PID Article

A DIAGNOSTIC APPROACH TO RECURRENT RESPIRATORY TRACT INFECTIONS IN CHILDHOOD: COULD IT BE PRIMARY IMMUNODEFICIENCY?

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SUMMARY

The recurrence of respiratory tract infections is a common problem in paediatric practice. Parental concerns around recurrent respiratory infections (RRTI) contribute significantly towards doctor visits. RRTI are also the most frequent presenting feature of primary genetic immunodeficiency (PID). There is a surprising lack of evidence, guidelines and appropriate ICD10 coding for RRTI. Many of the children who present with RRTI are immunologically "normal" children but it is important to recognise the features of a possible immune deficit or other underlying serious disorder.

The evaluation of children who present with RRTI requires close attention to the history and clinical findings in order to differentiate those who warrant more extensive investigations from those who need reassurance directed toward their concerned parents. PID may be responsible for around 10% of RRTI in children. More than 50% of these are due to antibody defects and the majority can be diagnosed and treated effectively. The question that arises is when to start more extensive investigations and when to accept that this child is otherwise healthy.

The purpose of this review is to assist the clinician with a diagnostic approach to differentiate the "normal" child from the child with a more serious underlying aetiology of RRTI, necessitating investigation.

INTRODUCTION

Respiratory tract infections (RTI) are common in young children and they are a frequent reason for consulting a doctor. Children who attend day-care centres may even suffer a 3-8 times higher burden of RTI. These consultations usually come with a parental low tolerance for symptoms such as an irritating cough, high expectations of prevention of further RTI, a demand for antibiotics, confusion created by a multitude of ineffective over-the-counter remedies and expectations of rapid improvement of the child so that the parents can return to work.

The differential diagnosis for RRTI in childhood is broad and the evaluation time consuming. There are no clear guidelines or evidence based data to advise clinicians on an approach to this common problem. Many children who present with RRTI will turn out to be "normal", while some may need further investigation to elicit a serious underlying cause. A serious diagnosis must not be missed as it may result in significant morbidity and even shortened lifespan. This review strives to offer a simplified aetiology based diagnostic approach towards childhood RRTI in the South African setting.

WHEN SHOULD RRTI RAISE CONCERN?

It is difficult to draft comprehensive guidelines for RRTI management due to the numerous features of RRTI that should alert the clinician towards further examination. An expert opinion based review by Bush[1] suggests the features that should suggest a need for further investigation. Some of these are summarised in Table I. It is however, not only the frequency or recurrence of RTI that should warn of a need for further investigation but relevant aspects of the history, including especially a family history, history of allergy, different social backgrounds and ethnicity, access to healthcare, specific clinical findings such as failure to thrive and dysmorphism, specific organisms identified and failure of infections to resolve to appropriate therapy.

With lack of evidence based guidelines, clinicians are

often prompted to investigate those RRTI that are too frequent in number, too severe, last too long, fail to resolve with standard treatment or which result in complications.[2] Parental concern must always be considered too. The decision on when to investigate, or when to stop investigating, relies on a good knowledge of the differential diagnosis, thorough history taking, sound clinical judgement and a sound understanding of the context of the problem. The same rules apply to the specific investigations that will be requested.

An aetiology based diagnostic approach to RRTI is discussed here.

AETIOLOGICAL BASED DIAGNOSTIC APPROACH TO RRTI

A number of different approaches may be followed when a child presents with RRTI. An aetiology-based diagnostic approach offers a simplified stepwise model for the clinician. The first step is to consider a possible secondary reason for RRTI such as human immunodeficiency virus (HIV)-related disease, protein losing diseases, diabetes mellitus and immunosuppressive treatment. The second step considers the three scenarios discussed below. According to Stiehm et al[2] approximately 50% of the children who present with recurrent infection, are actually "normal" children. A further 30% of recurrences result from underlying allergic inflammation, 10% from PID and the remaining 10% are caused by a variety of non-immune related chronic conditions (Figure 1).

