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Review Article

# Role of Immunity in Management of Chronic Rhinosinusitis and Allergic Rhinitis in Current Trying Times Like COVID-19

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## Abstract

The burden of COVID-19 is increasing all over the world. Patients affected with COVID-19 with a previous history of comorbidities, such as respiratory illnesses, are at a higher risk for severe illness, resulting in adverse outcomes. Up-regulation of the immune system by immunomodulators is crucial in the current scenario in India, especially in patients with recurrent respiratory tract infections such as allergic rhinitis (AR) and chronic rhinosinusitis (CRS). Current management options for AR and CRS include allergen avoidance and use of second-generation antihistamines (such as fexofenadine), leukotriene receptor antagonist (montelukast), and intranasal corticosteroids (INCS) aim for symptomatic relief. Antibiotics, such as azithromycin and amoxicillin–clavulanate (AMC), are prescribed for patients with CRS to treat acute bacterial exacerbations of CRS. Pidotimod is a potent allopathic immunomodulator available in India with proven clinical benefits in adult patients with respiratory infections in primary and secondary immune deficiencies. Studies have shown that Pidotimod adjuvant therapy can prevent cytokine cascade activation and potentiate immune responses against viruses. This consensus report summarizes expert opinion and views on the use of Pidotimod in trying times like COVID-19 in patients with mild-to-moderate symptoms of COVID-19 disease and in adult patients with a risk or established history of AR and CRS.

***Keywords:*** *COVID-19; SARS-Cov-2; Pidotimod; India; ENT; Chronic Rhinosinusitis; Allergic Rhinitis; Expert Opinion*

## Introduction

Allergic respiratory diseases have become a major health concern globally, with India being no exception. Upper respiratory tract infections (URTIs), such as allergic rhinitis (AR), are the prevalent manifestations of chronic allergy, affecting a substantial population of all ages in different parts of India [1]. Nearly 83% of patients presenting with an acute URTI have bacterial rhinosinusitis [2]. The current outbreak of the novel coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has worsened the situation. Patients affected with COVID-19 with a previous history of comorbidities, such as respiratory illnesses, are at higher risk for severe illness, resulting in adverse outcomes, such as acute respiratory distress syndrome (ARDS) and pneumonia [3]. Up-regulation of the immune system by immunomodulators is crucial in the current scenario, especially in patients with recurrent URTIs. Current treatment guidelines for chronic inflammatory airway diseases aim at symptomatic relief and rely on the use of corticosteroids, antihistamines, and infection control when necessary [4-6]. Studies have reported that the long-term use of corticosteroid therapy is associated with an increased risk of URTIs [6,7]. Acute URTIs are the most common reason for antibiotic prescriptions in adults, comprising 41% of all antibiotic prescriptions [8,9]. Overuse or misuse of antibiotics in URTIs and chronic inflammatory airway diseases have shown

to increase morbidity, higher treatment costs, and antibiotic resistance [6]. Modulation of the immune system with immunomodulators along with standard-of–care therapy (SOC) has proven benefits in the past two decades in patients with URTIs, such as AR and chronic rhinosinusitis (CRS) [6,10].

Two virtual advisory board meetings were convened on 23rd and 24th September 2020 to review the current unmet needs in the management of URTIs in India and evaluate the usage of Pidotimod in adult URTI patients based on expert panel discussions. The members of the panel were selected to best represent the breadth of knowledge and clinical experience in the field from all over India. The key purpose of the meetings was to: (i) evaluate the usage of Pidotimod in the current trying times of COVID-19 in patients with comorbidities; (ii) generate insights on the role of Pidotimod in adult patients with a risk or established history of AR and CRS; (iii) determine AR and CRS patient subgroups who would benefit from Pidotimod as adjuvant therapy. A literature review was carried out based on data from the PubMed Database to identify relevant articles between January 2001 and September 2020 using keywords such as "upper respiratory tract infections", "recurrent respiratory tract infections", "India", "adults", "burden", "coronavirus disease", "allergic rhinitis", "chronic rhinosinusitis", "immunostimulants", "immunomodulators", "Pidotimod", "guidelines", and "management". Key articles were shortlisted and circulated among the expert panel members before the board meetings as pre-reading materials. During advisory board meetings, a qualitative question-and-answer–based format was used to facilitate discussion. After the group discussion, key expert opinions were formulated based on the opinions and agreement of the majority. The main highlights of panel discussion for each of these topics were recorded and are summarized in this manuscript.

