



ITALIAN PRIMARY IMMUNODEFICIENCIES STRATEGIC SCIENTIFIC COMMITTEE

X-LINKED AGAMMAGLOBULINAEMIA

Recommendations for Diagnosis and Treatment

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AIM

The recommendations for the diagnosis and treatment of XLA have been devised following the guidelines adopted by AIEOP in drafting protocols for the diagnosis and treatment of blood cancers. The protocols have been drawn up by a team and are subject to ongoing reviews and updates. The highly positive results obtained by AIEOP have allowed an increasing number of centres nationwide to adopt the diagnostic and treatment protocols leading to improved care for children with blood cancers.

This approach is particularly suited to the diagnosis and treatment of “orphan diseases” like primary immunodeficiencies. Because of their rarity these diseases require shared experiences to offer an optimal global approach to individual centres treating small numbers of patients. Our aim is to offer all patients the best therapeutic protocols available and at the same time avoid patients and their families having to travel constantly. Shared diagnostic and therapeutic protocols and the analysis of results will allow the network of centres to make an objective assessment of the efficacy and side effects of therapy. They will also be able to test new treatments and thereby make beneficial innovations available to all patients.

Treatment recommendations are divided into four parts. The first part presents the state-of the-art on XLA from a clinical and pathogenetic standpoint. The second part outlines the proposed diagnostic protocol and treatment recommendations. The third part deals with the genetic aspects of disease prevention. The fourth and last part offers suggestions for the management of episodes of infection arising in XLA patients.

1. INTRODUCTION

1.1 What is X-linked agammaglobulinaemia?

X-linked agammaglobulinaemia, XLA or Bruton's disease, is an inherited disorder of the immune system affecting males but not females. It is the prototype of humoral immunodeficiencies and is characterized by low/absent serum immunoglobulin levels and the absence of circulating B cells. XLA patients are unable to produce antibodies due to a mutation in the XLA gene, Btk, located on the X chromosome. This gene encodes for a protein with kinase activity known as Btk (Bruton tyrosine kinase) and is essential for the normal differentiation of B cells.

1.2 Clinical features

The disorder presents towards the end of the first or during the second year of life as a tendency to develop bacterial infections. However, under favourable environmental conditions the onset may be later. Children with XLA almost always come to the doctor's attention for recurrent respiratory infections, namely purulent otitis media and bronchopneumonia. The pyogenic bacteria responsible are usually pneumococci, staphylococci, *H. Influenzae* and less commonly streptococci. Infections are often severe but respond to antibiotics, but tend to recur a few days or weeks after the end of treatment.

Sepsis, meningitis, pyodermitis, osteomyelitis or arthritis are among the symptoms of XLA onset. Sepsis is the presenting symptom in 5-10 % of cases, whereas it is much less common during follow-up, i.e. when immunoglobulin replacement therapy has already been initiated. In most patients sepsis is secondary to localized infection such as pyodermitis, cellulitis, pneumonia, abscess or osteomyelitis. In order of frequency the pathogens responsible are *Pseudomonas*, *H. influenzae*, *St. aureus* and *Salmonella*.

Meningoencephalitis is the symptom of onset in 5% of cases and is almost always bacterial in origin unlike the forms appearing later during replacement therapy which are usually viral, due to enterovirus (Echovirus, Coxsackievirus) or herpes virus. The most common form is viral encephalitis caused by Echovirus. The presenting or suspected symptoms of encephalitis due to Echovirus are behavioural and neurological (mood swings, diminished learning capacity, irritability, depression, ataxia, paraesthesia, headache), or may mimic a dermatomyositic syndrome (hard oedema, skin rash, myositis). Clinical presentation may also be sudden with fever, headache and convulsions.

Arthritis localised in the knee and ankles is also common (20% of cases) and rapidly resolved by immunoglobulin replacement. The etiology of these arthropathies is unknown in most cases although the response to replacement therapy and sometimes antibiotic therapy suggests a bacterial infection. Arthrocentesis is always indicated followed by morphological and cultural analysis of articular fluid to determine the nature of inflammation. The few cases of bacterial arthritis with positive articular fluid culture disclosed pathogens belonging to the mycoplasma family (*Ureaplasma urealiticum*, *Mycoplasma species*).

Neutropenia (probably of toxic origin) is not unusual at onset and rapidly resolved with replacement therapy. Onset may coincide with oral antipolio vaccination (Sabin vaccine with attenuated live virus) with all the symptoms of paralytic poliomyelitis (VAPP: Vaccine Associated Paralytic Poliomyelitis). It is not clear why the attenuated virus can cause the disease in XLA subjects. VAPP may lead to death or flaccid paralysis and muscle atrophy.

