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Anti-Inflammatory Therapy of Infections

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Introduction

Anti-inflammatory treatment of infections is challenging due to the heterogeneity of etiologic agents and complex immune interactions. Inflammation plays a central role in the pathophysiology of infections, being one of the principal body defensive mechanisms. Unfortunately, it also causes accompanying unpleasant symptoms. Typical manifestations of acute inflammation are pain (*dolor*), heat (*calor*), redness (*rubor*), swelling (*tumor*), and loss of function (*functio laesa*) (Signore, 2013). For this reason, anti-inflammatory medications of different classes have a long history of use in infections as supportive treatment to relieve accompanying symptoms. In addition, anti-inflammatory agents act as host response modifiers and might play a crucial role in managing acute and chronic infection with excessive inflammation preventing organ injury, e.g., COVID-19 (Rockwell and Ehrlich, 1990; Konstan et al., 1995). This article introduces the main groups of anti-inflammatory drugs, their use in treating infections, and associated risks. We also present a subsection on anti-inflammatory treatment in COVID-19.

Anti-inflammatory drugs in the treatment of infections

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain, lower fever, and decrease inflammation. Already Sumerians, ancient Egyptians, and Hippocrates reported the use of willow bark (the active ingredient in willow bark is salicin) as a remedy for fever, pain, and inflammation. One of the first systematic studies on anti-inflammatory drugs for infections was Edward Stone's study in 1763. He investigated the effectiveness of willow bark salicylates in treating malaria-related fever (Pearce, 2014; Norn et al., 2009).

The most popular drugs belonging to this group are ibuprofen, diclofenac, naproxen, and acetylsalicylic acid. In the United States, NSAIDs are one of the most popular drugs and account for 30 billion over-the-counter (OTC) medications sold (Green, 2001). These drugs inhibit the activity of cyclooxygenase enzymes (COX-1 and COX-2) responsible for synthesizing prostanoids from arachidonic acid. Prostanoids include prostaglandins, prostacyclins (PGE2, PGD2, PGF2, PGI2), and thromboxane (Tx). These lipid mediators exert many biological effects in the hematologic, pulmonary, renal, and cardiovascular systems. PGE2 and PGI2 are the primary pro-inflammatory prostanoids, which induce fever and increase vascular permeability, causing edema and leukocyte infiltration. PGD2 is produced by mast cells and causes an inflammatory reaction in allergic responses. Thromboxane has a central role in blood clot formation (Ehrenpreis and Kruchko, 2020).

By inhibiting COX enzymes, NSAIDs effectively reduce inflammation, fever, and pain. Thus, reducing infected patient's symptoms and signs of inflammation may provide a false sense of security and delay diagnosis of life-threatening infection (Stevens, 1995). In the early phase of the COVID-19 pandemic, public opinion started the concerns that ibuprofen may increase SARS-CoV-2 infection symptoms. The theoretical mechanism behind the severity of the disease suggested the upregulation of angiotensin-converting enzyme 2 (ACE2) receptors in human tissues. The SARS-CoV-2 virus uses these receptors to enter into human cells. In addition, some researchers also suggested that anti-inflammatory drugs may delay diagnosis leading to poor outcomes (Kragholm et al., 2021). However, a prospective cohort study conducted in the United Kingdom by Drake et al. (Drake et al., 2021) on 78,674 patients proved that NSAIDs use was not associated with in-hospital mortality, critical care admission, invasive ventilation, a requirement for oxygen, or acute kidney injury. Furthermore, a subanalysis did not indicate an increase in mortality in ibuprofen users compared to other NSAIDs-users and those not taking NSAIDs.