## Results and Discussion

### Pidotimod: New approach on covid-19 infection management

The COVID-19 disease manifests with a wide clinical spectrum, ranging from asymptomatic or paucisymptomatic forms to septic shock and multi-organ dysfunctions [11]. The reported Ear Nose Throat (ENT) manifestations in COVID-19 patients are sore throat (11.3%), headache (10.7%), pharyngeal erythema (5.3%), nasal congestion (4.1%), runny nose or rhinorrhea (2.1%), URTI (1.9%), and tonsil enlargement (1.3%) [11]. A study published by Diao B., *et al*. reported that around 82.1% of COVID-19 cases displayed low circulating T lymphocyte counts ($CD4^+$ and $CD8^+$ type) and surviving T cells appear functionally exhausted [12]. Up-regulation of the immune system by boosting the numbers and function of T cells in adult patients is important in times like COVID-19.

### Immune dysfunction in patients with URTIs and diabetes

Primary immune deficiencies are well-known causes of chronic rhinosinusitis (CRS) and allergic rhinitis (AR). A recent meta-analysis of immunodeficiency in patients with CRS reported a combined prevalence of IgG, IgA, and IgM deficiencies in 13% of patients with recurrent CRS and 23% of patients with difficult-to-treat CRS [13]. Patients with diabetes are at an increased risk of predisposition to URTIs due to metabolic derangements and suppressed innate and humoral immunity [14]. Chronic rhinosinusitis patients with diabetes are significantly more likely to have nasal polyps compared to CRS patients without diabetes [15].

### Role of pidotimod in patients with immune deficiencies

Various classes of immunomodulators (bacterial lysates, enzyme therapies, and herbal remedies) have been studied in the past few decades in patients with respiratory disorders, such as CRS, COPD, asthma, and allergic and non-allergic rhinitis [6,16]. OM-85 (lysate of 21 common bacterial respiratory pathogens) has demonstrated clinical efficacy in reduction in exacerbations in recurrent URTIs [6,17]. However, OM-85 BV is not available in India. Pidotimod is a synthetic dipeptide molecule (3-l-pyroglutamyl-l-thiazolidine-4carboxilic acid) with potent immunomodulatory activity that can ameliorate both innate and adaptive immune responses to fight recurrent respiratory tract infections [10,16,18]. Pidotimod was approved in India in 2011 by the Drug Controller General India for respiratory tract

infections in primary and secondary immune deficiencies with alteration of maturation in T cells in adults [16]. The immunostimulatory activity of Pidotimod has shown to affect the immune response in multiple ways: (i) induction of maturation of dendritic cells; (ii) up-regulation of human leukocyte antigen – DR isotype (HLA-DR), co-stimulatory molecules (CD83 and CD86) expression; (iii) increase in NK cells activity; (iv) promote phagocytosis; (v) up-regulation of toll-like receptor (TLR)-7 and TLR-2 signaling pathway in respiratory epithelium [10,16,18]. Several studies have showed the efficacy of Pidotimod in reducing the need for antibiotics in airway infections, increasing the level of immunoglobulins (IgA, IgM, IgG), and improving balance of Th1/Th2 cytokines [10,16,18]. The use of Pidotimod has shown to down-regulate monocyte chemoattractant protein-1 (MCP-1) that is considered as a master regulator in the inflammatory response associated with severe recurrent viral bronchiolitis [19]. Also, studies have reported that the use of Pidotimod can regulate neutrophil-mediated pulmonary parenchymal injury by upregulation of TLR-2 without increase in IL-8 levels [19]. Currently, Pidotimod is the only available and approved allopathic immunostimulant available in India. In a study published by Ucciferri C., *et al.* Pidotimod was used in paucisymptomatic COVID-19 patients (Brescia-COVID Respiratory Severity Scale 0) without any evidence of concurrent pneumonia [19]. The study concluded that Pidotimod was well tolerated among COVID-19 patients and associated with a rapid reduction of systemic symptoms, especially fever [19]. This was achieved by rebalancing action of Pidotimod on immune system that prevented the evolution of the SARS-CoV-2 infection in COVID-19 disease [19].