XLA onset with chronic diarrhoea and cachexia is rare and more typical of a severe combined form of immunodeficiency. Acute gastroenteritis caused by infection

(Salmonella, Yersinia, Campylobacter, Giardia) or subacute gastrointestinal symptoms are more common (10% of cases).

Few data are available on the presence of intestinal disorders due to celiac disease or chronic bowel disease which should be ruled out in the presence of chronic intestinal symptoms by bowel biopsy.

1.3 Complications

Since the advent of replacement therapy the worst complications are now: chronic bronchopneumopathy, encephalitis and tumours. Chronic bronchopneumopathy is relatively frequent in patients with late diagnosis XLA who failed to benefit early from the protective effects of replacement therapy. It is also common in XLA patients with poor replacement therapy compliance or those treated with an insufficient dose, too long intervals between treatments or intramuscular administration of immunoglobulins (hence at insufficient dose). All these conditions fail to maintain protective serum IgG levels against respiratory infection. In addition, just one episode of bronchopneumopathy prior to diagnosis increases the risk of developing subsequent chronic pneumopathy irrespective of appropriate replacement therapy. Recurrent lower airway infections lead to the development of bronchoectasias, atelectasic and/or emphysematous areas and hence progressive respiratory failure. Respiratory failure is the commonest complication in XLA patients leading to death in 38%.

Another common complication is chronic sinusopathy. This condition is less severe but highly invalidating for the patient and is virtually constant after the first or second decade of life. Intravenous immunoglobulin therapy and antibiotics bring little relief. Sinusopathy is often accompanied by nasal polyposis of unknown pathogenesis non correlated to atopy.

Encephalitis caused by enterovirus, namely Echovirus, occurs in 5-15% of XLA patients with poor prognosis in most cases.

Tumours are a further complication of XLA. A high prevalence of lymphomas and colorectal tumours has been reported in different case series. In particular, colorectal tumours are 30 times more common in XLA.

Another complication, linked to intravenous immunoglobulin replacement rather than XLA, is hepatitis C infection. Appropriate physical-chemical treatment and careful monitoring of blood products can curb the risk of transmitting this infection.

The mortality rate for XLA patients is around 15-20%. The average age at death varies according to the cause (**Table I**). The commonest causes of death are respiratory failure and encephalitis caused by Echovirus.

Table I: Causes of death in 30/170 XLA patients reported in three case series (Lederman and Winkelstein, 1985, n=96; Hermaszewski Webster, 1993, n=44; Ochs, unpublished n=30). (From Primary Immunodeficiency Diseases, eds Ochs HD, Smith CIE, Puck JM, Oxford University Press 1999)

Cause of death	Number of patients	Age at death (years) Average (range)
Pulmonary infections (acute/chronic)	9	20 (10 – 27)
Enterovirus infections		
ECHO	10	12 (6-23)
Coxsackie	1	28
Polio (vaccination)	1	4
Adenovirus infections	1	14
Hepatitis	3	12 (10-24)

Severe Staphylococcus infection	2	23 (20-26)
Amyloidosis	1	not known
Inflammatory bowel disease	1	not known

The studies listed in Table I are the only ones on XLA and many of the patients included were diagnosed before or during the seventies when intravenous gammaglobulins were not available. Hence it is likely that the mortality rate for patients diagnosed during or after the eighties has dropped, but no data are currently available.

1.4 Diagnostic criteria

The following criteria for the diagnosis of XLA were drawn up by WHO in 1994:

- Males
- Onset of symptoms in the early years of life
- Absence of circulating B cells
- IgG < 200 mg/dl with undetectable levels of IgA and IgM; absent antibody response to antigenic stimulation
- Normal cell-mediated immunity

If all these criteria are met but there is no evidence of maternal ascendance from other affected males in several generations (a less frequent form than the sporadic condition), certain diagnosis of XLA cannot be established. In fact, there are other forms of immunodeficiency (e.g. autosomal recessive agammaglobulinaemias) which present with a clinical and immunological phenotype identical to XLA. The genetic deficiency in this case is due to mutation of the gene coding for the μ chain, protein Ig α of the B cell receptor (BCR) or for the λ -5 component of the surrogate light chain. Conversely, some atypical forms of XLA have recently been described (IgG levels >200, presence of up to 2% circulating B cells) caused by new mutations in the Btk gene.

In view of this, the WHO diagnostic criteria are no longer considered adequate for XLA diagnosis and additional criteria have been devised to establish diagnosis at different levels of certainty.

