



**ITALIAN PRIMARY IMMUNODEFICIENCIES STRATEGIC SCIENTIFIC  
COMMITTEE**

# **TRANSIENT HYPOGAMMAGLOBULINAEMIA OF INFANCY**

**Recommendations for Diagnosis and Treatment**

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## **Aim**

The recommendations for the diagnosis and treatment of Transient Hypogammaglobulinaemia of Infancy (THI) have been devised to optimize the approach to the diagnosis and treatment of “orphan diseases” like primary immunodeficiencies.

Establishing a nationwide diagnostic and therapeutic protocol and analysing patient outcome will allow ongoing adjustments and updates designed to offer all patients uniform standards of care.

The primary aim is to:

- Define the clinical condition
- Devise a diagnostic protocol
- Observe the natural history of the disease
- Define preventive and therapeutic recommendations

The first part of these diagnostic and therapeutic recommendations presents the clinical and pathogenetic state-of-the-art of THI. The second part outlines the diagnostic protocol, while the third part offers suggestions for prevention and management when definite indications are lacking.

The secondary aim is to:

- Identify predictive markers of evolution to other immunodeficiencies
- On the basis of findings obtained from any controlled trials and information on age-related changes in immune response, devise the most appropriate preventive and therapeutic strategies.

The appendix contains the “pathogenetic” analyses available on request to all Centres in the network interested in this type of study.

## INTRODUCTION

### 1.1 What is Transient Hypogammaglobulinaemia of Infancy?

Transient Hypogammaglobulinaemia of Infancy (THI), described for the first time by Gitlin and Janeway in 1956, is a defect in the synthesis of one or more immunoglobulin histotypes in the early years of a child's life. The condition is **self-limiting** as the low antibody levels will reach normal levels with age. The underlying mechanism responsible for THI is not known and the condition may result from a number of factors. THI is usually considered a variant of the normal (age-related) development of the immune system, and should be distinguished from "physiological hypogammaglobulinaemia", the term applied to the normal nadir of IgG levels which occurs in babies between three and six months of life as IgG from the mother are gradually lost. After this immunoglobulin levels rise gradually throughout childhood reaching adult levels when children are about five years old. By contrast, infants with THI are unable to synthesize normal concentrations of IgG so that after IgG levels have reached the physiological nadir they fail to increase and remain low for age usually until two to four years of age. Despite the relatively low IgG levels, antibody function is usually intact and B and T cell values are normal. Unfortunately, by definition certain diagnosis of THI can only be established when a child fails to reach IgG levels appropriate for his/her age. Until that time it is essential to make every effort to distinguish THI from other diseases characterized by hypogammaglobulinaemia.

The prevalence of THI remains unsettled. In Japan it is though the represent 18.5% of all primary immunodeficiencies, whereas Walker claims its prevalence is similar to that of symptomatic selective IgA deficiency. According to some reports, THI accounts for less than 5% of all primary immunodeficiencies diagnosed by tertiary centres. The controversy surrounding the frequency of THI could be due to the fact that the condition is not necessarily accompanied by symptoms. Clinical manifestations vary from asymptomatic cases to children presenting with severe recurrent infections mainly involving the respiratory apparatus and gastrointestinal tract, episodes of fever of unknown origin or atopic dermatitis and other allergic manifestations. The broad spectrum of clinical manifestations and the variable underlying causes indicate that different factors are responsible for THI. The mechanisms implicated include: delayed functional maturation of B cells, helper T cell defects or defective T lymphocyte maturation which may affect B cell function due to partially effective signalling. There is recent evidence of an excessive Th1-type response in THI associated with an increased secretion of IL-12 and an elevated number of monocytes expressing intracellular IL-12. Increased IL-12 secretion had previously been reported in patients with common variable hypogammaglobulinaemia (CVD) and in patients with IgA defect (IgAD). CVD and IgAD may well represent the possible evolution or "complication" of THI. Although it remains unsettled whether the primary impairment lies in the IL-12/IF gamma circuit or below this activated circuit, evidence that CVD is genetically linked to IgAD as they share certain susceptibility genes supports the idea of a common pathogenetic denominator except that this possible defect is only transient in THI. Hence further knowledge of the mechanism underlying regained antibody production in THI is not only important in terms of treating correlated immunodeficiencies like CVD and IgAD, but also provides an excellent basis to assess the efficiency, immunogenicity and safety of different vaccine formulations in the neonatal period and later.

