An unexpected diagnosis: a 40 year-old man presenting with chronic diarrhea

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Case Report

- A **40-year-old ma**n from **Venezuela** with refractory celiac disease was admitted for chronic diarrhea.
- Also, he had **non-respond to corticoid treatment**, malabsorptive syndrome and loss of weight in the last month and a half.
- **Chronic diarrhea** since he was 15 years-old ➔ diagnosed with questionable refractory celiac disease in 2011
  - Anti-transglutaminase and endomysial antibodies +.
  - Duodenal biopsies performed by gastroscopy were negative.
  - Adbominal CT: diffuse inflammatory signs.
  - Genetic study wasn't performed.
- He admitted to having a non-strict gluten-free diet ➔ Corticoids were initiated because of persistent diarrhea. Initially 25 mg of prednisone daily ➔ maintenance dose of 20 mg daily since 2011, (lower doses didn't control the symptoms).
- January 2016 he moved to Spain: he has improved adhering to the gluten-free diet since living in Spain.

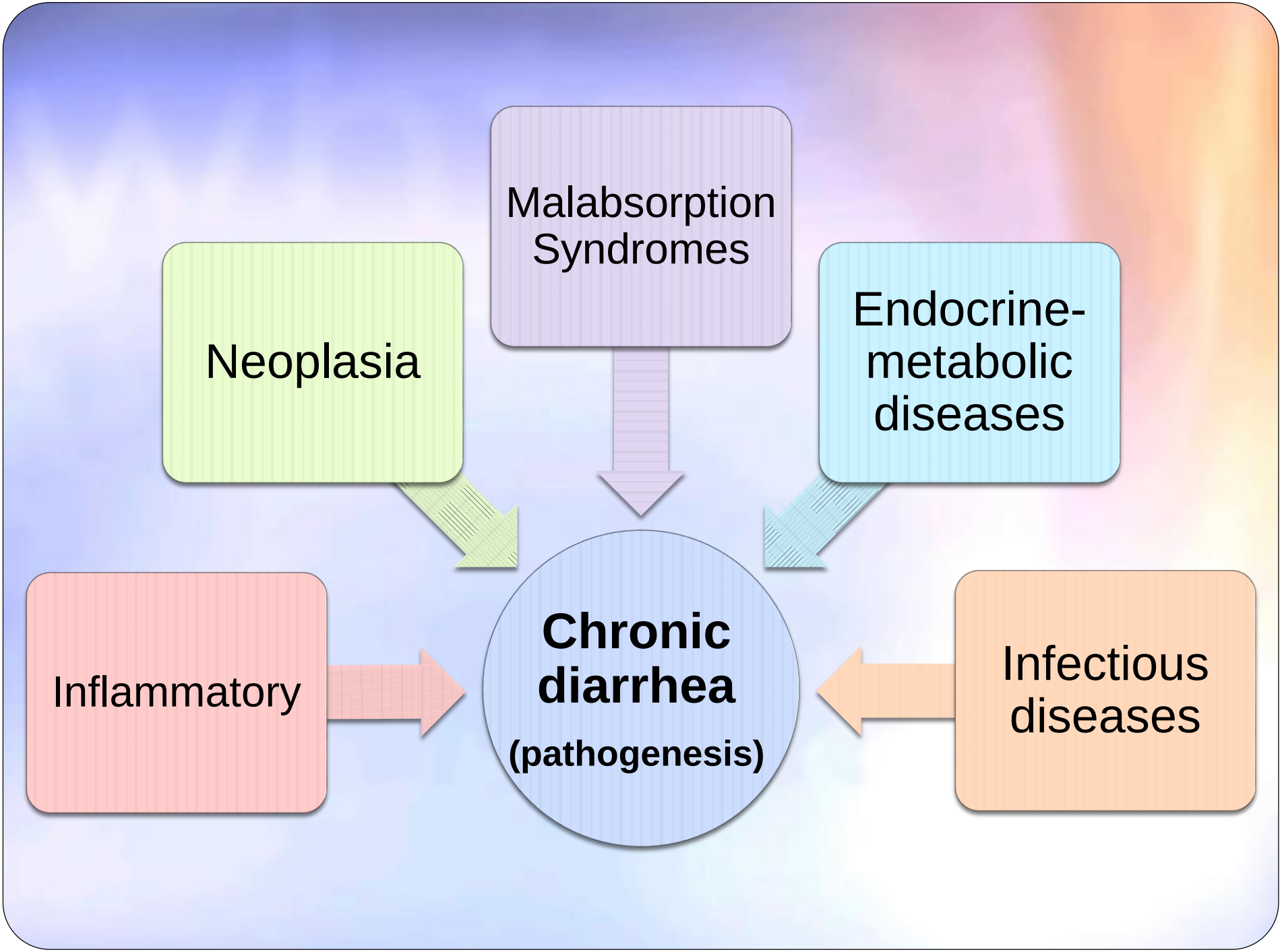
Case Report

- **Current disease:** The patient consulted the emergency department on October 2016 for:
  - Increase in the number of liquid stools, without pathological products the last month and a half.
  - Abdominal pain
  - Loss of weight (10 kg).
  - On admission, the patient was afebrile with no pathological findings reported in the physical examination.

- The patient was entered the hospital to complete the study.

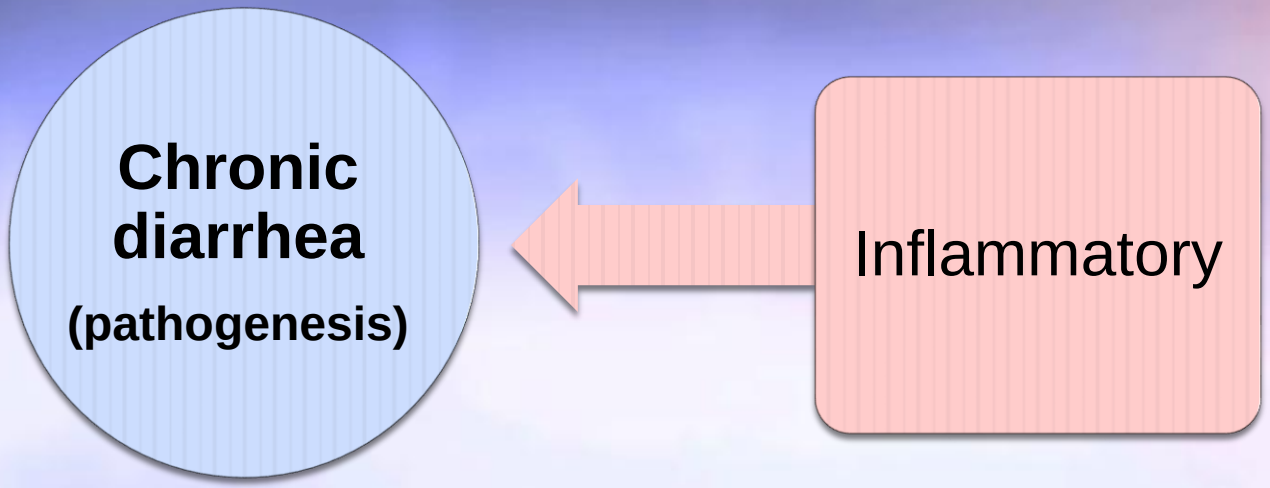
Diagnostic approach

- 40 year-old man from Venezuela but living in Spain since 2016
- Chronic diarrhea cataloged as **refractory celiac disease** (antibodies positive but pathology negative, from the age of 15 years old!!)
- Mild hypokalemia and other deficiencies (low levels of vitamin D and calcium, hypoproteinemia…)
- Chronic corticoid therapy and pathological fractures

