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Review Article

From Legacy to Innovation: Pidotimod's Expanding Therapeutic Horizon

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Abstract. Pidotimod, a synthetic dipeptide, has been utilized for over three decades as an immunomodulatory agent to prevent recurrent respiratory infections, particularly in immunocompromised populations such as children and the elderly. Originally developed for its ability to enhance innate and adaptive immune responses, pidotimod is now being revisited in light of new clinical insights and emerging therapeutic needs.

Recent studies have expanded its potential beyond traditional indications, with evidence supporting its role in patients with chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD), allergic rhinitis, and even viral infections, including SARS-CoV-2. Pidotimod exerts its effects by stimulating dendritic cells, enhancing toll-like receptor (TLR) expression, and promoting cytokine production, including IL-2 and IFN-γ, thereby supporting both cellular and humoral immunity. This broad-spectrum immune modulation makes pidotimod a promising adjunct in managing immune-mediated diseases and infections in both immunocompetent and immunocompromised individuals.

In this review, we examine pidotimod's pharmacodynamics, summarize clinical evidence from recent studies, and explore its evolving role in modern therapeutic strategies for infectious diseases. Given its safety profile and oral administration, pidotimod holds significant promise not only for preventing infections but also as part of a broader immunomodulatory approach in complex disease management.

Keywords: Immunomodulation; Recurrent Infections; Immunotherapy; Oral Immunomodulators; Adjunct Therapy.

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Introduction. During evolution, higher organisms have developed sophisticated defense mechanisms to counter infections, which can be mainly divided into two categories: innate immunity (nonspecific) and adaptive immunity (specific). Understanding these systems and the relationship between immunity and microorganisms is crucial to better addressing infectious diseases.

The immune system, as mentioned, carries out its functions through two main modalities: humoral and cellular mediators: innate immunity and acquired immunity.[1]

During infection, innate immunity is responsible for an immediate, nonspecific response against a wide range of pathogens and is considered the first line of defense in non-immunized individuals. This type of defense

mechanism is common to all multicellular organisms, including insects and plants.

Adaptive (specific) immunity develops as a result of the immune system's contact with microorganisms or external substances (antigens). Later, components of acquired immunity will develop a memory for specific antigens, producing antibodies against them. After the first exposure to a new antigen, the development of acquired immunity takes time. Once this mechanism is established, the specific antigen is remembered, and subsequent responses to it are faster and more effective than the first exposure. The main effectors of this immune response are T lymphocytes and B lymphocytes, which produce antibodies, as well as dendritic cells, cytokines, and the complement system.

These two systems, innate and acquired, are strongly interconnected and cooperate to ensure the immune system functions properly; for example, some immune cells, such as dendritic cells, are responsible for binding surface antigens in tissues and presenting them to B lymphocytes, or for internalizing and processing them before presenting them to T lymphocytes (**Figure 1**).

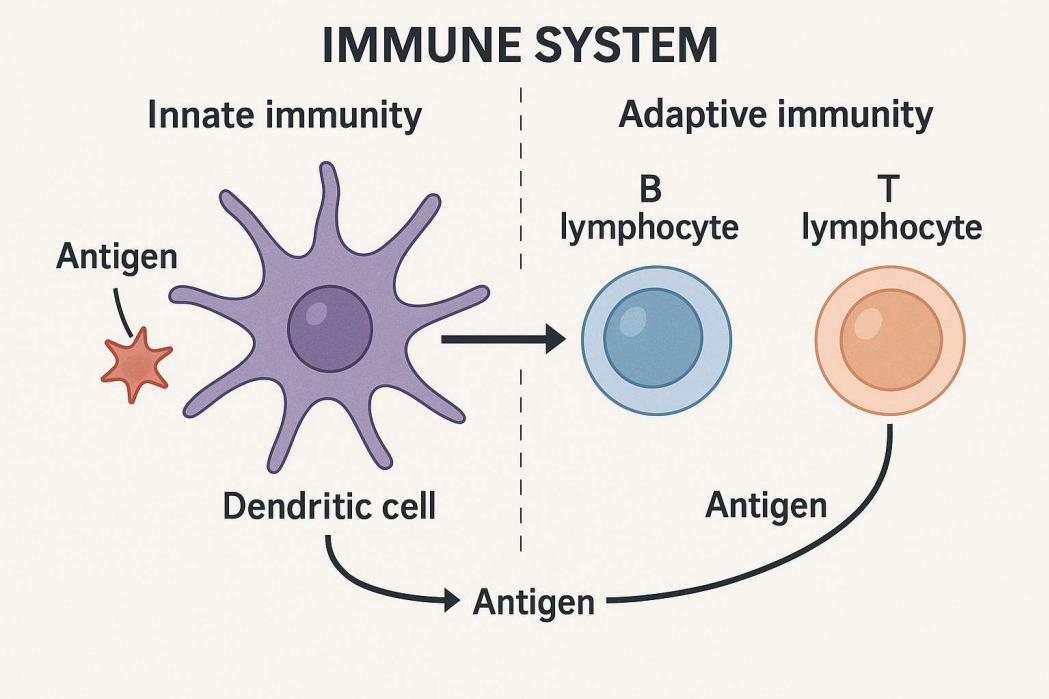

Figure 1. This diagram illustrates the interaction between the innate and adaptive immune systems. Dendritic cells, part of the innate immunity, capture antigens in peripheral tissues and migrate to lymph nodes, where they present these antigens to B and T lymphocytes, activating the adaptive immune response.

An immunological response to an infection is always associated with an inflammatory reaction. Similarly, both acute and chronic inflammatory processes are always accompanied by immune system involvement.[2]

Therefore, a functioning immune system is essential to counteract infections. Understanding the clinical picture of patients with infectious diseases is crucial. A weakened defense system could favor infections, as is the case with elderly patients, those with diabetes, or those with acquired immunological deficits. On the other hand, many individuals with abnormal immunologic responses to biological agents experience lethal outcomes or damage due to overly intense or misdirected immune reactions.