- 1) Definitive diagnosis of XLA. Males with fewer than 2% circulating B cells and at least one of the following:
 - Mutation in the Btk gene
 - Absence of RNAm for Btk in neutrophils and monocytes
 - Absence of Btk protein in neutrophils, monocytes or platelets
 - Cousins, uncles or nephews with fewer than 2% circulating B cells.

Probable diagnosis of XLA. Males with fewer than 2% circulating B cells and all of the following:

- Onset of recurrent infections before 5 years of age
- All serum gammaglobulin histotype levels below twice the standard deviation average for age
- Absence of isohaemoagglutinin and/or low response to vaccine antigens.

Possible diagnosis of XLA. Males with fewer than 2% circulating B cells and one of the following:

- Onset of recurrent infections before 5 years of age
- All serum gammaglobulin histotype levels below twice the standard deviation average for age
- Absence of isohaemoagglutinin and/or low response to vaccine antigens.

1.5 XLA biochemistry and genetics

XLA is caused by mutations in the Btk gene located on the long arm of the X chromosome (Xq21.3-22). The gene encodes for a cytoplasmic tyrosine kinase known as "Bruton's tyrosine kinase" which gave rise to the abbreviation Btk in honour of Odgen Bruton who first described the disorder in 1952. The Btk protein is expressed in B cells, mastocytes, erythroid and myeloid cells but not in T cells which is why no changes in the number and function of T cells are encountered in XLA patients. It is not clear why the Btk mutation blocks the maturation/differentiation of only B cells but not myeloid or erythroid cells, although the latter may possess other kinase proteins which compensate for the defective Btk protein.

The Btk gene is composed of 19 exons coding for a protein of 659 aminoacids in which different regions have different functions. Kinase activity is located in the SH1 region, while the SH2 region binds the phosphorylated tyrosine residues. The SH3 region interacts with proline-rich sequences while the TH and PH regions are involved in protein-protein interactions. On the one hand these proteins contain some of the aminoacid sequences with kinase activity able to phosphorylate certain aminoacids, and on the other aminoacid sequences able to recognise phosphorylated sequences. This structure favours a cascade protein-protein interaction: SH2 protein regions interact with the phosphorylated sequences present on another protein which in turn phosphorylates another protein through the SH1 kinase region thereby creating the basis for interaction with another protein. This cascade interaction pattern triggers the transduction of the B cell activation signal to the nucleus where the genes essential to B cell maturation and differentiation are activated. Mutations in any of these regions of the Btk gene give rise to a defective protein, which interrupts signal transduction leading to the clinical/immunological phenotype of XLA. Analysis of the mutation in the Btk gene in 282 XLA patients on the European register (data available at <http://bioinf.uta.fi/BTKbase/>) showed that the mutations vary in type and frequency and are distributed along the whole length of the gene. Roughly a third of them are missense mutations (nucleotide replacements entailing changes to a single aminoacid), one fifth are deletions, one sixth mutations at the splicing site (intro-exon junctions), one seventh are nonsense mutations (nucleotide replacements introducing a stop codon) and one tenth are insertions. Missense mutations are more common in the SH1 and SH2 regions whereas no missense mutations have been found to date in the TH and SH3 regions. All attempts to correlate the type of mutation with the clinical/immunological phenotype of XLA have proved inconclusive so far.

1.6 Genetic testing as a diagnostic tool

As specified above (section 1.4) certain diagnosis of XLA can be based on the clinical/immunological phenotype only when the family history is positive (affected males in other generations of the maternal line). If the patient has a negative family history and is therefore a sporadic presentation (70% of cases), certain diagnosis of XLA can be established only by analysis of the mutation in the Btk gene. This will distinguish XLA from other forms of immunodeficiency sharing the same clinical/immunological phenotype but which are caused by mutations in autosomal genes such as those coding for the μ chain of the IgM or the α chain of BCR or the λ -5 component of the surrogate light chain (autosomal recessive forms). It is also crucial to distinguish the X-linked forms from the autosomal recessive mutations for the purposes of genetic counselling.

1.7 Genetic testing as a means of prevention

1.7.1 Identifying carrier status

Once XLA diagnosis is certain, it is important to establish whether the mother is a disease carrier. Carrier status is not associated with clinical symptoms or changes in immunological parameters.

If several affected males are present in different generations of the maternal line, the mother is certain to be a healthy carrier and molecular analysis for mutation detection is not required.