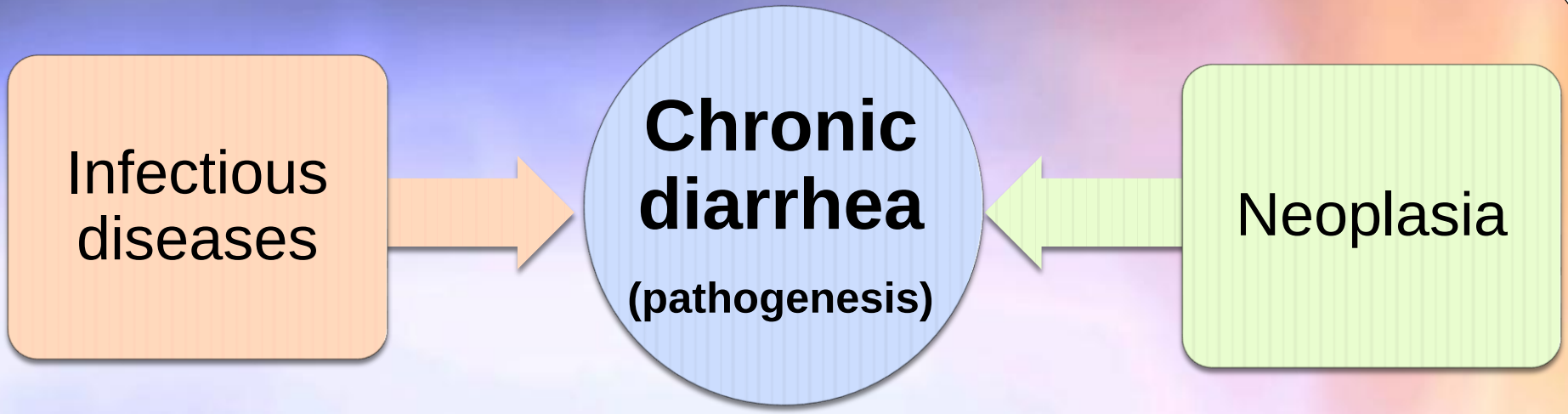

Malabsorption Syndromes
Neoplasia
Endocrine-metabolic diseases
Inflammatory
Chronic diarrhea
(pathogenesis)
Infectious diseases

Diagnostic work-up

- **To rule out iatrogenic cause:**
  - Chronic corticoid therapy
    - Muscular atrophy and weakness
    - Sodium retention and increase of renal losses of potasium
    - Gastric and duodenal ulcers, gastrointestinal bleeding→ Not diarrhea
- **Study of the previous diagnosis of refractory celiac disease**
  - Autoinmunity → Anti-tissue transglutaminase and anti-endomysial antibodies **negative**
  - HLADQ2 **positive**