A more recent example can be observed during the COVID-19 pandemic. Recurring lethal complications in COVID-19 were characterized by hyperactivation of the immune system, sustained by a massive release of proinflammatory cytokines, which resulted in multiorgan failure.[3]

During acute and/or chronic infections, immune function can be suppressed, slowing healing and promoting recurrence and/or coinfections.[4] Individuals with poorly functioning immune systems, such as primary and secondary immunodeficiency, are more susceptible to infection and autoimmunity.[5] Consequently, increasing the efficiency of the immune system is a strategy to consider in treating infections.

An "efficient" immune system is essential to prevent infections and avoid uncontrolled responses, particularly in individuals with suboptimal immune responses. In this scenario, scientific and pharmacological research plays a fundamental role in developing innovative therapeutic strategies that promote optimal immune responses.

Over the past 20 years, many products have been proposed as "immunostimulants," "immunomodulators," or "adjuvants". These products are substances that can

provide adequate immunity against harmful antigens and enhance the body's response to infections. These modifiers of immune reactivity are divided into natural physiological substances e.g., interferons, thymic factors, lactoferrin, probiotics), exogenous substances (e.g., bacterial lysates, milk enzymes), and synthetic substances (e.g., liposomes, imiquimod, pidotimod). These substances act differently on the immune system and produce varying results, so they should not be considered equivalent.

Synthetic immunomodulators can stimulate a more rapid and effective immune response. They interact directly with T lymphocyte receptors, leading to increased expression and activity. Among these, Pidotimod is a dipeptide consisting of L-pyroglutamic acid and L-thiazolidin-4-carboxylic acid. It can induce dendritic cell maturation, increase phagocytic activity and chemotaxis of macrophages and neutrophils (natural immunity), increase the number of T lymphocytes (cell-mediated immunity), stimulate differentiation toward a Th1 phenotype, activate NK lymphocytes, and stimulate B lymphocytes to increase antibody production.

Pidotimod has an oral bioavailability of 44% and a plasma clearance of 5 L/h. Its plasma half-life is about 4 hours, and it takes 1.3–2 hours to reach maximum plasma concentration. Oral bioavailability is reduced by up to 50% when co-administered with a meal, compared with its administration in a fasting state. It undergoes minimal hepatic metabolism, and the administered dose is excreted by the kidneys unchanged (95%). Pidotimod has shown low plasma protein binding and is not significantly metabolized, so no significant pharmacokinetic interactions are expected.[6,7] It has very low toxicity, with animal studies showing that it is not mutagenic or teratogenic in rats and rabbits, does not affect fertility, and has no peri- or postnatal toxicity in rats. While often used interchangeably, an "immunostimulant" broadly enhances immune responses, whereas an "immunomodulator" fine-tunes or balances them. Pidotimod is typically classified as an immunomodulator due to its ability to both stimulate and regulate various aspects of the immune system.

Several studies show that Pidotimod can influence innate and adaptive immunity, modulating the immune response in different clinical conditions, as depicted in Figure 2. Early human studies on innate immunity have shown that Pidotimod induces bactericidal activity in alveolar macrophages and activates innate immunity at the level of natural killer cell activity.[8,9] It also can affect dendritic cell (DC) maturation and increase the expression of the major histocompatibility complex class II cell surface receptor (HLA-DR), costimulatory molecules CD83 and CD86, and the production of proinflammatory molecules such as monocyte chemoattractant protein-1 and tumor necrosis factor (TNF)-α, which drive T cell proliferation and differentiation toward a Th1 phenotype.[10] The primary trigger for Pidotimod is the stimulation of Toll-like receptors (TLRs), which activate an innate immune response. Regarding adaptive immunity, Pidotimod increases the production of antigen-specific secretory immunoglobulin A (IgA)(**Figure 2**).[11]

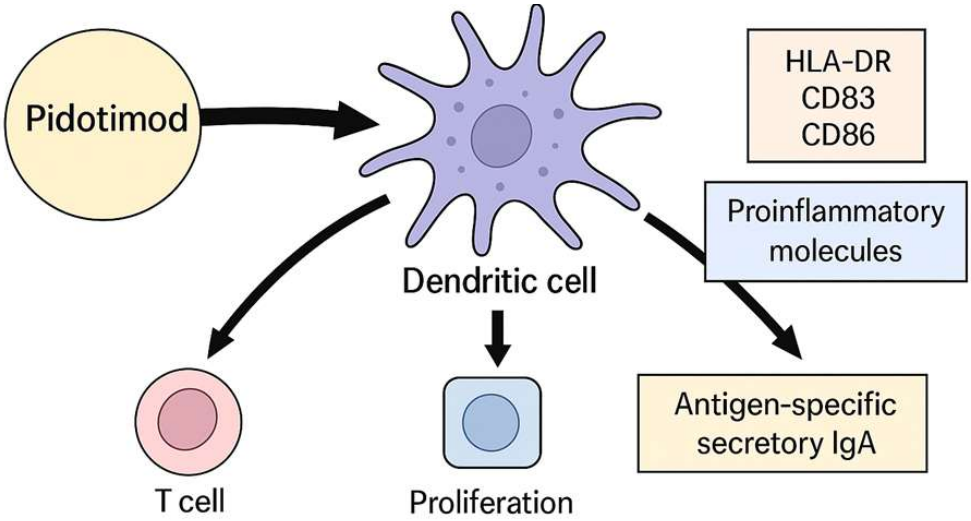

Figure 2. Mechanism of action of pidotimod on dendritic cells and the immune system.