### Experts' discussion on the role of pidotimod in times like COVID-19 in adults with immune dysfunction

The experts opined that in the current scenario, young adults with multiple comorbidities (such as diabetes, chronic lung disease, liver problems, respiratory tract infections, and cardiovascular disease) and immunocompromised elderly individuals (aged 60 and above) are at an increased risk of severe illness from COVID-19 due to reduced immunity. The administration of Pidotimod along with the standard-of–care (SOC) treatment in these patients could prevent adverse outcomes, such as ARDS, pneumonia, and death. Experts strongly opined that Pidotimod adjuvant therapy should be promoted in vulnerable patient groups, such as CRS, chronic adenotonsillitis, otitis media, laryngitis, and AR. Stimulation of innate and adaptive immune response by Pidotimod in this subgroup of patients could help in reducing disease severity in the acute phase, and prophylactic use can effectively reduce infectious disease recurrence. Also, early administration of Pidotimod in immunocompromised COVID-19 patients could prevent cytokine cascade activation and rebalance the dysfunctional immune system. Experts mentioned that the administration of Pidotimod in COVID-19 patients with high C-reactive protein (CRP) levels for 15 days led to a symptomatic improvement and reduction in CRP levels. They suggested that the prophylactic use of Pidotimod would be advantageous in adults and children in close contact with COVID-19 patients such as family members and healthcare professionals.

### Insights on the role of pidotimod in adults with risk or established history of URTIs in India

### Burden and prevalence of URTIs in India with a focus on AR and CRS

A hospitalization-based survey carried out in India showed that 20% - 30% of the Indian population experiences AR and 15% develop atopic asthma [1]. Sinusitis affects approximately 15% of the population in India [20].

### Experts' discussion on prevalence of AR and CRS

The experts opined that in their clinical practice, AR patients account for 30% - 33% of cases and CRS patients account for 15% - 30% of cases in the ENT outpatient department (OPD). Allergic atopic disorders, such as AR, are the result of systemic inflammatory reactions triggered by Th2 cell-mediated immune responses against allergens. The experts mentioned that increased air pollution and seasonal variations are closely associated with the increase in the number of AR cases. However, due to COVID-19 lockdown and reduced exposure to environmental pollutants, a decrease in the number of recurrent URTIs cases have been observed.

"Hygiene hypothesis" play a major role in AR patients, where Th1/Th2 balance is disturbed during allergy, and there is an increased production of interleukin (IL)-4, IL-5, IL-9, and IL-13 by Th2 cells.

## Challenges in the management of AR and CRS in India

The 2019 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend the classification of AR patients based on the duration of symptoms (intermittent or persistent) and the severity of the disease (mild, moderate, or severe) [21]. Current management options for AR include allergen avoidance, and the use of second-generation antihistamines and intranasal corticosteroids (INCS) for symptomatic relief [4]. In patients with moderate-to-severe AR, INCSs are the first-line treatment choice for controlling AR symptoms [4]. Fexofenadine is a second-generation non-sedating H1-antihistamine with greater selectivity for the H1 receptor with proven efficacy and safety in adults with AR [22]. Montelukast is a leukotriene receptor antagonist (LTRA) with similar benefits as antihistamines when used as monotherapy for the treatment of seasonal AR [22]. In a multicenter, prospective, randomized study published by Cingi C., *et al.* significantly better control of symptoms of nasal congestion was achieved in AR patients who received both fexofenadine and montelukast compared to AR patients who received only fexofenadine [23]. The combination of fexofenadine and montelukast therapy has shown to reduce the concentration of serum soluble intracellular adhesion molecule (s-ICAM-1), nasal and asthmatic symptoms in patients with persistent AR and newly diagnosed asthma [22]. Current options for the medical management of CRS are aimed at reducing mucosal inflammation, controlling infection, and restoring normal sinus physiology [5]. Intranasal corticosteroids constitute the first-line treatment option to reduce sinus inflammation and nasal polyp size [5]. Daily saline nasal irrigation has been advocated as an adjunct therapy for patients with CRS [5]. The incidence of patients with CRS requiring surgery is very low and reserved for patients who fail pharmacotherapy and in patients where nasal polyp disease is not adequately managed with medical therapy alone [5]. Antibiotics are also prescribed for patients with CRS to treat acute bacterial exacerbations of CRS [5].

