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SUPPLEMENT ARTICLE

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# Recurrent respiratory infections between immunity and atopy

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## Abstract

Recurrent respiratory infections (RRIs) are frequent in children and are characterized by more than 6 airway infections in 1 year or more than 1 upper airway infection per month in the period between September and April or more than 3 lower airway infections in 1 year. Often pediatric RRIs are related to predisposing factors, such as reduced airway size, poor tussive reflex, and immaturity of the immune system. RRIs due to immature immune system are a transient condition, with spontaneous resolution in the school age. However, some RRIs are expression of more complex diseases. Red flags are the onset of symptoms in the first year of life, the involvement of other systems, unusual pathogens, slowing of growth, severe infections of the lower airways, and recurrence of the infection site. To help the pediatrician in the RRI differential diagnosis, we have created a roadmap based on scientific literature data and clinical practice that identifies 6 macro areas: immunodeficiencies, simple minimal genetic immunodeficiency, atopy, obesity, nutritional deficiencies, autoinflammatory diseases, and complex diseases.

**KEYWORDS**
immunity, recurrent respiratory infections (RRIs)

## 1 | INTRODUCTION

Recurrent respiratory infections (RRIs) are a common problem in children. In Western countries, around 25% of children suffer from RRI in the first year of life, and 18% in the age between 1 and 4 years. RRIs affect the quality of life of children and their parents, also concerning school attendance. Antibiotics are widely used in the therapy of upper respiratory tract infections, despite a viral etiology is estimated in the 70%-80% of cases.[1] This medical behavior is an important cause of antibiotic resistance.

RRIs are defined by the presence of more than 6 airway infections in 1 year, or more than 1 upper airway infection per month in the period between September and April, or more than 3 lower airway infections in 1 year.[2] There are different predisposing factors for RRIs in the child, such as reduced airway size, poor cough reflex, and immaturity of the immune system. Environmental factors are early schooling, exposure to second-hand smoke, high number of cohabitants, and pollution.

The RRIs are often secondary to the aforementioned predisposing factors and usually disappear at school age. However, it is important to identify the children in whom RRIs imply a more complex pathogenesis. Red flags for these conditions are the onset of symptoms in the first year of life, the involvement of other systems, unusual pathogens, slowing of growth, severe infections of the lower airways, and recurrence in the same infection site.[1,2] To help the pediatrician in the differential diagnosis, we have created a roadmap of the RRIs based on scientific literature data and clinical practice. Our roadmap identifies six macro areas:

### 1.1 | RRIs and immunodeficiency

Ten red flags for a possible primary immunodeficiency have been identified: family history of immunodeficiency or unexplained early death

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(before 30 years old) among family members; failure to thrive; need for intravenous antibiotics and/or hospitalization to clear infection; 8 or more new infections in 1 year; 2 or more severe sinus infections in 1 year; 2 or more severe infections, such as sepsis, osteomyelitis, or meningitis in a lifetime; need of 2 or more months of antibiotic regimen with little or any effect; 2 or more pneumonia in 1 year; recurrent tissue or organ abscesses; persistent mouth ulcers or ulcers in other parts of the body after the first year of age. Another important sign of immunodeficiency is an infection by an opportunistic pathogen. The type of pathogen may help to orientate on the type of immunodeficiency: For example, infections sustained by extracellular bacteria are indicative of B lymphocyte deficiency; recurrent cutaneous and lymph node abscesses are typical of a phagocyte defect. Severe combined immunodeficiency (SCID) is characterized by early-onset (in the first weeks of life) and severe infections with several types of opportunistic pathogens (extracellular and intracellular bacteria, viruses, fungi, and protozoa).[3]

### 1.2 | RRIs and simple minimal genetic immunodeficiency

There are genetic diseases characterized by an impairment of a specific signaling pathway, associated with increased susceptibility to a specific pathogen. The main signaling pathways include immune receptors, such as interferon (IFN)-γ receptor (R), IFN α/β-R, interleukin (IL) 12/23-R, cluster of differentiation 40 (CD40), tumor necrosis factor (TNF)-α-R, Toll-like receptor (TLR)-3, or superfamily receptors (IL-6Rs, IL-10Rs, TNFRs, TLRs/IL-1Rs), adaptors such as myeloid differentiation primary response 88 (MYD88), kinases, such as IL-1 receptor-associated kinase 4 (IRAK-4) or tyrosine kinase 2 (TYK-2), signal transducers and activators of transcription such as signal transducer and activator of transcription (STAT) 1 and 3, regulatory subunits such as NF-kB essential modulator (NEMO), or inhibitors such as nuclear factor of kappa light polypeptide gene enhancer in B-cell inhibitor α (IkBα). The main cytokines secreted upon activation of these various pathways are therefore impaired with a consequent reduction in the defense toward a specific pathogen.[3]