Recent research has shown that Pidotimod can activate the G protein-coupled chemokine receptor CXC3, binding to guanosine-triphosphate-binding proteins and coordinating the T cell response in inflamed tissues, with a multifaceted mechanism of action.[12]

Other studies have shown that Pidotimod enhanced the anti-growth effect of cisplatin in a Lewis lung cancer model by promoting an antitumor response, with increased infiltration of DC and CD8+ T cells as well as enhanced expression of interferon (IFN)-γ.[13]

Recent reviews on Pidotimod have stated that it shows an optimal safety profile, with no increased frequency of reported adverse reactions or autoimmune disorders in treated patients. A recent review confirmed

that Pidotimod has a good local and systemic tolerability in children; vomiting, diarrhea, abdominal pain, erythema, and lack of appetite are the majority of adverse events reported as transient, with no significant difference between Pidotimod and placebo in the incidence of drug-related adverse events, indicating that long-term use of this immunostimulatory drug is safe.[14]

Pidotimod in Children: Key Findings. In the last decades, several studies have been conducted on the activity of Pidotimod in this population, considering various pathological conditions[15] as shown in a recent review (**Table 1**).[16]

Table 1. Summary of Key Trials of Pidotimod in Children.

Study	Population	Main Results
Therapeutic efficacy and safety of pidotimod in the treatment of urinary tract infections in children (E Clemente et al *Arzneimittelforschung 1994)*	**60 patients aged 2-8 years with recurrent urinary tract infections.** *Treatment group*: antibiotic + 400 mg pidotimod twice daily for 15 days, then pidotimod 400/day for 60 days *Control group:* antibiotic + placebo	**Clinical Findings** ↓ relapses within 60 days faster resolution of infection faster healing time ↓ significant reduction in the risk of relapses (69%) and in the case of relapses the fastest response
Analysis of Factors and T-Lymphocyte Subset Changes in Pediatric Recurrent Respiratory Infections Post-Pidotimod Treatment (Hu R et al. Altern Ther Health Med. 2025 Jan;31(1):470-475.)	**85 children diagnosed with RRTI** *Treatment group*: 45 received standard treatment with Pidotimod 400 mg bid x 2 weeks then 400 mg/day for 45 days *Control group:* 40 children received standard treatment	**Clinical Findings** ↓ symptoms (cough, fever and tonsillar enlargement) ↓ time to resolution of fever ↓ duration of infections ↓ number of infections **Laboratory Findings** ↑ CD3+, CD4+ e CD4+/CD8+ ↓ CD8
Efficacy and safety of pidotimod as adjuvant in the treatment of recurrent upper respiratory tract infections (URTI) in children *(Walavalkar KCP et al. Trends Med 2014; 14 (2):11-16)*	**193 patients aged 1-12 years with RRTI** *Treatment group:* 96 received amox/clav with Pidotimod 400 mg bid for 2 weeks then 400 mg/dayfor 45 days *Control group:* 97 received amox/clav plus placebo	**Clinical Findings** ↓ symptoms ↓ fever ↓ rhinorrea ↓ recurrences ↑ treatment effectiveness (6-month follow-up)
Efficacy and safety of pidotimod in the prevention of recurrent respiratory infections in children: a multicentre study *(Namazova-Baranova L.S. et al. Int J Immunopathol Pharmacol 27 (2014) 413-9)*	**157 children with RRTI** *Treatment group:* 78 received Pidotimod 400 mg/day for 30 days ± antibiotics *Control group:* 79 received ± antibiotics	**Clinical Findings** ↓ recurrences (6-month follow-up) ↓ severity of exacerbations, ↓ complications, ↓ antimicrobial prescription **Laboratory Findings** ↓ IgE ↓ IL-8
Pidotimod may prevent recurrent respiratory infections in children *(Licari A. et al Minerva Pediatr 2014;66:1-2)*	**100 children 3-10 years with RRTI** *Treatment group:* 50 patients Pidotimod 400 mg/day for 60 days *Control group:* 50 patients	**Clinical Findings** ↓ number of children with upper and lower respiratory ↓number of children with medication use ↓ pediatric visits ↑ school attendance ↑ doctor/parent satisfaction.
Pidotimod in the treatment of pediatric recurrent respiratory tract infection *(Xia L et al Pak J Med Sci. 2019 Jul-Aug;35(4):981-986)*	**132 children with RRTI** *Treatment group:* 66 patients with conventional drugs + Pidotimod 400 mg twice daily for 14 days, then pidotimod 400/day for 60 days *Control group:* 66 patients with conventional drugs	**Clinical Findings** ↓ symptoms, ↓ infection duration ↓ drugs use ↓ recurrences (12-month follow-up) ↑ overall efficacy
Prophylaxis with the Novel Immunomodulator Pidotimod Reduces the Frequency and Severity of Upper Respiratory Tract Infections in Children with Down's Syndrome (*La Mantia I et al J Chemothem. 1999Apr; 11(2): 126-30)*	**26 patients with Down syndrome.** *Treatment group:* 14 patients Pidotimod 400 mg/day for 90 days *Control group:* 12 patients.	**Clinical Findings** ↑ clinical improvement (mucosal hyperaemia, nasal secretion, airway obstruction) ↓ recurrences ↓ fever days ↓ antibiotic use ↓ antipyretic use