Azithromycin (AZM) is well known antibacterial macrolide antibiotic and can be produced at low cost [24-26]. It has anti-inflammatory and immunomodulatory properties [25-27]. *In vitro* studies have demonstrated the capability of AZM in reducing production of pro-inflammatory cytokines such as interleukin (IL)-8, IL-6, tumour necrosis factor (TNF) alpha, reduce oxidative stress, and modulate functions of T-helper cells [27]. The antiviral activity of AZM have been shown *in vitro* and *in vivo* on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, influenzae H1N1 virus, enterovirus, and rhinovirus [26]. Azithromycin up-regulates the production of type I and III interferons and genes involved in virus recognition such as melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I) [26]. Azithromycin has potent antibacterial effects which can prevent or treat co-infection by bacteria and SARS-CoV-2 virus [26]. Azithromycin is approved in Europe as monotherapy for URTIs, including acute bacterial sinusitis [28]. In the US, AZM is approved for the treatment of URTI conditions caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* in adults [28]. A study published by Henry DC., *et al.* compared the efficacy and safety of AZM vs. amoxicillin–clavulanate (AMC) in the treatment of bacterial exacerbations in adult sinusitis patients [28]. The use of AZM (500-mg dose OD for three days) in adult patients with bacterial sinusitis was shown to be as efficacious as amoxicillin–clavulanate (500 - 125 mg thrice-daily for ten days) with less treatment-related adverse events leading to less treatment discontinuation [28]. In a preliminary clinical study published by Gautret P., *et al.* the effect of combination of azithromycin and hydroxychloroquine was studied in COVID-19 patients and compared the results with hydroxychloroquine monotherapy. On day-6 post-inclusion, 100% of COVID-19 patients treated with a combination of hydroxychloroquine and azithromycin were virologically cured compared to 57.1% of patients treated with hydroxychloroquine alone, and 12.5% in the control group ($p < 0.001$) [29]. The study concluded that the combination of azithromycin and hydroxychloroquine was effective in reduction of SARS-CoV-2 viral load in COVID-19 patients; and its effect was reinforced by azithromycin therapy [29,30].

## Experts' discussion on challenges in the management of AR and CRS in India

In CRS patients with nasal polyps (CRSwNPs), epithelial innate immune function is suppressed by Th2 cytokines within the sinonasal mucosa. Surgical reestablishment and clearing of infection within the sinus cavities do not necessarily reverse and restore normal func-

tioning in chronic rhinosinusitis patients with nasal polyps patients. Also, long-term systemic steroid use in CRS is associated with significant side effects. Antibiotics play an important role in the medical management of CRS patients. It is prescribed to patients with lower bacterial load in sinuses and to treat acute bacterial exacerbations of CRS. The experts opined that antibiotic selection depends on the category of the infective organism and infection severity. Common organisms causing CRS are *Staphylococcus aureus* followed by *Pseudomonas aeruginosa.* The management of acute exacerbations of CRS can be done with the use of penicillins, amoxicillin-clavulanate (AMC), or azithromycin. Macrolide antibiotics, such as azithromycin and clarithromycin, are generally prescribed to treat inflammatory disorders of the airways in patients with recurrent respiratory tract infections. Experts mentioned that currently clarithromycin is preferred over azithromycin in CRSwNP patients. Inappropriate use of antibiotics in both primary care and hospital settings is common in India in patients with URTIs and has shown to increase morbidity, along with higher treatment costs and development of antimicrobial resistance. Also, overuse of antibiotics in URTIs is associated with significant side effects.

### Experts' discussion on determination of patient subgroup that can reap maximum benefits from pidotimod adjuvant therapy

Experts opined that Pidotimod adjuvant therapy along with SOC medications would be beneficial in patients with URTIs as it plays an important role in modulating the balance of Th1/Th2 cytokines. The stimulation of innate and adaptive immune responses by Pidotimod can reduce disease severity in chronic adenotonsillitis, otitis media, laryngitis, sinusitis, and AR patients. Experts suggested that patient subgroups who would experience maximum benefits from Pidotimod adjuvant therapy are: (i) mild-to-severe AR and CRS patients; (ii) URTI patients with comorbidities, such as diabetes; (iii) patients on frequent antibiotics due to infection-induced exacerbations; (iv) patients with CRS at early developmental stages of nasal polyps; and (v) patients with CRS at post polypectomy stages.