### 1.2 Diagnostic criteria

Diagnostic criteria for the different forms of immunodeficiency have been devised by the European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency (PAGID) establishing diagnosis with three degrees of accuracy: certain, probable or possible. Unfortunately, THI is one of the few immunodeficiencies for which a certain diagnosis cannot be established by molecular analysis, nor can a diagnosis be probable in the first years of life. Diagnosis is therefore

retrospective and is only obtained once the IgG synthesis defect (2 SD below normal for age) with or without an associated defect of other IgG histotypes (2 SD below normal for age) subsides and immunoglobulin levels have returned to within the normal range for age.

Since molecular analysis is not available and certain diagnosis is retrospective, a possible diagnosis of THI can only be established by ruling out all the other causes of hypogammaglobulinaemia listed below:

<b>Differential diagnosis of hypogammaglobulinaemia</b>
<p>Drug-induced:</p> <ul style="list-style-type: none"> <li>- antimalarials</li> <li>- captopril</li> <li>- carbamazepine</li> <li>- glucocorticoids</li> <li>- fenclofenac</li> <li>- gold salts</li> <li>- penicillamine</li> <li>- phenytoin</li> <li>- sulfasalazine</li> </ul>
<p>Genetic disorders:</p> <ul style="list-style-type: none"> <li>- hyper-IgM syndrome</li> <li>- transcobalamin II deficiency and hypogammaglobulinaemia</li> <li>- X-linked agammaglobulinaemia</li> <li>- X-linked (EBV-associated) lymphoproliferative syndrome</li> </ul>
<p>Chromosome abnormalities:</p> <ul style="list-style-type: none"> <li>- chromosome 18q syndrome</li> <li>- monosomy 22</li> <li>- trisomy 8</li> <li>- trisomy 21</li> </ul>
<p>Infectious diseases:</p> <ul style="list-style-type: none"> <li>- HIV</li> <li>- congenital rubella</li> <li>- congenital CMV infection</li> <li>- congenital Toxoplasma infection</li> <li>- mononucleosis</li> </ul>
<p>Tumours:</p> <ul style="list-style-type: none"> <li>- chronic lymphoid leukaemia</li> <li>- hypogammaglobulinaemia with thymoma (Good's syndrome)</li> <li>- non Hodgkin's lymphoma</li> <li>- B-cell tumours</li> </ul>
<p>Systemic diseases:</p> <ul style="list-style-type: none"> <li>- immunoglobulin hypercatabolism immunodeficiency</li> <li>- immunodeficiency due to excessive immunoglobulin loss (nephrosis, severe burns, lymphangectasia, severe diarrhoea)</li> <li>- cryoglobulinaemia</li> </ul>

***Explanatory note.***

***Like the previous recommendations for XLA, CGD and CVID, this document aims to identify cases of THI for the purposes of setting up nationwide epidemiological surveillance (immunological tests can be undertaken at any Centre) and to establish the natural history of the disease by:***

- ***filling in and collecting forms (registration, diagnosis and follow-up) listing clinical and immunological data from enrolment up to three years of age.***

***The data obtained will yield information required to devise recommendations for early diagnosis and treatments tailored to the clinical needs of THI patients.***

***In addition, it is possible to take part in the “pathogenetic” study of THI designed to clarify the pathogenetic mechanisms underlying this immunodeficiency and if possible to identify markers predictive of evolution to other immunodeficiencies, i.e. selective IgA deficit and common variable immunodeficiency with the target of:***