Effects of Pidotimod on recurrent respiratory infections in children with Down syndrome: a retrospective Italian study (*Valentini, D. et al. Ital J Pediatr 2020.46, 31*)	**33 children with Down Syndrome** *Treatment group:* Pidotimod 400 mg/day for 20 days/mount for 6 mounts *Control group:* same patients in the previous year same period	**Clinical Findings** ↓ upper/lower RTIs ↓ hospitalizations **Laboratory Findings** ↑ B-cell function (antibodies, proliferation)
Immunomodulating activity of Pidotimod in children with Down syndrome *(Zuccotti GV et al J Biol Regul Homeost Agents. 2013 Jan-Mar;27(1):253-8)*	**18 patients aged 3-10 years with Down Syndrome** *Treatment group:* 9 patients with Pidotimod 400 mg/day for 90 days plus influenza vaccination *Control group:* 9 patients with influenza Vaccination	**Laboratory Findings** ↑ **u**pregulation of genes involved in the activation of innate immunity and in antimicrobial activity ↑ increment in flu-specific IgG1/G3
Proposal for a new therapeutic high dosage of Pidotimod in children with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome: a randomized controlled study. (*Manti S et al. Ital J Pediatr 46 2020:106)*	**22 children aged 3-8 years with PFAPA** *Treatment group:* Pidotimod 400 mg bid for 90 days + betamethasone on demand *Control group:* betamethasone on demand only **crossover after 3 months.**	**Clinical Findings** ↓ fever episodes, ↓ pharyngitis ↓ stomatitis ↓ betamethasone use.
Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia. *(Esposito M. et al J Transl Med (2015) 13:288).*	**20 children with non-complicated pneumonia.** *Treatment group:* cefotaxime i.v. for 4 days followed amox/clav for 6 days + clarithromycin for 14 days + Pidotimod 400 mg bid x 2 weeks. *Control group:* cefotaxime i.v. for 4 days followed amox/clav for 6 days + clarithromycin for 14 days	**Laboratory Findings** ↑ dendritic cells, ↑TNF-α ↑ IL-12 ↑ TLR monocyte activation. ↑ mRNA expression of antimicrobial peptides
Effect of pidotimod combined with azithromycin on children with mycoplasma pneumonia and the expression levels of IL-10 and G-CSF in serum *(Shi H et al Exp Ther Med. 2019 Jul 3;18(3):1800–1806)*	**149 children with pneumonia** *Treatment group*: 79 children treated with azithromycin + Pidotimod 400 mg bid x 2 weeks. *Control group:* 70 children treated with *azithromycin only*	**Clinical Findings** ↑ symptom improvement ↓ adverse events. **Laboratory Findings** ↓IL-10 ↓G-CSF
Immune modulator pidotimod decreases the in vitro expression of CD30 in peripheral blood mononuclear cells of atopic asthmatic and normal children. *(Gourgiotis D. et al . J Asthma 41 (2004) 285-7)*	**22 children with atopic asthma** 13 atopic asthmatic and 9 normal children	**Laboratory Findings** ↓ CD30 ↑ Improve TH1/Th2 balance
Effect of pidotimod combined with montelukast sodium in the treatment of patients with asthma and its influence on the inflammatory factors and immune function *(Lingling FU Chinese Journal of Primary Medicine and Pharmacy 12 (2020) 2885-2889.)*	**102 children bronchial asthma** *Treatment group:* 51 used pidotimod 400mg/day for 30 days combined with montelukast sodium *Control group:* 51 used only montelukast	**Clinical Findings** ↑ FVC ↑ FEV -1 **Laboratory Findings** ↑ CD 3+ ↑ CD 4+ ↑ CD 4+ /CD 8+
Pidotimod in recurring respiratory infection in children with allergic rhinitis, asthma, or both conditions (*Vargas Correa J.B. Rev Alerg Mex 49 (2002) 27-32.)*	**73 children 2-12 years with asthma and allergic rhinitis** *Treatment group:* 400 mg pidotimod twice daily *Control group:* standard therapy	**Clinical Findings** ↓ episodes of RRTI ↓ sick days.
Influence of pidotimod on the IL-16, immunoglobulin and T cell subsets in asthmatic children. *(Sun YX. Et al. J Clin Pediatr 29 (2011) 777–779)*	**Children with asthma** *Treatment group* : 55 children pidotimod +control for 2 months *Control group:* 35 children	**Laboratory Findings** ↓ IL-6
Efficacy of Pidotimod use in treating allergic rhinitis in a pediatric population *(Brindisi G et al. Ital J Pediatr. 2020 Jul 7;46(1):93)*	**70 children with rhinitis/adenoid hypertrophy** *Treatment group* : 57 children Pidotimod 400 mg /day for 30 days *Control group:* 13 children	**Clinical Findings** ↑ nasal airflow ↓ nasal obstruction, ↓airway inflammation.

- **Recurrent urinary tract infections.** A multicenter, randomized, double-blind trial evaluated 60 patients (ages 2–8 years) with recurrent urinary tract infections. One group received a 15-day administration of antibiotics and Pidotimod 400 mg twice daily, followed by another 60 days of Pidotimod 400 mg once daily, while the other group received a placebo. In the 60-day follow-up, four relapses were observed in the Pidotimod-treated group and 13 in the placebo group. The infection resolution was faster in the Pidotimod group (6.9 days vs. 8.3 days), with a significantly reduced risk of relapse (69%) and a faster clinical response in these patients.[17]
- **Recurrent Respiratory Tract Infections.** Recurrent respiratory tract infections in children lead to increased absences from school, worse quality of life, and further respiratory complications, including bronchiectasis. For this reason, adequate prevention and treatment are essential. A recent model analysis showed that pidotimod is a cost-effective strategy to reduce the incidence rate of recurrent respiratory tract infections in children.[18] Many studies have documented the role of Pidotimod: in a retrospective cohort study of children with recurrent respiratory tract infections, symptoms such as cough, fever, wet rales, and enlarged tonsils resolved significantly faster with Pidotimod, with a reduction in recurrent infections. Moreover, post-treatment levels of CD3+, CD4+, and CD4+/CD8+ were elevated in the Pidotimod group compared with the control group.[19] Another study in 100 children emphasized that Pidotimod could reduce the frequency and severity of infections, making it a valuable adjunct in paediatric prevention strategies.[20]

In a multicenter, prospective, randomized, double-blind controlled trial with 193 pediatric patients aged 1–12 years (mean age of 6.7) with recurrent respiratory infections and impaired immunologic function, a group treated with Pidotimod 400 mg x 2/day for 15 days plus Amoxicillin/Clavulanic acid followed by maintenance with Pidotimod 400 mg showed statistically significant improvements ($p<0.05$) in fever, ear pain, cough, expectoration, rhinorrhea, and otalgia scores compared to the placebo+antibiotic group after 30 days of maintenance. In conclusion, the study showed that the drug enables symptom relief in the acute phase compared with the placebo group and prevents episodes during the subsequent 30 days of maintenance.[21]