The problem of carrier status is crucial for genetic counselling when there are no affected males in other generations. A female carrying the mutation for Btk has a 50% risk of transmitting the disease to males in subsequent pregnancies. If the mother is not a carrier and the disease arose from a new mutation in the germinal cells the risk of disease recurrence in other males is virtually nil. The sole exception to this rule is the case of germinal mosaicism in which the mutation is present to varying degrees in the ovarian germinal line cells.

Identification of carrier status should be extended to other females of fertile age (over 14 years) in the maternal line irrespective of a positive family history.

Carriers of XLA can be identified by analysis of the mutation in the Btk gene or studying the pattern of X chromosome inactivation (see section 4).

1.7.2. Prenatal diagnosis

As for all diseases caused by known genetic mutations, prenatal diagnosis is possible for carriers of XLA (see section 4). Genetic counselling should be offered beforehand in order to give the couple a detailed picture of disease characteristics and currently available treatments.

2. DIAGNOSTIC PROTOCOL

2.1. Inclusion criteria

Males with all the following clinical and laboratory criteria can be included:

- Fewer than 2% circulating B cells (CD19 and CD20), preferably in two separate determinations and a normal percentage of T cells (CD3, CD4 and CD8);
- Serum IgG levels below:
 - 200 mg/dl in infants aged < 12 months
 - 500 mg/dl in children aged > 12 months

or

- Normal IgG levels with IgA and IgM below 2SD

A registration form (**Form 1.03**) and a diagnosis form (**Form 20.01**) will be filled in for patients meeting these inclusion criteria (XLA phenotype) Annual follow-up forms (**Form 20.02**) will then be filled and sent to the AIEOP Operation Office in Bologna.

All subjects meeting the inclusion criteria will follow the set therapeutic recommendations.

2.2 Checking the inclusion criteria

Typing of lymphocyte subpopulations (CD3, CD4, CD8, CD19 and CD20) can be checked at the Coordinating Centre on request of a centre in the network.

2.3 Diagnosis

Patients enrolled according to the inclusion criteria belong to three categories:

2.3.1 Patients belonging to families in which the XLA phenotype is present in males belonging to different generations of the maternal line (positive family history). The inclusion criteria alone establish certain diagnosis of XLA in these patients.

2.3.2 Patients with sporadic presentation, i.e. patients with no other males with the same clinical-immunological phenotype in their pedigree (negative family). The inclusion criteria only establish a probable diagnosis of XLA in these patients.

2.3.3 Patients whose XLA phenotype is present in several males of the same phratry and there are no males with the same phenotype in other generations. Again the inclusion criteria only establish a probable diagnosis of XLA in these patients.

Certain diagnosis of XLA can only be established by analysis of the mutation in the Btk gene in the patients in sections 2.3.2 and 2.3.3:

- Diagnosis of XLA is certain in the presence of mutations in the Btk gene;
- The absence of mutations indicates a probable autosomal recessive form of the disease with a clinical/immunological phenotype the same as XLA.

It is crucial to distinguish the X-linked forms of agammaglobulinaemia from the recessive autosomal mutations for the purposes of genetic counselling.

To enhance diagnostic certainty mutation analysis will be performed on both genomic RNA and DNA. The DNA genome analysis will be done at the Brescia Centre while the Rome centre will analyse the RNA.

2.4 Sending samples

On request of a centre in the network, the Coordinating Centre will undertake typing of the lymphocyte subpopulations (CD3, CD4, CD8, CD19 and CD20) to confirm the immunologic inclusion criteria and detection of the mutation in the Btk gene for certain diagnosis of XLA.

The following must be sent for these tests:

- one test tube containing 5 ml blood in EDTA;

- The samples must be sent at room temperature to one of the following addresses:

BRESCIA: Prof. Alessandro Plebani
Laboratorio di Biologia Molecolare
e Genetica Medica
Clinica Pediatrica
Spedali Civili
P.le Spedali Civili 1
25123 Brescia

ROMA: Prof. Paolo Rossi
Laboratorio Immunologia e
Biotecnologie molecolari
Università Tor Vergata
Torre E Nord, sesto piano
Via di Tor Vergata, 135
00133 ROMA

- Samples must be accompanied by **n° 1 National Health Service request form** duly filled in (date of sampling, patient details with place and date of birth, place of residence, health card number, tax code number, reason: Btk molecular screening).
- Samples must also be accompanied by **Form A** duly compiled and sent via TRACO 10 service which guarantees delivery of samples by 10 a.m. on the following day.
- Samples must be sent from **Monday to Wednesday** each week.
- If diagnostic confirmation is requested, the results of the test will be notified within 2 days and the outcome of mutation analysis within 2 months.

