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Review Article

# X-Linked Agammaglobulinaemia: Outcomes in the modern era

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ABSTRACT

Colonel Ogden Bruton reported X-Linked Agammaglobulinaemia in 1952 and treated the child with replacement immunoglobulin therapy. Over 60 years later, the treatment for XLA has largely remained unchanged. Replacement immunoglobulin lacks the isotypes IgA and IgM, leading to concerns that patients continue to experience recurrent sinopulmonary tract infections and be at increased risk of bronchiectasis. There is potential hope of earlier diagnosis with newborn screening, and a potential cure for these patients, in the form of gene therapy. However, it is first necessary to evaluate current management and outcomes to aid decisions regarding further research and clinical trials. This article reviews current management and outcomes of XLA, whilst identifying gaps in our knowledge base that may need answering before we proceed with novel diagnostic methods and treatment for XLA.



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## 1. Background

X-Linked Agammaglobulinaemia (XLA), caused by defects in *Btk* encoding Bruton Tyrosine Kinase (Btk), accounts for 85% of cases of congenital agammaglobulinaemia [1,2] and is estimated to affect 2–3 patients per million population in the United Kingdom [3]. This defect results in the failure of B-lymphocyte maturation, absent or very low serum immunoglobulin levels and failure of specific antibody production [1,4].

The resulting agammaglobulinaemia forms the basis of the clinical phenotype. Patients typically become symptomatic after transferred

*Abbreviations:* XLA, X-Linked Agammaglobulinaemia; Btk/*btk*, Bruton Tyrosine Kinase; IVIG, Intravenous Immunoglobulin; SCIG, Subcutaneous Immunoglobulin; HSCT, Haematopoietic Stem Cell Transplantation; GvHD, Graft versus Host Disease; PID, Primary Immune Deficiency; IBD, Inflammatory Bowel Disease; USIDNet, United States Immune Deficiency Network; QoL, Quality of Life; CF, Cystic Fibrosis; SGRQ, St. George's Respiratory Questionnaire; IM, Intramuscular; HRCT, High Resolution Computed Tomography; SF12v2, Short Form 12 version 2; SF36v2, Short Form 36 version 2; TREC, T-lymphocyte Receptor Excision Circle; KREC, Kappa-deleting recombination excision circles.

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maternal IgG antibodies decline from 4 to 6 months of age [5]. Before diagnosis and instigation of treatment, patients experience recurrent, often life-threatening infections [5], particularly those caused by encapsulated bacteria (especially *S. pneumoniae* and *H. influnezae*) as well as *Giardia lamblia* [5]. T-lymphocyte function is normally maintained and they are able to eliminate fungi and most viruses competently. The notable exception to this is the enterovirus family from which these patients are particularly susceptible to vaccine-associated polio, ECHO 11 and Coxsackie [5]. These viruses can cause life-threatening disease in this cohort [5].

The disease was first reported by Colonel Ogden Bruton, after whom the gene and protein kinase are named [6]. Bruton identified a young boy experiencing recurrent invasive pneumococcal infections and, using the recently developed technique of electrophoresis, confirmed agammaglobulinaemia [6–8]. Bruton successfully treated this boy with replacement immunoglobulin therapy [6].

Now in 2017, over half a century later, treatment for XLA has largely remained unchanged. There have been no major advancements aside from the switch to intravenous and subcutaneous immunoglobulin therapy (IVIG/SCIG) in the early 1980s. Furthermore, there are concerns regarding the lack of adequate IgA and IgM in current donor immunoglobulin and the subsequent risk of recurrent respiratory tract infections and development of bronchiectasis, as well as other end-organ damage.

It is possible to screen for XLA in the newborn period, enabling pre-symptomatic diagnosis and pre-emptive treatment, possibly reducing the risk of future complications. Haematopoietic stem cell transplantation (HSCT) is not routinely offered due to the risks of GvHD and the associated mortality of 10–15% [9,10]. However, with curative gene therapy in XLA murine models [11,12] and the promising results from gene therapy trials for other PIDs, a potential cure for XLA is on the horizon.

There are an increasing number of reports of patients with 'atypical' XLA. Some of these patients present with low-normal or even normal B-lymphocyte numbers in the presence of reduced or abnormal Btk expression [13,14]. These patients, whilst not necessarily having completely absent antibody levels do have a clinically significant level of hypogammaglobulinaemia [13]. These patients demonstrate a wide phenotype presentation and can present well into adulthood [15].

This article reviews current management and outcomes of patients with XLA, whilst identifying gaps in our knowledge base that may need answering to help evaluate the potential introduction of newborn screening and to justify further research into gene therapy.