A randomized clinical trial conducted in Russia with children more susceptible to respiratory infections demonstrated that a 30-day course of Pidotimod led to a reduction in the number of acute respiratory infection episodes over a 6-month follow-up. The treatment group also exhibited faster recovery, with rapid symptom resolution and a normalization of serum immunological markers. Most notably, interleukin-8, a proinflammatory cytokine, normalized faster in the treatment group, confirming Pidotimod's immunomodulatory effect.[22] This data was also confirmed in a Pakistani clinical study, which showed that Pidotimod significantly decreased the number of infection episodes and improved immune parameters, such as immunoglobulin levels and T-cell subsets.[23]

A 2019 meta-analysis involving 29 RCTs and 4344 pediatric patients found that Pidotimod significantly reduced the frequency of recurrent respiratory infections. Specifically, the rate ratio (RR) for fewer infections was 1.59 (95% CI 1.45-1.74, $p < 0.00001$). It also lowered the use of antibiotics, improved serum immunoglobulin levels (IgG, IgA, IgM), and enhanced T lymphocyte subtypes (CD3+, CD4+). Furthermore, Pidotimod was not associated with an increased risk of adverse events (RR = 1.05, 95% CI 0.72-1.54, $p = 0.80$).[24]

- **Down's Syndrome.** Several studies have investigated the immunomodulatory effects of Pidotimod in children with Down syndrome, a population particularly vulnerable to recurrent respiratory infections. La Mantia demonstrated that Pidotimod significantly reduced the frequency and severity of respiratory tract infections in this group, likely due to enhanced immune response.[25] Similarly, another study reported improvements in mucosal immunity and infection control, supporting the use of Pidotimod as a preventive therapy.[26] Additional evidence confirmed its role in modulating immune parameters, including T-cell function, suggesting that Pidotimod may contribute to strengthening both innate and adaptive immunity in children with Down syndrome.[27]

- **Periodic fever, ulcerous stomatitis, pharyngitis, adenitis syndrome (PFAPA).** A crossover study with 22 children suffering from PFAPA syndrome (a rare condition with few treatment options) showed that Pidotimod significantly reduced the frequency of fevers, episodes of pharyngitis, and aphthous stomatitis. The need for betamethasone (a corticosteroid) also decreased. 86.4% of patients showed improvement. No serious side effects were observed during the study period.[28]
- **Community-acquired pneumonia.** In a study of children hospitalized with community-acquired pneumonia, 20 children were randomized to receive Pidotimod, administered alongside standard antibiotics (cefotaxime + clarithromycin) or standard antibiotics alone. Blood samples were analyzed under the following conditions: without any stimulus, in the presence of a mixture of eight pneumococcal polysaccharides, or of lipopolysaccharide. Blood

analysis revealed that Pidotimod improved the activation and costimulatory molecule expression in dendritic cells, resulting in higher secretion of TNF-α, IL-12, and enhanced TLR-2 expression, suggesting that Pidotimod enhances the immune response, potentially aiding in faster recovery and better handling of bacterial infections like pneumonia.[29] Another retrospective cohort study involving 149 children with Mycoplasma pneumonia comparing azithromycin alone versus azithromycin plus pidotimod, found that the combination therapy significantly increased overall treatment efficacy (94.9% vs. 81.4%, $p < 0.05$), shortened symptom resolution times, reduced adverse reactions, and lowered serum levels of inflammatory markers IL-10 and G-CSF more than azithromycin alone.[30]

- **Asthma.** Several studies have shown that Pidotimod helps improve the inflammatory profile in asthmatic children by reducing markers like IL-4, CD30, and IL-6, while increasing IgA levels. This results in a reduction in respiratory infections in asthmatic children.[31-36] One Chinese observational study showed that combining Pidotimod with Montelukast (a medication used for asthma) improved cough scores and FEV1 (a measure of lung function) in children, compared to the group treated with Montelukast alone. This combination therapy could offer synergistic benefits for children with asthma who suffer from frequent infections.[32] Interestingly, in a study of children aged 6 to 12 years with allergic rhinitis, Pidotimod significantly improved nasal airflow, bringing it to levels comparable to those of healthy controls in children with allergic rhinitis (AR). This clinical benefit occurred despite the absence of detectable alterations in the nasal microbiota, suggesting that the effect of pidotimod likely arises from modulation of local inflammatory processes rather than microbial alterations.[37]

Pidotimod in Adults: Key Findings. Few well-conducted studies in the adult patient guide the use of pidotimod in various pathological conditions (**Table 2**).[38,39]