3. TREATMENT RECOMMENDATIONS

3.1 Intravenous immunoglobulin replacement therapy

The current recommendations aim to ascertain the efficacy and tolerability of replacement therapy based on administration of Standard Human Immunoglobulins for intravenous use (IVIG) at a dosage designed to maintain serum IgG levels constantly above 500 mg/dl. This will allow us to plan subsequent controlled therapeutic trials with other protocols.

Products: All products current available in Italy can be deemed equally effective (**Table II**), but they differ in terms of side-effects. If a product is well tolerated the patient should continue the treatment with the same product. Conversely, if a patient has recurrent side-effects with a certain product another product prepared by a different method should be tried.

Dose: A dose of 400 mg/kg/21 days usually maintains serum IgG levels above 500 mg/dl, considered the protective limit.

If serum IgG levels checked before each infusion are < 500 mg/dl, the dose of IVIG should be increased to 500 mg/kg/21 days or the interval between IVIG administrations shortened to 15 days.

If serum IgG levels checked before each infusion are still < 500 mg/dl, the IVIG dose should be further increased maintaining the treatment interval at 21-15 days.

Higher doses (600-800 mg/Kg) can be used in the case of severe complications (chronic pulmonary disease, chronic diarrhoea, autoimmune disease).

3.1.1 What to do at the first infusion

3.1.1.1 Ask the patient, or his parents if the child is under age, for informed consent (**Form B**) to the administration of immunoglobulins after a detailed and readily understandable explanation of the benefits and risks of the treatment.

3.1.1.2 Take a blood sample for determination of:

- serum immunoglobulins (IgG, IgA, IgM), haemochrome, transaminase levels;
- hepatitis C (HCV-RNA) and HIV (HIV-DNA) markers;
- azotaemia, creatinine.

3.1.1.3 Start the infusion as follows (child weighing over 20 Kg):

first hour: 30 ml

second hour: 60 ml

third hour: 90 ml

fourth hour: 120 ml

subsequent hours: 120 ml/h

Infusion speed should be gradually increased without hurrying but adapted to each individual patient. If the patient feels unwell during the infusion, especially during the first treatment sessions, the infusion should be slowed down.

If the patient weighs less than 20 Kg, infusion speed should never exceed 60 ml/h.

3.1.2. What to do before each infusion

3.1.2.1 Take a detailed history of recent infections and examine the patient. The presence of fever (> 38.5 °C) is usually an indication to postpone the administration of intravenous immunoglobulins.

3.1.2.2 Record the amount and batch number of the immunoglobulin product to be administered in the patient's clinical records.

3.1.2.3 Take a blood sample and send it to the laboratory for serum immunoglobulin determination. The values should be checked before each infusion **for the first 4 infusions** and in any case until IgG levels > a 500 mg/dl are reached. Thereafter, serum IgG levels should be checked before every 4th infusion according to the scheme below.

3.1.2.4 Do liver (SGOT, SGPT) and kidney (azotaemia, creatinine) function tests every 3 months. If transaminase levels are raised a search for HCV-RNA should be made according to the following scheme:

Tempo 0 (Before the 1st infusion)	Before the 2nd, 3rd and 4th infusion	Every 4th infusion
- Haemochrome	Immunoglobulins	Haemochrome
- Immunoglobulins		Immunoglobulins
- SGOT, SGPT, azotaemia, creatinine.		*SGOT, SGPT azotaemia, creatinine
- HCV-RNA, HIV-DNA		
* if raised search for HCV-RNA and other possible causes of raised transaminase levels.		

3.1.3 Reactions to intravenous immunoglobulin administration

Intravenous immunoglobulin administration gives rise to two main side-effects:

- 1) Allergic and/or inflammatory reactions which may be vasoactive or anaphylactoid reactions or generalized anaphylaxis;
- 2) Intravenous transmission of infectious agents.

3.1.3.1 Vasoactive or anaphylactoid reactions usually appear within the first 30 minutes of infusion and are characterized by abdominal pain, low back pain, nausea and vomiting, fever, headache, muscle pain and weakness lasting up to several hours after the end of infusion. Dyspnoea and hypotension seldom occur.

Reactions usually arise during the first infusions and during multiple chronic episodes of infection since a Herxheimer reaction probably takes place with the massive release of endotoxins by the many bacteria destroyed by immunoglobulin infusion.