## 2. Infection rates

The aim of the management of XLA is to reduce infection rates, thereby reducing the subsequent risk of developing serious complications, most notably bronchiectasis, and maintaining a quality of life comparable to that of the background healthy population.

Survival rates of recent cohorts have dramatically improved compared to historic cohorts, with patients now expected to survive into adulthood [16]. Reported annual mortality rates for patients with XLA are now approximately 1% versus historical reports of 17–25% [16–19]. This reflects a dramatic reduction in invasive, life-threatening infections as a result of more timely diagnoses and the switch from intramuscular to intravenous and subcutaneous immunoglobulin therapy [20]. In particular, since the advent of modern management, rates of invasive disease and sepsis have plummeted [16,17]. Additionally, rates of chronic enterovirus infection, (often fatal in XLA patients), have become extremely rare.

Recent advances in the optimisation of immunoglobulin therapy have had a positive impact upon patient's lives, but treatment is likely to be limited in efficacy to reduce infection rates given the lack of IgA and IgM in current products. These isotypes play a major role in protecting the mucosal surfaces, most notably the sinopulmonary tract [21,22]. Without adequate replacement, it is logical to assume that patients will continue to experience recurrent sinopulmonary infections [16]. This concern is supported by examining patients with isolated IgA deficiencies who, despite normal IgG and IgM levels, experience four times as many respiratory, gastrointestinal and skin infections compared to matched healthy controls, increasing their risk of serious long-term complications [23].

Although there are limited data showing incidence rates, recent studies from Italy and the USA consistently demonstrate that patients experience recurrent respiratory tract infections despite adequate immunoglobulin therapy [16,17,24]. In the Italian cohort of 73 XLA patients, Plebani et al. reported 37 episodes of pneumonia requiring hospital admission over a median follow-up of 7 years [16]. Winkelstein et al. in the US cohort of 201 XLA patients reported frequent rates of otitis, sinusitis and pneumonia [17].

Rates of chronic sinusitis in XLA patients remain high with reported rates of 48%–59% despite treatment [16,17]. Plebani et al. found that only duration of follow-up was associated with an increasing risk of sinusitis and there was no correlation with IgG trough levels [16]. Despite its high frequency in XLA there are no data examining its impact on patients' lives, nor is there consensus on its management on XLA. Earlier work has demonstrated that chronic sinusitis is often refractory to treatment and may require surgical intervention [25]. In contrast, Rusconi et al. demonstrated in their antibody deficiency cohort that sinus disease can be well controlled with a medical regiment of antibiotics, steroids (intranasal/oral) and saline nasal washes, as used in the immunocompetent population [26]. This recent work suggests, that active, combined therapy can be effective in this cohort, and could reduce the burden sinusitis can place on patients' lives [26].

Gastrointestinal manifestations also represent a significant burden on this population. A recent analysis of the United States Immune Deficiency Network (USIDNet) registry reported 35% of XLA patients suffered from gastrointestinal complications ranging from recurrent infections to inflammatory bowel disease (IBD) [27]. There is scant literature examining the progression of gastrointestinal disease in this cohort and potential management strategies.

There exists a risk of vaccine associated paralytic poliomyelitis in this cohort, although this risk has been reduced with many programmes switching to the inactivated polio vaccine [28,29]. The XLA cohort is susceptible to chronic meningoencephalitis following enteroviral infections [19], although this risk has decreased with modern therapy [16]. Prognosis has traditionally been poor [30,31], however a recent case report has demonstrated the potential benefit of fluoxetine in these cases [32].

Whilst it is recognised that sinopulmonary tract infections are the most common infections in XLA, accurate annual infection rates are not known in large cohorts. In a recent study, examining fifteen patients with congenital agammaglobulinaemia in northern England, the infection rates in adults and children post diagnosis were quantified as 2.12 and 0.74 infections/patient/year respectively [33]. This difference could represent a lingering effect of previous suboptimal care in the adult cohort or the natural evolution of XLA.

## 3. Respiratory health

The development of bronchiectasis is a leading cause of mortality and morbidity for these patients, diminishing their quality of life (QoL) [16,34–36]. It is often progressive, refractory to treatment and, in some cases, necessitates radical surgery or even lung transplantation [37]. Defined as a permanent and abnormal dilatation of the bronchial airways [38], it leads to a further increased susceptibility to infections with additional damage and inflammation leading to a spiral of damage (Fig. 1) [38]. In non-cystic fibrosis (CF) bronchiectasis, the 5–8 year mortality rate is reported as 10% and 13-year mortality as 30% [39–41], although the specific mortality for patients with XLA is unknown. Factors independently associated with mortality in non-CF bronchiectasis are