Infection history
Exclude treatable autoimmune cases of psychosis. Defines baseline humoral immunity. Sample available for rapid retrospective analysis. Clinical screening for warning signs of recurrent or severe infection.
During first 6 months of therapy
Vaccination including:
Influenza (annual)
Pneumococcal (PCV13 then PPSV23 after 12 months)
Consider Hepatitis B
Smoking cessation
Epidemiological evidence strongly suggests this group at increased risk of pneumonia and hepatitis.
Address other risks predisposing to pneumonia and chronic obstructive pulmonary disease.
Treatment resistant schizophrenia (TRS)
Decision to initiate clozapine (20-30% patients)
Current clozapine treated patients
At time of clozapine initiation
Check:
Serum IgG, IgA, IgM
Vaccine specific responses
Infection/antibiotic history
Exclude hypogammaglobulinemia due to treatable secondary causes prior to clozapine therapy (Box 1).
Revaccinate if fall in levels below protective threshold.
Every 6-12 months thereafter
Check:
Serum IgG, IgA, IgM
Infection history
Early identification of falling immunoglobulin levels &/or recurrent severe infections not explained by neutropenia.
Continuing therapy
Box 1: Important (treatable) causes of secondary antibody deficiency
Infection: HIV/AIDs, malaria.
Haematological malignancy: Myeloma, Chronic Lymphocytic Leukaemia (CLL), lymphoma.
Medication: corticosteroids, anti-epileptics, disease modifying anti-rheumatics, chemotherapy, anti B-cell agents
Protein loss: renal e.g. nephrotic syndrome, gastrointestinal e.g. inflammatory bowel disease, cutaneous e.g. burns.
Other: malnutrition. See further reference (11).
Identification of hypogammaglobulinaemia
(below 5th percentile expected for age e.g. IgG <6g/L, IgA <0.6g/L, IgM <0.24g/L)
Exclude secondary causes (see box 1)
Discuss with immunology
Consider standby antibiotics or prophylaxis
Immunological assessment inc. vaccine response assessment (e.g Pneumococcal, S. Typhi, H. Influenzae, Tetanus) and B-cell phenotyping. See further– Ref [11]
IgG <4g/L warrants urgent discussion/referral with consideration of IgRT and antipsychotic review.

Table 1. Mortality and risk of pneumonia in schizophrenia.

Cohort studies investigating overall mortality, mortality for pneumonia and risk of pneumonia in all schizophrenia or clozapine-treated patients compared to general population or clozapine-naïve patients. Various studies differ in study design, population analysed, outcome considered and statistical methods, thus limiting comparison of results. SMR = standardized mortality rate; MRR = mortality rate ratio; AHR = adjusted hazard ratio; HR = hazard ratio; OR = odds ratio; RR = relative risk; ARR = adjusted risk ratio.

Study	Year	Outcome	Statistical indicator	Result	95% C.I.
Overall Mortality in Schizophrenia					
John et al. (1)	2018	Overall mortality in schizophrenia compared to general population	SMR	2.9	2.8-3.0
Hayes et al. (2)	2017	Overall mortality in schizophrenia compared to general population	HR	2.08	1.98-2.19
Pneumonia Risk and Mortality in Schizophrenia					
John et al. (1)	2018	Mortality for pneumonia in schizophrenia compared to general population	SMR	3.8	3.5-4.2
Shen et al (3)	2017	Risk of pleural empyema in Taiwanese patients with schizophrenia relative to matched control group from general population	AHR	2.87	2.14 - 3.84

Seminog et al (4)	2013	Rates of pneumococcal pneumonia in England based on linked hospital episode statistics	RR	2.5	1.9-3.2
Chou et al. (5)	2013	Risk of pneumonia in schizophrenia compared to general population	HR	1.77	1.67-1.88
		Mortality for pneumonia in schizophrenia compared to general population	HR	1.39	1.29-1.50
Overall Mortality in Clozapine-treated					
Vermeulen et al. (6)	2018	Overall mortality in clozapine-treated compared to clozapine-naïve schizophrenia patients	MRR	0.56	0.36-0.85
Tiihonen et al. (7)	2009	Overall mortality in clozapine-treated compared to clozapine-naïve schizophrenia patients	AHR	0.74	0.6-0.91
Risk of Pneumonia in Clozapine-treated					
Stoecker et al. (8)	2017	Risk of pneumonia in clozapine-treated compared to general population	OR	4.07	2.25-7.36
Kuo et al. (9)	2013	Risk of pneumonia in clozapine-treated compared to clozapine-naïve schizophrenia patients	ARR	2.01	1.54-2.61
		Risk of pneumonia in patients treated with clozapine + any other antipsychotic compared to clozapine-naïve schizophrenia patients	ARR	4.78	3.68-6.23
Haddad et al. (10)	2013	Risk of pneumonia in clozapine-treated compared to no-drug-use controls	RR	3.18	2.62-3.86

NB EDITORIAL NOTE THE REFERENCES HERE DO NOT MATCH ARTICLE

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