What to do

- a) Suspend the infusion which can be resumed a few minutes later reducing the speed.
- b) If fever and/or headache and/or muscle pain are present give salicylates (10-20 mg/Kg) or paracetamol (10 mg/Kg) before resuming infusion.
- c) When a patient has presented systemic symptoms corticosteroids (hydrocortisone 10 mg/Kg) and antihistamines (clorphenamine 0.1 mg/Kg) should be administered intravenously about an hour before the start of subsequent infusions. If fever was the only symptom premedication with paracetamol is sufficient.
- d) If the reaction was severe, a product prepared by a different method should be tried. The new product should be infused adopting the same criteria as for the first infusion (**Table II**).

3.1.3.2 Anaphylactic reactions presenting the classic symptoms of IgE-mediated anaphylaxis: dyspnea, rash, vomiting, cardiocirculatory collapse and loss of consciousness up to generalized shock are rare and usually arise during the first infusions at the start of infusion.

What to do

- a) Suspend the infusion immediately and send for a resuscitation expert.
- b) Administer adrenaline 1:1000 subcutaneously at a dose of 0.01 ml/Kg to be repeated 15 minutes later. If the patient's general and cardiocirculatory conditions fail to recover administer adrenaline 1:10.000 intravenously at a dose of 1 ml in bolus (irrespective of the patient's weight) followed by continuous intravenous infusion of 1-4 µg/Kg/minute of the same solution until arterial pressure is resumed.
- c) It is essential to keep the venous access used for IgG infusion patent as it may be required in case of shock caused by administration of emergency fluids or drugs (other vasodilators and bronchodilators in addition to adrenalin).
- d) IgG infusion must not be resumed on the same day even if the patient recovers promptly.
- e) After an anaphylactic reaction subsequent intravenous immunoglobulin infusion should be undertaken in a facility with an intensive care physician present adopting the same criteria as for the first infusion and infusing a different product. If the reaction should reoccur, intravenous immunoglobulin treatment should be suspended and continuous antibiotic prophylaxis with a cephalosporin or co-trimoxazole instituted at half/third of the dosage taken in a single evening dose.

A specific form (**From 20.03**) is available for patients presenting anaphylactic reactions and should be sent to the AIEOP Operation Office: the data collected will constitute a database to devise specific laboratory tests, nationwide surveillance of adverse reactions to intravenous immunoglobulin administration and to plan safe and adequate intervention strategies.

3.1.3.3. Intravenous transmission of infectious agents

The Cohn fractionation process adopted in preparing the gammaglobulin fraction guarantees the elimination of hepatitis B and HIV viruses. Thanks to this treatment no case of HIV transmission by IgG infusion has ever been reported even in the years when it was not possible to identify infected blood products. Unfortunately the hepatitis C virus is more resistant to Cohn fractionation and this accounts for the cases of hepatitis C recently encountered. It has now been recommended that manufacturers include an acid pH treatment with pepsin or heat in the IVIG manufacturing process to inactivate the hepatitis C virus. Nowadays donated blood and blood products are also tested for HIV, HBV and HCV further reducing the risk of disease transmission. In any case it is extremely important to update the surveillance of viral diseases transmitted by IgG infusion. Dr. Quinti ("La Sapienza" University of Rome) has volunteered to coordinate this type of study and she will draft a specific notification form to be discussed at one of the forthcoming meetings.

Table II. Immunoglobulin products for intravenous administration available in Italy

Product	Formulation	Treatment
Biaven (Farma Biagini)	10 ml=0.5 g; 20 ml=2.5 g; 50 ml= 1 g; 100 ml=5 g	pH 4 and pepsin
Endobulin (Immuno)	5 ml=0.25 g 10 ml=0.5 g; 20 ml= 1 g; 50 ml= 2.5 g; 100 ml=5g 50 ml=7.5 g 200 ml=10 g	Precipitation with PEG
Globuman (Berna)	1; 2.5; 5 g	Ion exchange chromatography
Haimaven (Aima)	10 ml=0.5 g; 20 ml=1 g; 50 ml=2.5 g; 100 ml=5 g	pH 4 and pepsin
Ig vena (Sclavo)	5 ml=0.25 g 10 ml=0.5 g; 20 ml= 1 g; 50 ml= 2.5 g; 100 ml=5g 200 ml=10 g	Reduction and alchylation
Intraglobin (Biotest)	1;2.5;5;10 g	Beta- propiolactone
Isiven (ISI)	10 ml=0.5 g; 20 ml= 1 g; 50 ml= 2.5 g; 100 ml=5g	Beta- propiolactone
Sandoglobina (Sandoz)	1;3;6;12 g	pH 4 and pepsin
Venimmun (Behring)	10 ml=0.5 g; 50 ml= 2.5 g; 100 ml=5g 200 ml=10 g	Suphonation
Venogamma (Alfa Biotech)	0.25;0.5;1;.2.5;5; 10 g	Stabilisation with PEG
Gammagard S/D (Baxter)	0.5;2.5;5.0;10 g	Ion exchange chromatography

4. PREVENTION

4.1 Disease carrier status

Identification of disease carrier status is essential for genetic counselling and is indicated for the mothers of patients and collateral females of the maternal line of the patient's family.