### 1.3 | RRIs and allergy

Allergy may promote RRIs as allergic inflammation induces overexpression of adhesion molecules that make allergic patients more susceptible to viral infections, impairs interferon production, and promotes microbial overgrowth.[4-6]

### 1.4 | RRIs and obesity

Adipose tissue is responsible for releasing proinflammatory cytokines with a consequent minimal inflammatory state that predisposes to RRIs. This systemic inflammatory state has been demonstrated by high serum HMGB1 levels in obese children. The HMGB1 is classified as a damage-associated molecular pattern (DAMP) molecule that acts in the onset and perpetuation of inflammatory processes. It is the ligand for membrane receptors RAGE or TLRs, such as TLR-2 and TLR-4, with consequent activation of a cascade of intracellular signaling and the final induction of NF-kB transcriptional activity. This causes the production and secretion of various proinflammatory cytokines and the amplification of the inflammatory process. In the obese child, it is also present an immune dysregulation characterized by impaired complement and B-cell, T-cell, and NK cell activity; phagocyte deficiency; and decreased levels of anti-inflammatory cytokines, such as IL-10. All these factors predispose the child to RRIs.[7,8]

**Key Message**

This paper was written to help the pediatrician in the Recurrent Respiratory Infections (RRIs) differential diagnosis. We have created a roadmap based on scientific literature data and clinical practice, that identifies six macro areas in wich more severe RRIs can be framed: Immunodeficiencies, Simple Minimal Genetic Immunodeficiency, Atopy, Obesity, Nutritional Deficiencies, Autoinflammatory Diseases, and Complex Diseases.

### 1.5 | RRIs and nutritional deficiencies

The deficiency of some vitamins (such as vitamin D3, B12, A, E, and C) or micronutrients (such as zinc, selenium, and iron) may lead to immune dysregulation with consequent appearance of RRIs.[9]

### 1.6 | RRIs and autoinflammatory diseases

When the fever episodes show a specific periodicity with healthy intervals, it is important to think about genetic periodic fevers. Periodic fever syndromes are a group of diseases characterized by serositis and elevated serum acute-phase reactant level caused by dysregulation of inflammation pathway. This immune dysregulation is caused by mutations of genes coding for some proteins with the regulation role. Innate and adaptive immune systems are involved. The familial Mediterranean fever (FMF) is the most common monogenic periodic fever in the Mediterranean area, with an autosomal recessive transmission. It is characterized by short-term fever (1-3 days) associated with serositis that causes abdominal pain (peritoneum involvement) and chest pain (pleura and pericardium involvement). Other less common monogenic periodic fever disorders include hyperimmunoglobulin D (hyper-IgD) syndrome, chronic infantile neurologic cutaneous and articular (CINCA) syndrome, Muckle-Wells syndrome, familial cold urticaria, and TNF receptor-associated periodic syndrome (TRAPS). Another common disorder is the PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) that has no genetic transmission. The PFAPA is characterized by episodes of

3-5 days with high fever every 2-12 weeks. Clinical diagnostic criteria include periodic recurrent fever episodes with an early age of onset (<5 years of age); symptoms in the absence of upper respiratory tract infection, with at least one of the following clinical signs: aphthous stomatitis, cervical lymphadenitis, pharyngitis (often exudative tonsillitis); exclusion of cyclic neutropenia, completely asymptomatic interval between episodes, and normal growth and development. Another typical feature is the good response to a single dose of oral cortisone, with a prompt and persistent remission.[10]

## 1.7 | RRIs and complex diseases

Complex diseases include cystic fibrosis, primitive ciliary dyskinesia, and immunodeficiencies associated with genetic syndromes, such as chronic mucocutaneous candidiasis, Wiskott-Aldrich syndrome, Di George syndrome, Down syndrome, ataxia-telangiectasia syndrome.

### CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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