The three scenarios encountered are:

1. The "normal" child with RRTI (50%) where it is important to avoid unnecessary investigations and treatment and to inform and address the anxiety of the parents.
2. The child with a non-immune related cause (10%) and RRTI in need of investigation to identify and manage a possible more sinister problem.
3. The child with dysregulated immune function and RRTI where it is equally important to make a diagnosis for effective management. Immune dysregulations usually manifest with either "over activity" or allergy (30%), or "under activity" or PID (10%) or combinations of both. "Misdirected immunity" or auto-immunity may be noted in later life.

The goal of a thorough history and clinical evaluation should be to identify the most likely scenario for RRTI and to guide further investigation and ideally lead to the correct diagnosis. These different scenarios will be discussed briefly, however, it is beyond the scope of this article to offer a detailed review of each differential diagnosis.

SCENARIO 1: THE "NORMAL" CHILD WITH RRTI

Acute respiratory infections (ARI), especially viral colds and infections of the upper respiratory tract, occur

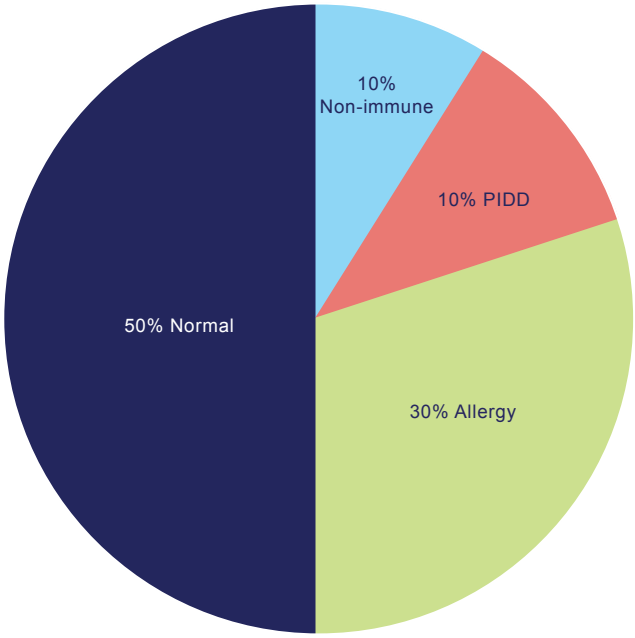

Figure 1: Aetiologic based diagnostic approach to RRTI

frequently in "normal" children. The average child suffers 4-8 respiratory infections per year.[3] The symptoms of an uncomplicated ARI last an average of 8-14 days and 10% of children may still cough at 25 days post infection.[4] The number of respiratory infections can increase 2-8 fold with larger group exposure such as in day-care settings. Characteristics of the "normal" child with RRTI include: milder and often self-limiting infections, complete recovery between episodes, normal growth and development and the absence of findings that would suggest an underlying chronic illness. Recurrent infection that is always limited to the respiratory tract, and not of other systems, further supports a more innocent aetiology.

The management of such a child and family is mainly supportive and has to be reviewed in the context of the child's environment and include allowance for possible excess anxiety of parents. The reassuring advice of the doctor is often sufficient to alleviate parental concern of the otherwise "normal" child.

SCENARIO 2: THE CHILD WITH A NON-IMMUNE RELATED CAUSE AND RRTI

Non-immune RRTI **may account for 10%** of causes and may result from various conditions (Table II). Most of these are important to diagnose promptly and therefore deserve a high index of suspicion.

Cystic fibrosis (CF) is caused by compromised cystic fibrosis transmembrane conductance regulator (CFTR) protein channel function resulting in decreased hydration of secretions. Nearly 2,000 gene mutations have been identified that may code for changes in the production, transport, membrane expression and activity of the CFTR channel.[5] The clinician that only considers CF in