- ***analysing certain immunological parameters (see Appendix).***

***The data obtained will yield information required to establish a possible correlation between a variation in data and the onset of complications both to clarify the ability to develop an adequate immune response during ontogenesis. This could be particularly useful for the purposes of developing vaccines.***

## 2. DIAGNOSTIC PROTOCOL

### 2.1 Inclusion criteria

This protocol applies to male and female infants aged between **12 and 36 months** with all of the following clinical and laboratory evidence:

- male or female patients with a marked reduction (below 2 SD for age) of one or more Ig with or without a reduction below 2 SD for age of IgA or IgM (see Table 1)
- B cell values exceeding 2%

**Table 1: Normal for age immunoglobulin concentrations**

Table 1: Normal for age serum immunoglobulins; mean ( $\pm$  2DS)

Age	IgG	IgA	IgM
	<b>m <math>\pm</math> 2DS (mg/dl)</b>		
Umbilical cord	1112(862 – 1434)	Could not be measured	9(5-14)
1-3 months	468(231-495)	24 (8-74)	74(26-210)
4-6 months	434(222-846)	20(6-60)	62(28-39)
7-12 months	569(351-919)	29(10-85)	89(38-204)
13-24 months	801(264-1509)	54(17-178)	128(48-337)
2-3 years	889 (462-1710)	68(27-173)	126(62-257)
4-5 years	1117(528-1959)	98 (37-257)	119(49-292)
6-8 years	1164(633-1016)	113(41-315)	121(56-261)
9-11 years	1164(707-1919)	127 (60-270)	129(61-276)
12-16 years	1105(604-1909)	136(61-301)	132(59-297)

From "Il bambino immunodepresso: perchè lo è e come va difeso" Ugazio AG et al, CEA, 1995.

A registration form (**Form 1.01**) and a diagnosis form (**Form 24.01**) will be filled in for all patients meeting these inclusion criteria. Annual follow-up forms (**Form 24.02**) will then be filled in and sent to the AIEOP Operation Office in Bologna. All subjects meeting the inclusion criteria will follow the set therapeutic recommendations.

## 2.2 Tests at onset and during follow-up:

### **On enrolment:**

Haemochrome + F  
Azotaemia, creatininaemia  
Transaminase levels  
Protein electrophoresis  
Autoantibodies  
IgG, IgA, IgM  
IgG subclasses  
Anti-tetanus Ab, Anti-hepatitis B Ab  
Isohaemoagglutinin  
PRIST  
CD3, CD4, CD8, CD19, CD16

### **Every 12 months:**

Haemochrome + F  
IgG, IgA, IgM  
IgG subclasses  
Autoantibodies

### 3. TREATMENT RECOMMENDATIONS

*No treatment protocol is currently available*, but generally speaking support treatment and appropriate antibiotic therapy are sufficient in symptomatic cases. Intravenous immunoglobulin replacement therapy is not usually entertained unless the patient presents infections that are severe or resistant to standard treatments. In these cases it is important to remember that immunological assessment ruling out other causes of immunodeficiency must be regularly reconfirmed.

#### 3.1 Vaccinations

Give all compulsory vaccinations + Anti-Hemophilus i. + Anti-pneumococcus  
No data are currently available on the efficacy of live attenuated virus vaccines or possible side effects.

#### 3.2 Antibiotic therapy

Prompt administration of antibiotics is recommended to treat acute infections.

#### 3.3 Intravenous immunoglobulin replacement therapy

Severe cases of THI resistant to standard antibiotic treatments may need to resort to intravenous immunoglobulin replacement therapy.

This protocol aims to ascertain the efficacy and tolerability of a replacement therapy based on the administration of polyvalent human immunoglobulins for intravenous infusion at doses designed to maintain **pre-infusion** serum IgG levels constantly above 500 mg/dl. This will allow the therapeutic protocol to be tailored to individual needs.

