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existing software and can increase citations of articles. The appearance of new protocols and standards for data sharing on the web makes developing new applications easier and more straightforward. The VCCLAB can be used as a prototype to develop such projects. The developed technology allows integration of new third-party applications, which could be made available to the worldwide community.

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# Novel treatment options for infectious exacerbations

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In acute exacerbations and the onset of asthma, considerable data exist that implicate the role of infectious agents, particularly atypical bacteria, *Chlamydia pneumoniae* and *Mycoplasma pneumonia*, and the common cold viruses, respiratory syncytial virus and rhinovirus. These agents have been identified in the airways of stable asthmatics and are presumed to contribute to chronic lower-respiratory inflammatory disease. It is current practice for treating acute exacerbations of asthma, although perhaps inappropriate albeit typical, to prescribe antibiotics. This occurs despite the fact that respiratory viruses represent the primary trigger of an exacerbation. However, consistent with this approach, macrolides have been shown to confer immune modulatory effects beneficial to those suffering from chronic pulmonary inflammatory syndromes. Using macrolide concentrations below the minimal inhibitory concentration can modulate expression of virulence factors, which could prevent establishment or expansion of an infection. Herein, we detail characteristics shared between two common therapeutic approaches, macrolide antibiotic therapy and systemic corticosteroids, in an attempt to propose an alternative treatment paradigm.

## Macrolides: empirical therapy

Weinberger [1] recently reviewed treatment strategies for respiratory infections and asthma, highlighting the typical practice of prescribing antibiotics for acute exacerbations, although such events are often elicited by respiratory viruses. In addition to macrolide-directed inhibition of bacterial protein synthesis via binding to the 50S ribosomal subunit [2], documented reports of improved


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patient outcomes in noninfectious diseases suggested macrolide-specific enhancement of the immune response. For over two decades, it has been recognized that macrolides are beneficial for those suffering from chronic pulmonary inflammatory syndromes, such as diffuse panbronchiolitis (DBP), cystic fibrosis, asthma and bronchiectasis. Indeed, antimicrobial agents within this multi-membered lactone ring class of compounds have been consistently associated with reduced hospitalization period and mortality when used alone or in combination with other antibiotics for treating chronic pulmonary inflammatory syndromes [3]. Although the mechanism(s) of action remains unclear, the anti-inflammatory rather than anti-bacterial contribution of long-term macrolide therapy has been suggested to be pivotal in improving the survival of patients, most notably those suffering with DBP.

The non-antibacterial benefits conferred by macrolides on an inflamed diffuse panbronchiolitis pulmonary system are likely numerous. For example, chronic erythromycin dosing imparts a dose-dependent decrease in sputum and mucus production in animal studies [4]. Further, the ability to decrease the inflammatory sequela has been consistently demonstrated. Specifically, low-dose administration of macrolides readily suppresses the overabundance of lung neutrophils, most likely by reducing their chemotactic properties [5]. Suppression of acute inflammation often confers secondary benefits, such as improved pulmonary function and decreased acute exacerbations. Notably, there is often inconsistency as to when the clinical benefits of macrolide treatment appear, ranging from a few to over 16 months, when comparing efficacy in DPB, asthma, bronchiectasis or cystic fibrosis; however trial design in these studies varied significantly [5].

**Macrolides: immune benefits**

The effects of low macrolide concentrations on bacterial virulence factors and host immune functions with respect to clinical significance were recently reviewed [6]. Macrolides, such as clarithromycin, exhibit anti-inflammatory properties to reduce neutrophil and lymphocyte accumulation [7], improve asthma symptoms perhaps by decreasing mucus production and sputum eosinophils, alleviate bronchial hyperresponsiveness and decrease pulmonary expression of tumor necrosis α (TNF-α), interleukin IL-3, IL-4, IL-5 and IL-8 in clinical and preclinical settings ([8] and reviewed in [9]). In addition, clarithromycin-mediated suppression of pro-inflammatory cytokines from lipopolysaccharide-primed monocytes *in vitro* further substantiates the anti-inflammatory contribution of macrolides seen in preclinical rat carrageenan injection models [10,11].

As a therapeutic agent, clarithromycin has been reported to exert a glucocorticoid-sparing effect in patients with severe steroid-dependent asthma, allowing tapering or discontinuation of prednisone [12]. Although altered steroid metabolism has been proposed as one mechanism of action, modulation of host factors, such as nuclear factor-κ (NF- κB) activation status, might in fact represent a critical means of intervention. Desaki *et al.* [13] demonstrated, by using human bronchial epithelial cells, that macrolides directly suppress the activation of NF-κB and the subsequent production of pro-inflammatory cytokines when stimulated by TNF-α or phorbol 12-myristate 13-acetate. Further, they validated this finding using an erythromycin derivative that maintains anti-inflammatory properties, independent of anti-bacterial activity. Taken together, the pleiotropic properties of macrolides are presumed to culminate in reducing lower-airway inflammation.

Of note, prednisone has been shown to exert an immunosuppressive effect on cytokine production by T lymphocytes and to cause a significant decrease in nuclear translocation of NF-κB in Jurkat cells, implicating NF-κB dysregulation as a common anti-inflammatory property of macrolide antibiotics and systemic corticosteroid therapies [14].

**Toll-like receptor modulators**

Overall, the data presented above suggest that agents capable of interfering with NF-κB activation in a more specific manner, that is, through targeting of a specific tissue or cell population, could represent better anti-inflammatory therapies than macrolides or systemic antibiotic therapies. Such therapeutic intervention could involve targeting Toll-like receptor signaling. Toll-like receptors (TLR), a family of pattern-recognition receptors that constitute an important component of the innate and adaptive immune system, are activated by specific microbial components or host molecules. These type I transmembrane proteins contain an extracellular leucine-rich repeat region and an intracellular domain homologous to the IL-1 receptor to mediate activation of the NF-κB pathway, resulting in the production of pro- and anti-inflammatory cytokines, a key event in bridging the innate and adaptive arms of the immune response [15].

Given the important role for TLR activation in initiating and perhaps sustaining the inflammatory response, immune modulatory agents aimed at interfering with TLR activation could represent an effective anti-inflammatory approach for the treatment of infection-associated inflammatory diseases. Furthermore, the unique expression profile of distinct sets of TLRs in defined tissues or cell populations might provide additional selectivity for TLR-based therapies. Selective downregulation of the TLR-activated pathological response, rather than global immune suppression therapy typified by steroid treatment, is a potentially better alternative.

Recently, Park *et al.* [16] reported that, although clarithromycin treatment suppressed monocyte-derived TLR4 mRNA levels in an *Heliobacter pylori* infection, this did not affect IL-8 production by peripheral blood mononuclear cells. By contrast, production of IL-8 induced by *Escherichia coli* lipopolysaccharide (LPS) was suppressed by clarithromycin-directed downregulation of TLR4 message. Differences in pathogenicity and the inability of *H. pylori*-expressed LPS to robustly activate TLR4 might account for this [16]. Alternatively, use of agents that nonspecifically alter TLR expression or operate at the level of a single TLR, might be less effective in modulating infection-associated inflammation, because the immune response to pathogens is the sum of signals from multiple TLRs and other cooperating receptor molecules [17].

It remains attractive to speculate that novel agents capable of modulating TLR functions could supplant steroid therapies and represent a more potent and specific host immune-response modulator for infectious airway exacerbations than macrolide therapy. Those

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with infection-associated inflammatory diseases such as asthma exacerbations might one day be benefited by using novel TLR-based anti-inflammatory agents, either alone or in combination with an agent that specifically targets the pathogen responsible for the respiratory event.

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