TABLE I: WHEN SHOULD RRTI RAISE CONCERN? FEATURES THAT MAY POINT TOWARDS AN EARLIER NEED FOR INVESTIGATION

FINDING	POINTERS FOR FURTHER INVESTIGATION
Marked chronic upper airway symptoms	Snoring, stridor, chronic rhinitis, chronic sinusitis
Early onset of symptoms	Onset of symptoms since birth or soon after birth
More severe symptoms	Continuous, unremitting or worsening symptoms
Vomiting & choking	Pain on feeding or On or after feeds
Viral cold	≥ 15 episodes per annum
Acute tonsillitis	≥ 7 episodes in 1 year or ≥ 5 episodes per annum in 2 consecutive years or ≥ 3 episodes per annum in 3 consecutive years
Acute otitis media	≥ 3 episodes in 6 months or ≥ 4 episodes in 1 year
Acute sinusitis	≥ 2 episodes in 1 year requiring IVI antibiotic treatment
Acute pneumonia	≥ 2 hospital admissions in 1 year or ≥ 2 episodes of radiologic shadowing in 1 year or ≥ 3 episodes in total
Persisting cough	Daily for > 4 weeks Persisting wet cough
Mucus	Persisting and coloured mucus
Wheeze	High frequency and severe Non-remitting and not responsive to correctly administered asthma medication Asymmetric Fixed monophonic Young age of onset
Abnormal findings on general examination	Inadequate growth, failure to thrive or weight loss Digital clubbing Anaemia Absence or exuberance of lymph tissue
Clinical features of allergic disease	Atopic eczema Allergic conjunctivitis Allergic rhinitis Food allergy Asthma
Involvement of different systems	Respiratory infections accompanied by infections of other systems
Cardiac abnormality	Signs of cardiac disease
SPUR infections	Severe, persistent, unusual and recurrent infections

a "traditional" presentation of severe CFTR dysfunction will under diagnose this important and relatively frequent condition in South Africa. CF is not limited to Caucasians and the CF phenotype is heterogenous. The severity of CF varies according to the underlying CFTR mutations, environmental factors and modifier genes that interact with CFTR mutations.[6] CF should always be considered in RRTI and especially in the setting of RRTI with failure to thrive or as a mimic of young onset asthma. Sweat tests should be requested in all children where RRTI is further investigated. There are many good reviews on this topic and the 2013 South African CF consensus document offers further guidance. [7]

TABLE II: EXAMPLES OF SCENARIO 2 - THE CHILD WITH NON-IMMUNE RELATED CAUSE AND RRTI

MECHANISM	CONDITION
Ineffective mucus clearance	Primary ciliary dyskinesia (PCD) Cystic fibrosis (CF) Nervous system and muscular abnormalities with ineffective cough Bronchiectasis
Airway obstruction	Eustachian tube dysfunction Sinus ostia obstruction Tonsil and adenoid hypertrophy Lymph node hyperplasia Tumours Foreign body aspiration Vascular rings Airway malacia
Increased pulmonary blood flow	Cardiovascular abnormality
Congenital airway abnormality	Developmental abnormalities of the airways and lungs
Chronic infection	Mycobacterium tuberculosis Persistent bacterial bronchitis (PBB)
Recurrent re-infection	Day-care attendance
Exposure to irritants	Cigarette smoke Gastro-oesophageal reflux disease (GORD)

Primary ciliary dyskinesia (PCD) is generally under diagnosed and seldom considered. The reported prevalence is 1:10,000-20,000.[8] Important reasons for under diagnosis include a misconception that situs inversus will be present and the limited availability of reliable special investigations. Mirror image organ arrangement and other forms of heterotaxy is only present in 40-50% of PCD.[8] Chronic rhinorrhoea from birth, unexplained respiratory distress in the term baby, repeated upper and lower airway symptoms, chronic muco-purulent otorrhoea, nasal polyps and early loss of hearing should be warning signs of possible PCD.[1]

Gastro-oesophageal reflux (GOR) and gastro-oesophageal reflux disease (GORD) is often over diagnosed as a reason for RRTI. GOR is a physiologic phenomenon in healthy infants and children[9] and there is controversy over whether the cough is the reason for GOR or whether GOR the reason for the cough. GORD, and associated pulmonary aspiration, should be considered as a cause of RRTI in children with neurodisability, swallowing dysfunction, CF and previous tracheoesophageal fistula fistula repair. Associated findings may include chronic vomiting, frequent choking, failure to thrive, pain during feeding, Sandifer posturing and dental caries.