- **Chronic bronchitis.** Represents the first disease in which the use of pidotimod in adults has been studied. Ciaccia et al. studied Pidotimod in adults with chronic bronchitis; subjects were randomized to receive pidotimod (n=251) or placebo (n=263) for 2 months, followed by 3 months of follow-up. Pidotimod-treated patients had longer intervals between exacerbations (105 vs. 98 days, $P < 0.01$), with reduced antibiotic use and fewer sick leaves.[40] These data were also confirmed in a multicenter, randomized, double-blind study involving 181 patients with chronic bronchitis, where the use of pidotimod significantly reduced the incidence of infectious exacerbation and hospitalizations.[41]
- **Chronic Obstructive Pulmonary Disease (COPD).** In a randomized, double-blind study enrolling 52 patients, Pidotimod (800 mg twice daily for 30 days) was shown to enhance T-cell activity in COPD patients. The effect on T-cell function was observed after 15 days of treatment and persisted for up to 5 weeks.[42]
- **Pneumonia and Respiratory system.** Trabattoni conducted a randomized controlled trial in hospitalized adults with community-acquired pneumonia (PSI III–IV or CURB-65 0–2), adding pidotimod (800 mg twice daily) to standard levofloxacin therapy. Immunological assessments showed a significant up-regulation of antimicrobial/immunomodulatory proteins, increased percentages of cells expressing TLR-2, TLR-4, CD80, and CD86, and a marked reduction in TNF-α-producing cells.[43] Xu evaluated elderly patients with Mycoplasma pneumoniae infection. Adjunctive pidotimod led to a significant decline in inflammatory cytokines (including IL-10 and G-CSF), improved respiratory function, clinical recovery timelines, and lower reinfection rates compared to controls.[44] D'Amato explored metabolic changes in bronchiectasis patients receiving pidotimod. They demonstrated pidotimod altered metabolic pathways linked to inflammation and oxidative stress, suggesting it may mitigate exacerbation in chronic inflammatory lung disease.[45] Another study examined patients with allergic rhinitis and asthma and recurrent respiratory infections treated with pidotimod, highlighting a reduction in the frequency of infections, the use of antibiotics and corticosteroids, and improved immune parameters.[46]
- **Human Immunodeficiency Syndrome (HIV).** Antiretroviral therapy has significantly prolonged the lifetime of HIV-infected patients. However, individuals with HIV infection have residual systemic inflammation and persistent immune activation, with complications not pertaining to the classic manifestations of AIDS. A randomized trial with 40 HIV patients on antiretroviral therapy revealed that Pidotimod (800 mg twice daily for 4 weeks) led to a reduction in proinflammatory cytokines, with a corresponding increase in anti-inflammatory cytokines. This rebalancing also improved the CD4/CD8 ratio, salivary IgA secretion, and cystatin C levels, a marker for inflammation and cardiovascular risk. The immunologic benefits of Pidotimod persisted even after treatment cessation.[47]

SARS CoV2 INFECTION/COVID-19. Several studies were produced during the Coronavirus disease 2019 (COVID-19) pandemic that significantly impacted human lives, and with which we,

unfortunately, had to cope. During the first phase of the pandemic, there was considerable confusion among physicians and the public about how to manage this serious disease. Many treatments were proposed, but most proved ineffective. Early in the pandemic, several researchers explored Pidotimod as a potential therapy, given its immunomodulatory effects and potential to influence T lymphocyte responses, which are critical in fighting viral infections like SARS-CoV-2.[48] A predictive mathematical model also suggested that Pidotimod could play a role in eradicating the virus by modulating T lymphocyte responses to viral.[49] In the first half of 2020, initial clinical work was produced evaluating the role of Pidotimod in patients with COVID-19 who did not exhibit respiratory failure. The first clinical paper in early 2020 recruited 20 patients, who were randomized into two groups: one received symptomatic therapy plus Pidotimod (800 mg twice daily for 10 days), while the other group received symptomatic treatment only. The results were promising, with Pidotimod-treated patients showing faster clinical recovery, as evidenced by a significant reduction in fever duration (4.10 ± 2.18 days in the treatment group vs. 7.50 ± 2.63 days in the control group, P = 0.006)(50). Later, an Indian study with 140 patients (all without oxygen desaturation) confirmed these findings. The study reported that Pidotimod significantly reduced inflammatory markers and other biological indicators associated with COVID-19. The authors concluded that Pidotimod may play a significant role in managing SARS-CoV-2 infections, particularly in reducing the inflammatory response.[51]

A large retrospective case-control study involving 1231 unvaccinated patients with mild to moderate COVID-19 infection was conducted. From this cohort, 184 patients were selected and divided into two groups: 97 patients received Pidotimod (800 mg twice daily for 7-10 days) and 87 received only symptomatic therapy. Primary endpoints of the study included emergency room access for COVID-19-related pathology, hospitalizations, and deaths. The secondary outcome was the duration of illness. The results showed a 50% reduction in hospitalizations (P = 0.008) for patients treated with Pidotimod, shortened duration of illness (P = 0.005) in the treatment group, reduced corticosteroid use (P < 0.001), and improved oxygen saturation during the Walking Test (P = 0.01). Therefore, the authors concluded that Pidotimod can prevent worsening of COVID-19 infection and facilitate more rapid virologic clearance.[52]

In another study, Santus et al. examined the impact of Pidotimod on immunologic biomarkers and clinical severity in patients with mild to moderate COVID-19 pneumonia. Patients received standard care plus Pidotimod (800 mg twice daily). Results showed no significant differences in duration of hospitalization, mortality, or intubation rates compared to historical controls. Pidotimod-treated patients had a lower neutrophil-to-lymphocyte ratio (P = 0.037) and progressive increases in eotaxin and IL-4 levels (P < 0.05). In vitro, Pidotimod enhanced the expression of IFN-γ (P < 0.05) and TLR. The study suggested that Pidotimod may help accelerate healing by boosting the innate immune response to the viral infection.[53]

Further research evaluated the effects of co-administration of Pidotimod with monoclonal antibodies in obese COVID-19 patients (BMI ≥ 35 kg/m²) versus normal-weight patients. The study found that Pidotimod showed similar effects in both groups, despite obesity being an independent risk factor for hospitalization, suggesting that Pidotimod may provide benefits in both obese and non-obese individuals, regardless of BMI.[54]

- **Vaccinations.** In real practice, an interesting use of Pidotimod has shown promise as an adjuvant to vaccination. An excellent response to a vaccine is closely linked to a fully functioning immune system; however, vaccinations are used in individuals who often respond poorly to vaccines (elderly, immunocompromised patients, and children). Consequently, enhancing the immune response with immunomodulators could be a valuable strategy to improve vaccine efficacy.