4.1.1 When to identify disease carrier status

4.1.1.1 Identification of disease carrier status is indicated in both the mothers of patients and in collateral females of the maternal line of the family in patients with a negative family history (sporadic presentation) (section 2.3.2) or patients affected only in the same phratry and not in other generations (section 2.3.3).

4.1.1.2 Healthy carrier status is certain in the case of patients with a positive family history (affected males in different generations) (section 2.3.1) so that confirmation by molecular analysis is not needed. Identification of disease carrier status is nonetheless required in collateral females of the maternal line.

4.1.2 How to identify disease carrier status

4.1.2.1 Direct mutation analysis

This test is indicated whenever the patient's Btk mutation is known. If the same mutation is present in the heterozygous state in the mother, then she is an XLA carrier and there is a likelihood that other collateral females in the female branch of the family will also carry the mutation. Instead if the mother is homozygous for the normal sequence, she is not an XLA carrier and her son's disease is due to a de novo gene mutation.

4.1.2.2 Analysis of X chromosome inactivation

Analysis of X chromosome inactivation to identify carrier status is indicated for the mothers of males with sporadic disease presentation or with more than one son affected in the same phratry with no males affected in other generations if the patient's Btk mutation has not been determined. Mutation analysis need only be done later if necessary to study the whole gene.

4.2 Sending samples

At the request of centres in the network, the coordinating centre will undertake genetic testing to identify carrier status.

Testing requires a sample of:

- **5 ml of blood in EDTA** for identification of carrier status by mutation analysis
- **32 ml of blood in 8 ml ACD** for identification of carrier status by X chromosome inactivation.

Blood samples should be prepacked and sent at room temperature to the following address:

Prof. Alessandro Plebani
Laboratorio di Clinica pediatrica
Spedali Civili
P.le Spedali Civili n° 1
25123 Brescia.

- samples must be accompanied by **Form C** duly compiled and sent by sent via TRACO 10 service which guarantees delivery of samples by 10 a.m. on the following day.
- Samples must be sent from **Monday to Wednesday** each week.
- Results will be notified within 2 months.

4.3 Prenatal diagnosis

Prenatal XLA diagnosis requires certain diagnosis established in the family. All invasive prenatal diagnostic techniques (chorionic villi sampling, amniocentesis, umbilical cord blood sampling) carry a risk of pregnancy termination. Although this risk is low (from 0.5% for amniocentesis to 1.5% for umbilical cord blood sampling), it is only justified when there is clear evidence that the family is actually affected by XLA.

Before proceeding to prenatal diagnosis, the couple must be offered genetic counselling to give them a detailed picture of disease characteristics and currently available treatments.

Before prenatal diagnosis the Coordinating Centre should be contacted to establish the technical details of sampling and dispatch of samples. Some technical points are listed below.

For XLA families with a known mutation prenatal diagnosis is done by sampling the chorionic villus (from the 10th week of pregnancy) or amniotic fluid (at the 16th-18th week).

This material is used for:

- DNA extraction from the specimen
- fetal karyotype analysis (on the same sample)
- if the foetus is male, a search for the mutation on the extracted DNA;
- it is important to rule out contamination by maternal tissues on the same DNA sample (by molecular analysis by highly polymorphic markers).

In the past, prenatal diagnosis of XLA was also done on foetal blood sampled at the 20th week for the presence/absence of B cells. This technique is no longer used as false positives and false negatives can result from the variable number of B cells in the foetus and the possible passage of maternal lymphocytes. For the same reasons, expression of the Btk protein on cells obtained after chorionic villi sampling can no longer be used for prenatal diagnosis.

5. RECOMMENDATIONS ON TREATING INFECTIONS

5.1. Upper airway infections

5.1.1 purulent rhinitis: should be treated promptly with antibiotics until symptoms have resolved completely (**Table III**).

In addition, given the frequency with which trivial viral rhinitis is complicated by bacterial infection, it may be advisable to start antibiotics whenever any minor upper airway infection occurs, depending on the patient's clinical history.

The choice of antibiotic is based on epidemiological findings showing that *H. influenzae*, *St. pneumoniae* and *M. catharralis* are the most common pathogens responsible for infection.