Protracted bacterial bronchitis (PBB) has recently been recognised as an important entity and cause for RRTI.[1] It often follows after an initial viral airway infection in younger children and manifests with an isolated wet cough that lasts for longer than 4 weeks. The cough is usually more prominent on reclining, in the early morning hours and during exercise. PBB patients may cough for the entire night and suffer from disrupted sleep. It is a neutrophil

disease with associated biofilm production in the airway. Non-typable *Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis* are the most frequent colonising bacteria. PBB patients are commonly misdiagnosed as being asthmatic. Associated findings include wet rattles in both lung fields, stained sputum and other biofilm manifestations like chronic middle ear effusion and sinusitis. It remains a diagnosis of exclusion and should be differentiated from bronchiectasis and chronic suppurative lung disease. Recurrent PBB raises concern, as underlying risk factors to PBB may be present. Detailed investigation is needed in children who present with recurrent PBB.[10]

SCENARIO 3: THE CHILD WITH DYSREGULATED IMMUNE FUNCTION AND RRTI

Allergy accounts for 30% of causes of RRTI and is a common finding in paediatric practice. Clinicians should pay special attention to history and clinical findings that may indicate allergic rhinitis, asthma and comorbidities. The symptoms of allergic rhinitis and asthma are often mistaken for those of viral ARI. Importantly allergic children, especially if poorly controlled, also suffer from increased susceptibility to RRTI due to a number of factors. These include enhanced adherence of pathogens to inflamed epithelium, decreased muco-ciliary clearance, increased mucosal permeability and altered host immune response to pathogens.

There are also overlaps between allergy and PID with co-existing allergy in 31% of PID patients.11 Allergic features may be a component of selective IgA (sIgA) deficiency, common variable immunodeficiency (CVID), chronic granulomatous disorder (CGD) and Di George syndrome (22q deletion syndrome). Elevated IgE is seen in the Hyper IgE syndrome (HIES), Wiskott Aldrich syndrome, Omenn syndrome and immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX).

TABLE III: SIGNATURE INFECTIONS - HELPFUL IN ALERTING TO DEFICIENCIES IN THE RESPECTIVE PATHWAYS OF THE IMMUNE SYSTEM

PIDD DEFECT	SIGNATURE INFECTION
Antibody (B-cell) deficiency: - XLA - IgA, IgG subclass - Specific antibody - CVID	*H. influenzae* *S. pneumoniae* *G. lamblia* ECHO virus Salmonella spp. *M. pneumoniae*
T-cell deficiency & SCID: - ADA deficiency - Hyper IgM syndrome - Major histocompatibility complex deficiency - Wiskott-Aldrich syndrome	Herpes simplex, zoster CMV, EBV, measles, RSV *P. jiroveci* Streptococci, *H. influenzae* Candida, Aspergillus Mycobacteria Cryptosporidium
Phagocyte defects: - Chronic granulomatous disease (CGD) - Familial, cyclical or auto-immune neutropenia - Leukocyte adhesion defects - Hyper IgE syndrome	*S. aureus* Streptococci Candida, Aspergillus Enteric Gram-negative bacteria
Complement deficiency: - Complement deficiency - Mannose binding lectin deficiency (MBL) - C3 or C5 deficiency	*S. pneumoniae* *H. Influenzae* *N. meningitides*

PID, although only accounting for 10% of RRTI, must be excluded, as it most frequently presents with symptoms of RRTI. This group of conditions causes significant morbidity and mortality and must be diagnosed early and treated appropriately. PID is still regarded as rare, however, a population based prevalence study in the United States has revealed a frequency of up to 1:2,000.[12] The hallmark of PID related infections are captured by the acronym SPUR, which stands for Severe, Persistent, Unusual or Recurrent infections and is modelled on the more extensive Jeffrey Modell Foundation 10 warning signs.[13] These hallmark or warning signs of PID have to be evaluated against the very different social background of South African patients.

Although the classification of PID has evolved far beyond the traditional 4 categories of immune function deficit, it is still useful for an initial approach to start with the 4 basic immune category abnormalities. For updated PID classifications the reader is referred to the IUIS classification or clinical diagnostic guidelines.[14] Recurrent viral or bacterial infections may point to different deficiencies of the immune system within the domain of B-cell abnormalities (50-65%), T-cell abnormalities (20-30%), phagocyte deficiencies (18%) and complement deficiencies (2%). This distribution of PID seems to also apply to the South African situation as reflected on the South African PID Registry.