**Products:** All products currently available in Italy can be deemed equally effective from the therapeutic standpoint. Therefore, if a product is well tolerated the patient should continue the treatment with the same product. Conversely, if a patient has severe adverse reactions or mild side-effects not controlled by the usual measures (reducing the speed of infusion, administration of antipyretics antihistamines or steroids) another IVIG product should be tried.

**Dose:** A dose of 400 mg/kg/month usually maintains serum IgG levels above 500 mg/dl, considered the protective limit for the main infections. If serum IgG levels are < 500 mg/dl after the first six months of infusions (the time usually required to reach a plateau), the interval between IVIG administrations should be shortened or the dose of IVIG increased maintaining the same treatment interval.

##### 3.3.1 How to start the treatment

Give a detailed explanation and ask for signed informed consent (for treatment with blood products)

Take a blood sample when required and when clinically indicated

Record the type of product, batch number and expiry date in the patient's clinical records

If the patient weighs less than 20 kg infusion speed **should never exceed 60 ml/h** as follows:

first hour: 10-15 ml  
second hour: 20 ml  
third hour: 30 ml  
fourth hour: 45 ml  
subsequent hours: 60 ml/hour

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.

### 3.3.2 What to do before each infusion:

- Take the history and examine the patient, recording the type, batch number and expiry date of the IgG product in the patient's clinical records

### 3.3.3 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.

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 (chlorphenamine 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.

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 recur, 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 (**Form 24.03**) 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.

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## 5. APPENDIX

This section is not an integral part of the diagnostic and therapeutic recommendations for THI, but offers additional options belonging to the secondary targets of the protocol.

Centres in the network are invited to participate in the “pathogenetic study” which has adopted specific immunological pathogenetic parameters to be investigated on enrolment and to be repeated every 12 months if negative.

### **Immunological pathogenetic parameters:**

B cell pattern (transitional, mature and memory B cells)

Test of B cell proliferation to different stimuli (Ag PS, *LPS*, PWM)

In Vitro Ig production

Anti-pneumococcal antibody response

### **Sending samples**

The local Centre will send blood samples from THI patients to the Centres which have agreed to act as national reference centres to test the above immunological parameters (with prior notice). Samples must be sent by a courier guaranteeing delivery within 24h.

Centres/Laboratories available for :

B cell pattern (transitional, mature and memory B cells) and Test of B cell proliferation to different stimuli (Ag PS, *LPS*, PWM) (**5 ml blood in EDTA required**)

ROME: Dott.ssa Rita Carsetti / Dott.ssa Silvia Di Cesare  
Laboratorio Immunologia eBiotecnologie molecolari/Laboratorio di Immunologia e  
Biotecnologia Pediatrica  
Ospedale Bambino Gesù/Università Tor Vergata  
Torre E Nord, quinto piano  
Via di Tor Vergata, 135  
00133 ROMA  
e-mail: [carsetti@Med.uniroma2.it](mailto:carsetti@Med.uniroma2.it); [di.cesare@Med.uniroma2.it](mailto:di.cesare@Med.uniroma2.it)  
tel.: 06-72596823/06-72596825  
Fax: 06-72596822

**In Vitro Ig production (5 ml blood in heparin required)**

PAVIA: Dott.ssa Maria Antonia Avanzini /  
Dott.ssa Rita Maccario/ Dott. Massimo Marconi  
Lab. 1° piano Cl. Pediatrica  
Policlinico S. Matteo  
Ple Golgi, 2  
27100 – PAVIA  
e-mail: [avanzini@smatteo.pv.it](mailto:avanzini@smatteo.pv.it)  
tel: 0382-502909

**Anti-pneumococcal antibody response (1 ml of serum)**

ROME: Prof.ssa Isabella Quinti  
Dipart. Medicina Clinica  
Università La Sapienza  
Viale dell'Università, 37  
00186 ROMA  
Tel.06/49972036  
Fax 06/4466209  
e-mail : [isabella.quinti@uniroma1.it](mailto:isabella.quinti@uniroma1.it)

The laboratory will notify the requesting physician of test results by e-mail or post.