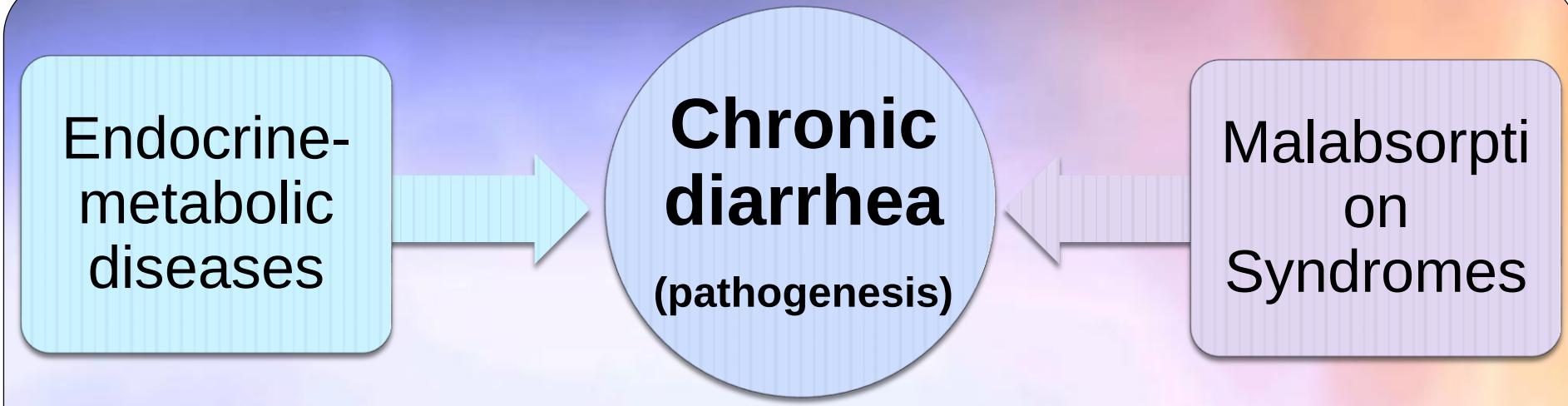


- **Faecal calprotectin**: 809 mg/Kg (<50)
- **Gastroscopy**: Gastric folds atrophy. Villus atrophy.
- **Colonoscopy**: Internal hemorroids. Normal colonoscopia and ileoscopy
- **Biopsies from**:
  - Stomach: Squamous and glandular mucosa with complete intestinal metaplasia without dysplasia. Chronic active gastritis
  - Duodenum: Slight chronic inflammation of the lamina propria
  - Terminal ileon: Without significant microscopic abnormalities
  - Transverse and right colon: Acute and chronic inflammation in the lamina propria and acute crypt
- **Abdominal CT scan:** No significant radiological findings.



- **HIV 1-2**: Negative
- **HBV immunization:** Anergy
- **Quantiferón-TB:** Negative
- **Stool culture (x5) and parasite determination**: Negative
- **Hydrogen breath test:** Negative

- **Radiologic and endoscopy findings**: None
- **Beta-2-microglobulin**: 4,30 mg/L (0,70 - 1,80)
- **Chromogranin A**: 123,6 ug/L (0 - 100)



- **Thyroid stimulating hormone:** 1,15 mUI/L (0,30 - 5,00)
- **Study of anemia**:
  - Iron tests and folate level: Normal
  - Vitamin B12: 64 pmol/L (150 - 650) → Anti parietal cell and anti intrinsic factor antibody: Negative (Pernicious anemia?, B cell deficiency)
- **Lymphocyte subpopulations** : B cells 0,16 % (6-16%), inversion of the CD4/CD8 ratio

- **Immunoglobulins:**

  IgG quantification 357 mg/100ml (723-1.685)
  IgA quantification 62,20 mg/100ml (69-382)
  IgM quantification 15,40 mg/100ml (40-230)

Common Variable Immunodeficiency (CVID)

- **Features:**
  - Heterogeneous disorder characterized by defective B cell differentiation with impaired secretion of Ig and markedly reduced serum levels of immunoglobulin (Ig) G and low IgA or IgM, with impaired antibody responses, despite the presence of B cells.
  - Most prevalent form of severe antibody deficiency affecting both children and adults. Frequency of 1:25,000. Diagnosis is usually established between 20-45y.
  - "Variable" refers to the heterogeneous clinical manifestations of this disorder, which include recurrent infections (affecting different organ systems, especially the upper and lower respiratory tracts and gastrointestinal tract), chronic lung disease, autoimmune disorders, inflammatory conditions, gastrointestinal disease, and susceptibility to lymphoma.
  - CVID affect multiple organ systems, and patients often have been evaluated by several specialists by the time they are diagnosed.