Specific organisms are helpful in alerting to deficiencies in the respective pathways of the immune system referred to as the “signature“ infections of PID (Table III).[15]

A family history of PID or early infant death to infection is a most important and useful alerting feature, which may be present in 30% of patients with PID. This is even more frequently elicited in regions with consanguineous marriages. Other important PID warnings include persistent lymphopaenia and low globulin fractions, failure to thrive, chronic muco-purulent secretions, lethargy and absenteeism, recurrent diarrhoea, skin and soft tissue infections, two or more severe infections, dysmorphic features, absence or exuberance of lymph tissue, skin rashes, complications from a live vaccine and auto-immune disease. However, if PID cannot be diagnosed through basic screening with full blood count and differential count, serum immunoglobulin levels, vaccine antibody responses and total complement level in the face of SPUR infections, the child must be referred to a specialist centre. Other PID such as innate immune defects, immune defects relating to dysregulated immunity and overlapping deficiencies may then need to be evaluated further.

CONCLUSION

RRTI are common in paediatric practice. The differential

diagnosis is broad. The challenge is to not over-investigate or over-treat the normal child, but also not to miss important causes with significant morbidity and potential of shortened lifespan. Such conditions include allergy, genetic primary immune deficits and non-immune chronic conditions. An aetiological diagnostic approach helps to guide a targeted history, clinical evaluation and relevant investigations. Sound clinical judgement is crucial for the correct diagnosis and management of RRTI. The clinician who keeps these scenarios in mind can be more confident in the management of patients with RRTI.

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- Step 3 treatment for persistent symptoms and/or exacerbations despite low-dose ICS is a combination ICS/long-acting beta-2-agonist (LABA) such as the fixed-combination dry powder inhaler (Symbicord® 80(160)/4,5 Turbuhaler®), the fixed-combination metered dose inhaler Vannair® 80(160)/4,5 Inhaler or the use of separate inhalers i.e. Pulmicort® Turbuhaler® together with the LABA in Oxis® Turbuhaler®. The use of low-dose budesonide/formoterol as both maintenance and reliever therapy, such as Symbicord® SMART, has been shown to reduce the risk of exacerbations, compared with maintenance controller treatment plus as-needed SABA.
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S4 Vannair® 80:4,5 (Inhaler). Reg. No: A39/21.5.1/0506. S4 Vannair® 160:4,5 (Inhaler). Reg. No: A39/21.5.1/0507. Each single actuation contains as active constituents, Budesonide 80 or 160 µg and formoterol fumarate dihydrate 4,5 µg. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues. INDICATIONS: Asthma: VANNAIR® 80:4,5 & 160:4,5 µg/dose is indicated in the treatment of asthma in adults and children 6 years and older where continued use of a combination (inhaled corticosteroid and long-acting beta-2-agonist) is appropriate. COPD: VANNAIR® 160:4,5 µg/dose is indicated in the regular treatment of patients with moderate to severe chronic obstructive pulmonary disease (COPD), with frequent symptoms and a history of exacerbations. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

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S3 Rhinocort® Aqua 32 (Nasal Spray). Reg. No: 32/21.5.1/0608. S3 Rhinocort® Aqua 64 (Nasal Spray). Reg. No: 32/21.5.1/0609. Each metered dose contains budesonide 32 µg or 64 µg. Contains potassium sorbate 0,12 % m/v as preservative. PHARMACOLOGICAL CLASSIFICATION: A 21.5.1 Corticosteroids and analogues INDICATIONS: Seasonal and perennial allergic rhinitis in adults and in children 6 years and older. For full prescribing information refer to the package insert approved by the medicines regulatory authority.

S2 Bricanyl® Turbuhaler® 0,5 mg/dose (Inhaler). Reg. No: X/10.2/155. Each dose contains: terbutaline sulphate 0,5 mg. PHARMACOLOGICAL CLASSIFICATION: A 10.2 Bronchodilators. INDICATIONS: Bronchial asthma, chronic bronchitis, emphysema and other lung diseases where bronchospasm is a complicating factor. For full prescribing information refer to the package insert approved by the medicines regulatory authority. .

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