  In patients with COPD, it helped improve the immune response to influenza vaccination, leading to fewer flare-ups.[55] Similarly, in healthy adults receiving the COVID-19 vaccine, Pidotimod improved antibody responses and reduced vaccine side effects, particularly enhancing IgM production (P = 0.02), suggesting that Pidotimod could enhance immunological memory, potentially improving vaccine efficacy in populations prone to poor responses (e.g., elderly, immunocompromised).[56]

Study	Population	Main Results
Pidotimod activity against chronic bronchitis exacerbations. *(Ciaccia A. Arzneimittelforschung /Drug Research 1994)*	**514 patients with COPD** *Treatment group*: 251 patients, Pidotimod 800 mg once daily for 60 days without antibiotics, antivirals, or vaccines *Control group:* 263 patients, placebo without antibiotics, antivirals, or vaccines	**Clinical Findings** ↓ number of exacerbations during treatment and 2-month follow-up ↓ duration of infectious episodes during treatment and follow-up ↓ work or activity absence
Evaluation of the efficacy of pidotimod	**181 patients with COPD**	**Clinical Findings**

in the exacerbations in patients affected with chronic bronchitis *(Bisetti A. et al. Arzneimittelforschung, 1994 Dec;44(12A):1499–502)*	*Treatment group*: 93 patients treated with 800 mg Pidotimod once daily for 60 days, without antibiotics, vaccinations, or other immunostimulants *Control group*: 88 patients treated with placebo, without antibiotics, vaccinations, or other immunostimulants	↓ recurrence rate ↓ recovery time ↓ hospitalization duration **Laboratory Findings** ↑ respiratory function
Ex vivo evaluation of pidotimod activity in patients with chronic obstructive pulmonary disease *(Benedetti GP et al. Arzneimittelforschung/Drug Research 1994)*	**52 patients with COPD** Pidotimod 800 mg twice daily for 30 days with follow-up 5 weeks	**Laboratory Findings** ↑ early improvement of T cell activity post-treatment ↑ macrophage activity ↑ granulocyte activity
Immunomodulatory effects of pidotimod in adults with community-acquired pneumonia undergoing standard antibiotic therapy *(Trabattoni D. et al. Pulm Pharmacol Ther 2017 Jun:44:24-29)*	**16 patients with community-acquired pneumonia** *Treatment group:* 9 patients treated with Pidotimod 800 mg twice daily for 10 days + levofloxacin *Control group:* 7 patients treated with levofloxacin only	**Laboratory Findings** ↓ pro-inflammatory cytokine gene expression (IL-1β, TNF-α) ↑ CD14+ monocytes expressing TLR2 and TLR4 ↑ gene expression of IFN-1, IL-6, IL-12 ↑ CD80+ and CD86+ dendritic cells
Effects of adjuvant pidotimod therapy on levels of inflammatory factors and expressions of serum GM-CSF and KL-6 in elderly patients with mycoplasma pneumonia *(Xu L. et al. Am J Transl Res. 2021 Oct 15;13(10):11899–11907)*	**104 elderly patients with mycoplasma pneumonia** *Treatment group:* 52 patients treated with azithromycin + ambroxol + Pidotimod 800 mg twice daily for 7 days *Control group:* 52 patients treated with azithromycin + ambroxol	**Clinical Findings** ↓ dyspnea ↓ hospitalization duration ↑ FEV1 ↑ FEV1/FVC **Laboratory Findings** ↓ TNF-α ↓ IL-6 ↓ IL-8 ↓ GM-CSF
The Immune-Modulator Pidotimod Affects the Metabolic Profile of Exhaled Breath Condensate in Bronchiectatic Patients: A Metabolomics Pilot Study *(D'Amato et al. Front Pharmacol 2019 Oct 3;10:1115)*	**40 Bronchiectatic Patients:** *Treatment group:* 20 patients treated with Pidotimod 800 mg twice daily, 21 days/month for 6 months *Control group:* 20 patients, no therapy	**Clinical Findings** ↓ recurrence **Laboratory Findings** ↑ FENOImproved metabolotype
Pidotimod as add-on therapy in patients with pollen-induced allergic rhinitis and asthma and associated respiratory infections *(Marogna M et al.. J Biol Regul Homeost Agents. 2021; 35(3):1053–1058)*	**90 patients with rhinitis/asthma** *Treatment group:* 45 patients with standard therapy + Pidotimod 800 mg daily for 10 days/month for 3 months *Control group:* 45 patients with standard therapy only	**Clinical Findings** ↓ nasal symptoms ↓ bronchial symptoms ↓ medication use ↑ lung function **Laboratory Findings** ↓ nasal eosinophilic infiltrate
Pidotimod and Immunological Activation in Individuals Infected with HIV *(Ucciferri C. et al., Current HIV Research, 2021)*	**36 patients with HIV infection** *Treatment group:* 26 patients with antiretroviral therapy + Pidotimod 800 mg twice daily for 4 weeks *Control group:* 10 patients with antiretroviral therapy only	**Laboratory Findings** ↓ pro-inflammatory cytokines ↑ anti-inflammatory cytokines ↑ IgA secretion in saliva and mucosa ↑ CD4+/CD8+ ratio ↑ immune rebalancing→ effect persisted post-therapy
Pidotimod in Paucisymptomatic SARS-CoV2 Infected Patients *(Ucciferri C. et al. Mediterr J Hematol 12, e2020048 2020)*	**20 patients with COVID-19 infection** *Treatment group:* 10 patients, symptomatic therapy + Pidotimod 800 mg twice daily for 10 days *Control group:* 10 patients, symptomatic therapy only	**Clinical Findings** ↓ days with fever
Efficacy and Safety of Pidotimod in SARS-CoV-2 Management: A Real-world Evidence Study. *(Pradyut Waghray GP et al*	**127 patients with COVID-19 infection** *Treatment group:* 77 patients with symptomatic therapy + Pidotimod 800 mg twice daily for 14 days *Control group:* 50 patients with symptomatic	**Clinical Findings** ↓ fever duration ↓ symptom duration **Laboratory Findings** ↓ swab negativization time