Common Variable Immunodeficiency (CVID)

- **Definition:** (ESID working definitions for clinical diagnoses of primary ID)

At least one of the following:
- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency

AND marked decrease of IgG and marked decrease of
levels (measured at least twice; <2SD of the norm
AND at least one of the following:
- poor antibody response to vaccines (and/or absen
i.e. absence of protective levels despite vaccinati
- low switched memory B cells (<70% of age-relate

AND secondary causes of hypogammaglobulinaemia h
separate list)
AND diagnosis is established after the 4th year of life (
before)
AND no evidence of profound T-cell deficiency, defined
(y=year of life):
- CD4 numbers/microliter: 2-6y <300, 6-12y
- % naive CD4: 2-6y <25%, 6-16y <20%, >1
- T cell proliferation absent

Gastrointestinal disease:
- 10-20% of CVID patients
- May be the presenting disorder
- **Diarrhea** (most common), malabsorption, abdominal pain, weight loss, vitamin and electrolyte deficiencies
- **Gastrointestinal infections**: norovirus, Campylobacter jejuni, Salmonella, chronic giardiasis, cytomegalovirus, cryptosporidium
- **Specific disorders**: Inflammatory bowel-like disease, Sprue-like illness, Nodular lymphoid hyperplasia, Pernicious anemia, Bacterial overgrowth, Protein-losing enteropathy, Nonspecific malabsorption

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- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency

AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age);

AND

- emagglutinins);
- e defined
- l value)

AND n excluded (see

AND otoms may be present

Immunoglobulin levels:

- IgG: 357 mg/dl (723-1.685) (Mandatory)
- IgA: 62,20 mg/dl (69-382) (Mandatory)
- IgM: 15,40 mg/dl (40-230) (Optional)
- Generally normal reference range is ± 2SD
- Ig levels should be confirmed

AND no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life):

- CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200
- % naive CD4: 2-6y <25%, 6-16y <20%, >16y <10%
- T cell proliferation absent

Common Variable Immunodeficiency (CVID)

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At least one of the following:

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- autoimmune manifestations

Poor/absent immunological response:

- IgG to tetanus and diphtheria – response to protein-based vaccines
- IgG to 14-23v pneumococcal vaccine – response to polysaccharide-based vaccines
- Very low levels of natural antibodies such as isohemagglutinins

- poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined
- low switched memory B cells (<70% of age-related normal value)

Flow cytometry:

- Reduced levels of circulating memory B cells (CD27+ B cells) and especially low levels of isotype switched memory B cells (CD27+ IgD- IgM-)

(y=year of life):

- CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200
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- autoimmune manifestations

Secondary hypogammaglobulineaemia:

- Drugs: glucocorticoids, Rituximab, anti-epileptics
- Malignancies: lymphocytic leukemia, lymphoma, multiple myeloma, Waldenström's macroglobulinemia
- Systemic illnesses causing bone marrow suppression
- Thymoma with hypogammaglobulinemia (Good syndrome)
- Protein-losing enteropathies, nephrotic syndrome, burns, trauma

AND secondary causes of hypogammaglobulinaemia have been excluded (see separate list)

AND diagnosis is established after the 4th year of life (but symptoms may be present before)

AND no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life):

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Final diagnoses and treatment

- Hypogammaglobulinemia and B cell deficiency. Suggesting common variable immunodeficiency with chronic diarrhea and sprue-like disease associated
- Atrophic gastritis with squamous metaplasia
- Chronic corticoid treatment with pathological fractures

- **Inmunoglobulins**: 0,4 grams/kilogram, 2-3 cycles and monitoring Ig levels (ideally should reach levels > 600)
- Antimicrobial profilaxis **is not** generally recommended
- **Immunomodulators**:
  - Glucocorticoids: May be indicated at low doses for short periods of time. Recurrences following discontinuation of treatment are common

Key points

- Multiple disorders are associated with chronic diarrhea. In developed countries, common causes are irritable bowel syndrome, inflammatory bowel disease, malabsorption syndromes (such as lactose intolerance and celiac disease), and chronic infections (particularly in patients who are immunocompromised)
- There is no firm rule as to what testing should be done. The history and physical examination may point toward a specific diagnosis for which testing may be indicated
- Primary immunodeficiencies are suspected in people who have recurrent or chronic infections difficult to eradicate and infections by opportunistic or unusual germs.
- Patients with more than two lobar pneumonias make it necessary to rule out an immunological deficit as well as patients who has had two of the serious life-threatening infections