Table III. Treatment of acute purulent rhinitis/otitis/sinusitis

<u>First choice Ab</u>	<i>Dosage in mg/Kg/die</i>	<i>N° administrations</i>	<i>Route</i>
Amoxicillin	40	3	os
Amoxicillin/ Clavulanic acid	50	2-3	os
TMP/SMX	7/35	2	os
<u>*Second choice Ab</u>	<i>Dosage in mg/Kg/die</i>	<i>N° administrations</i>	<i>Route</i>
Ceftibuten	9	1	os
Cefixime	8	1	os
Cefuroxime	20-40	2	os
Cefaclor	40	3	os
Ceftriaxone	40-80	1	im
Clarithromycin	15	2	os
Azithromycin	10	1	os
* in case of intolerance or no improvement of symptoms after first choice drugs or in case of recurrence			

5.1.2 otitis and sinusitis: should be treated promptly with appropriate antibiotics (**Table III**). A nasal or pharyngeal swab is of little or no use in selecting the antibiotic to use for these infections and the choice of drug is based on epidemiological findings showing that *H. influenzae*, *St. pneumoniae* and *M. catharralis* are the most common pathogens responsible for infection.

Duration of treatment is 10 days for otitis and around three weeks for sinusitis because it is recommended to continue treatment for at least one week after the resolution of symptoms.

Initial parenteral antibiotic treatment is recommended in case of complications like mastoiditis or cellulitis.

In case of recurrent otitis and sinusitis it is advisable to follow treatment of the acute episode with a six-month period of antibiotic prophylaxis (usually in autumn to winter)

using amoxicillin, amoxicillin/clavulanic acid or co-trimoxazole at half the dosage taken in a single evening dose.

The first choice drugs for antibiotic prophylaxis remain amoxicillin, amoxicillin/ clavulanic acid and co-trimoxazole.

Add-on treatment with anti-inflammatory drugs (inhalation of corticosteroids: 2 puffs per nostril twice a day) during antibiotic treatment of an acute episode of sinusitis has proved effective in adults but is a matter of ongoing debate in children.

Appropriate treatment of sinusitis in XLA patients is an effective means of preventing bronchitis and bronchopneumonia.

5.1.3 chronic sinusopathy. Adequate treatment of acute sinusitis is the best means of preventing the onset of chronic sinus disease.

Treatment of chronic sinusitis requires close cooperation with otolaryngologist colleagues and includes:

- fibroscopy with possible culture and slide smear of specimens to gain information for targeted medical management

- surgery to resect accumulated inflammatory tissue readily subject to infection.

Aerosol inhalation of antibiotics is only indicated in patients undergoing surgical cleansing to restore access to the paranasal sinuses.

5.1.4 nasal polyposis is a relatively common complication in XLA patients. The pathogenesis is unknown and non correlated to atopy. Treatment is difficult and often frustrating. Except for anecdotal reports, there is insufficient evidence that topical steroids are effective and their widescale use is not recommended at present. Surgical resection of the polyps is recommended when breathing is impaired but recurrence is common.

5.2 Lower airway infections

Antibiotics should always be given for lower airway infections. If the patient has a productive cough and expectoration is possible treatment should be preceded by excretion culture. The first choice antibiotic is empirical and must be chosen according to the patient's age and the pathogens most likely to be responsible for infection in relation to age (**Table IV**).

Table IV. Etiological agents responsible for pneumonia at different ages

< 4 months	<i>Streptococcus agalactiae</i> <i>Chlamydia trachomatis</i>
4 months-4 years	Viruses (adenovirus, RSV, influenza viruses) <i>Streptococcus pneumoniae</i> <i>H. influenzae</i> <i>Staphylococcus aureus</i>
> 4 years	<i>Streptococcus pneumoniae</i> <i>H. influenzae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> <i>Staphylococcus aureus</i> Viruses (adenovirus, influenza viruses)

Treatment options for lower airway infections are listed in **Table V**.

If a specific strain is isolated treatment will obviously be instituted according to the antibiogram.

Continuous antibiotic prophylaxis is recommended accompanied by a programme of respiratory physiotherapy as prescribed by the physiatrist in patients presenting more than one episode of bronchopneumonia a year (recurrent BPN), or those with chronic bronchopneumopathy or chronic bronchitis. To standardise treatment and prophylactic measures in chronic lung disease, Dr. Franca Rusconi of the De Marchi Paediatric Clinic in Milan has offered to draft specific guidelines to be presented at a forthcoming meeting.