### Experts' discussion on dosage and duration of pidotimod in patients with AR and CRS

Experts opined that Pidotimod is clinically safe, well-tolerated, and effective in reducing the number and duration of recurrent exacerbations in patients with URTIs. Experts suggested the recommended dosage of Pidotimod in adult patients with URTIs: (i) treatment: 800 mg twice a day (BD) for the first 8 days (loading dose) followed by 800 mg once-daily (OD) for the next 52 days (maintenance dose) on an empty stomach for 2 - 3 months along with SOC medications; (ii) prophylactic dosage: 800 mg OD on empty stomach for two months. Experts suggested that Pidotimod should be consumed on an empty stomach two hours before meal or two hours after meal for reaping its full benefits food intake reduces the bioavailability up to 50%. Experts mentioned that very few patients have felt nausea and weakness with initial BD dosing of Pidotimod, which got relieved with OD evening dosing later. Experts strongly recommended that Pidotimod adjuvant therapy should be taken for a duration of two months to realize initial clinical benefits. Experts mentioned that full clinical benefits in terms of reduction in duration and frequency of infectious episodes with Pidotimod adjuvant therapy can only be assessed after long-term usage (after 1 - 2 years). However, symptomatic improvement in patients can be seen initially with a loading dose of 800 mg BD in 15 days. For URTI patients with mild-to-moderate symptoms, experts suggested once-a-year Pidotimod adjuvant therapy. However, for patients with severe symptoms, experts suggested Pidotimod therapy twice a year to realize its full clinical benefits.

## Conclusion

In this consensus report, we have attempted to summarize expert opinions on the burden and current unmet needs in the medical management practices of AR and CRS in India. The current treatment options for AR and CRS aim for symptomatic relief and not the upregulation of the dysfunctional immune system. Pidotimod is a potent allopathic immunostimulant and immunomodulator available in India with proven clinical benefits in patients with respiratory infections in primary and secondary immune deficiencies in adults. The use of Pidotimod adjuvant therapy along with the SOC treatment has shown to reduce the intake of intranasal corticosteroids and antibiotics in patients with recurrent respiratory tract infections. Experts opined that the administration of Pidotimod in severe AR and

CRS patients along with SOC could reduce the number of attacks and help in faster remission of symptoms. Surgical reestablishment and clearing of infection within the sinus cavities do not necessarily reverse and restore normal functioning in CRS patients with nasal polyps. The use of Pidotimod adjuvant therapy would be beneficial in this category of CRS patients as it plays an important role in modulating the balance of Th1/Th2 cytokines.

Pidotimod adjuvant therapy can be a valid ,new approach for CRS management particularly in the current trying times of COVID 19. It has shown to prevent cytokine cascade activation and associated with rapid reduction of systemic symptoms, especially fever. The use of Pidotimod rebalances the dysfunctional immune system and prevents the evolution of the SARS-CoV-2 infection in COVID-19 patients. Experts mentioned that in times like COVID-19, the administration of Pidotimod in vulnerable patient subgroups, such as diabetes, CRS, chronic adenotonsillitis, otitis media, laryngitis, and AR, can help prevent adverse outcomes.

## Key Highlights

- Upper respiratory tract infections (URTIs) such as AR and CRS affect substantial population of all ages in different parts of India.
- Current management options for AR and CRS include allergen avoidance and use of second-generation antihistamines, leukotriene receptor antagonist, and INCS for symptomatic relief. Inappropriate use of antibiotics in both primary care and hospital settings is common in India in patients with URTIs and has shown to increase antimicrobial resistance.
- Pidotimod is a potent allopathic immunostimulant and immunomodulator available in India with proven clinical benefits in patients with respiratory infections in primary and secondary immune deficiencies in adults.
- The use of Pidotimod adjuvant therapy along with the SOC treatment has shown to reduce the intake of INCS and antibiotics in patients with recurrent URTIs.
- In current trying times like COVID-19, young adults with underlying health conditions and older adults (aged 60 and above) are at an increased risk of severe illness from COVID-19 due to reduced immunity. The use of Pidotimod rebalances the dysfunctional immune system and can prevent the evolution of the SARS-CoV-2 infection.
- Experts opined that the administration of Pidotimod in severe AR and CRS patients along with SOC could reduce the number of attacks and can help in faster remission of symptoms. Pidotimod adjuvant therapy should be promoted in vulnerable patient groups such as CRS, chronic adenotonsillitis, otitis media, laryngitis, and AR as it can prevent adverse outcomes.
- Experts suggested that patient subgroups who would experience maximum benefits from Pidotimod adjuvant therapy are: (i) mild-to-severe AR and CRS patients; (ii) URTI patients with comorbidities, such as diabetes; (iii) patients on frequent antibiotics due to infection-induced exacerbations; (iv) patients with CRS at early developmental stages of nasal polyps; and (v) patients with CRS at post polypectomy stages.

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