International Journal of Clinical Skills 15 (2021) 510-517)	therapy only	↓ CRP ↓ IL-6 ↓ ferritin ↓ D-dimer
New Therapeutic Options in Mild Moderate COVID-19 Outpatients *(Ucciferri C. et al. Microorganisms. 2022 Oct 27;10(11):2131)*	**184 patients with COVID-19 infection** *Treatment group:* 97 patients with symptomatic therapy + Pidotimod 800 mg twice daily for 7–10 days *Control group:* 87 patients with symptomatic therapy only	**Clinical Findings** ↓ hospitalization ↓ mortality ↓ disease days ↓ corticosteroid use ↑ sO2 ↑ walking test **Laboratory Findings** ↓ swab negativization time
Anti-Inflammatory Effects of Immunostimulation in Patients with COVID-19 Pneumonia *(Santus P.et al . J Clin Med. 2021 Dec 9;10(24):5765)*	**32 hospitalized COVID-19 patients** *Treatment group:* 16 patients, with standard therapy + Pidotimod 800 mg twice daily *Control group*: 16 patients with standard therapy	**Laboratory Findings** ↓ neutrophil/lymphocyte ratio ↑ eotaxin ↑ IL-4 ↑ IFN-γ ↑ TLR
Are monoclonal antibodies effective in patients with severe obesity in SARS-CoV-2 infected? *(Ucciferri C. et al. Immun Inflamm Dis. 2023;11:e771)*	**32 COVID-19 outpatients** *Treatment group:* 22 obese treated with single-dose monoclonal antibodies + cholecalciferol 2000 IU + Pidotimod 800 mg twice daily for 10 days *Control group:* 10 non-obese patients treated with single-dose monoclonal antibodies + cholecalciferol 2000 IU	**Clinical Findings** no difference between obese and non-obese patients
Pidotimod activity in patients affected by COPD *(Cogo R. Minerva Pneumologica 53 (2014) 21-6)*	**85 patients with COPD** *Treatment group:* 40 patients treated with Pidotimod 800 mg daily, 15 days/month for 2 months + flu vaccination *Control group:* 40 patients treated with flu vaccination only	**Clinical Findings** ↓ number of exacerbations in the 4 months after vaccination
Improving BNT162b2 mRNA Vaccine Tolerability without Efficacy Loss by Pidotimod Supplementation *(Ucciferri C. et al. Mediterr J Hematol Infect Dis. 2022; 14:e2022023)*	**30 vaccinated healthcare workers** *Treatment group:* 10 subjects, SARS-CoV2 vaccination + Pidotimod 800 mg twice daily for 6 days *Control group:* 20 subjects, SARS-CoV2 vaccination only	**Clinical Findings** ↓ vaccine-related adverse events **Laboratory Findings** ↑ IgM

Table 2. Summary of Key Trials of Pidotimod in adults.

Conclusions.

Respiratory Infections and Immunomodulatory Effects. Most acute respiratory tract infections are viral, and in this circumstance, the widespread misuse of antibiotics has contributed to the rise of antibiotic resistance. To counter this, there is increasing interest in alternative approaches such as enhancing the immune response, especially in vulnerable populations like the young and the elderly. Pidotimod, an immunostimulant, has shown potential in this context.

A 2019 review highlighted Pidotimod's immunostimulatory properties and its pharmacokinetic profile, emphasizing its role in treating and preventing acute respiratory infections. The authors conclude that Pidotimod was effective in:

- Reducing reinfection rates (OR 0.20, 95% CI 0.12-0.33; $p < 0.00001$).
- Lowering antibiotic use (mean difference -2.65, 95% CI -3.68 to -1.62; $p < 0.00001$).
- Decreasing the need for rescue medication.
- Reducing absenteeism (mean difference: -2.99, 95% CI -4.03 to -1.95; $p < 0.00001$).

Therefore, Pidotimod is a viable option for individuals at higher risk for recurrent respiratory infections.[57]

Application in COPD. A recent study in India explored the use of Pidotimod in patients with Chronic Obstructive Pulmonary Disease (COPD), demonstrating its efficacy in managing recurrent respiratory infections. The study also identified certain subgroups of COPD patients who may benefit most from Pidotimod, including:

- Chronic smokers
- Patients with severe COPD, or other comorbidities, particularly those with frequent exacerbations.

All this suggests that Pidotimod can be an effective immunostimulant for managing COPD-related infections.[58]

Pediatric Use. A meta-analysis of 29 randomized controlled trials (RCTs) involving 4344 pediatric patients focused on the use of Pidotimod in the treatment and prevention of recurrent respiratory infections in children. Key findings include:

- Increased proportion of children with fewer respiratory infections (RR 1.59; 95% CI 1.45-1.74; $p < 0.00001$).
- Reduction in the duration of cough and fever.
- Significant decrease in antibiotic use.
- Improvement in serum levels of immunoglobulins (IgG, IgA, IgM) and T lymphocyte subtypes (CD3+, CD4+).

The results support the use of Pidotimod as an effective therapeutic option for pediatric patients, particularly for reducing recurrent respiratory infections. The treatment also showed benefits in reducing recurrent urinary tract infections in children.

Immunological Effects and Vaccination. Pidotimod may also have a role in improving the efficacy and acceptability of vaccinations. It could enhance the immune response to vaccines, though large-scale studies are still needed to support this use firmly. Elderly individuals, who often have reduced immunological capacity and are at higher risk for infections, might particularly benefit from Pidotimod in combination with vaccines.

Application in Outpatient COVID-19 Management. An exciting area of application for Pidotimod is in outpatient COVID-19 patients. Pidotimod has emerged as a preferred therapy for those who do not qualify for antiviral treatments, based on the quality and number of studies demonstrating its efficacy in reducing inflammatory markers and improving recovery in mild to moderate COVID-19 cases. This positions Pidotimod as a potential immunomodulatory therapy for managing COVID-19, particularly in outpatient settings where antiviral drugs may not be indicated.

Conclusions. Pidotimod has demonstrated significant benefits in treating respiratory infections, particularly in vulnerable populations such as the elderly, children, and COPD patients. It helps enhance immune responses, reduce reinfection rates, lower antibiotic usage, and improve clinical outcomes. While further studies are needed, Pidotimod's potential as an immunomodulatory treatment for conditions like COVID-19 and its ability to improve vaccination responses make it a promising option in various infectious disease settings.

Founding. No funding has been received from the pharmaceutical companies that produce Pidotimod.

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