While using NSAIDs to treat infections, we must remember that they reduce the formation of prostaglandins and affect other components of the immune system. For example, NSAIDs inhibit granulocytes functions (aggregation, degranulation, chemotaxis, and phagocytosis). Besides, NSAIDs also enhance cytokines production, including tumor necrosis factor (TNF). Thus, even a minor

infection, usually well-controlled by an immune system, may develop life-threatening infectious processes (sudden onset of shock, organ failure, or aggressive infection) (Stevens, 1995; Kaplan et al., 1984; Giagoudakis and Markantonis, 2005; Oates et al., 1991). Furthermore, studies on mice have shown that using ibuprofen during streptococcal soft tissue infection worsens its course. Ibuprofen-treated mice had a higher mortality rate and significantly higher levels of tumor necrosis factor-alpha and interleukin 6. Based on the study results, the authors concluded that the use of ibuprofen in streptococcal soft tissue infections might cause severe necrotizing infections (Weng et al., 2011).

There is a piece of evidence that the use of NSAIDs in children may cause a worse course of some infectious diseases. For example, the use of ibuprofen in the management of varicella should be discouraged because current evidence shows an increased risk of subsequent skin and soft-tissue infections, mainly caused by group A streptococcal (GAS) (Mikaeloff et al., 2008; Lesko et al., 2001). There is also evidence indicating a strong association between the use of NSAIDs and severe necrotizing soft tissue infections in patients with chickenpox (Souyri et al., 2008). In addition, the pre-hospital use of ibuprofen in children may increase the risk of complicated pneumonia in children, including empyema (François et al., 2010; Le Bourgeois et al., 2016). Evidence shows the cumulative effect of ibuprofen dosing on a more significant risk of pneumonia complications in children with community-acquired pneumonia (CAP) (Krenke et al., 2018). In this research, preadmission cumulative dose of ibuprofen exceeding 78.3 mg/kg was a factor of 2.5 higher odds ratio for pneumonia complications. For these reasons, ibuprofen is not recommended to administer in children with suspicion of lower respiratory tract infection (Quaglietta et al., 2021). Some case reports also suggest a connection between the use of NSAIDs and the progression of streptococcal infections to shock and multi-organ failure (Stevens, 1995). Undertaken in the United Kingdom, population-based surveillance showed that taking NSAIDs was independently associated with increased risk for streptococcal toxic shock syndrome in patients with severe *Streptococcus pyogenes* infection (Lamagni et al., 2008). Therefore, symptomatic treatment with NSAIDs should be used cautiously during infections because a range of scientific arguments shows an increased risk of severe bacterial complications. For this reason, parallel antibiotic therapy should always be considered (Stevens, 1995; Le Bourgeois et al., 2016; Micallef et al., 2020). For recommended dosages of anti-inflammatory medications in various infections see Table 1.

Table 1 Dosage of main anti-inflammatory drugs used in infectious diseases (Tunkel et al., 2004; de Almeida et al., 2014; The Recovery Collaborative Group, 2021; Jenson, 2000; Marx and Chan, 2011).

Disease	*Anti-inflammatory medication*	*Dosage*
Infectious mononucleosis	Dexamethasone	0.25 mg/kg every 6 h i.v. for 1–3 days
	Methylprednisolone	1 mg/kg every 6 h i.v. for 1–3 days
	Oral prednisone	40 mg p.o. daily for 1–3 days
Bell's palsy	Prednisone	60 mg per day followed by the five-day taper, with a reduction of a previous day's dose by 10 mg per day
Bacterial meningitis	Dexamethasone	0.15 mg/kg i.v. every 6 h for 2–4 days
Tuberculous meningitis	Dexamethasone	12 mg/day (adults), 8 mg/day (children $<$ 25 kg) i.m. for 3 weeks, followed by gradual taper for next 3 weeks OR 1 week of each (0.4 mg/kg/day, 0.3 mg/kg/day, 0.2 mg/kg/day, and 0.1 mg/kg/day), followed by 4 weeks of tapering oral dexamethasone therapy
COVID-19 in adults	Dexamethasone If not available:	6 mg daily
	Prednisone	40 mg daily
	Methylprednisolone	36 mg daily
	Hydrocortisone	160 mg daily
Inflammatory diseases in children	Ibuprofen (Children 1 year old or older)	30-50 mg/day in 4 divided doses Doses greater than 40 mg/kg/day may increase the risk of adverse effects; doses $>$50 mg/kg/day are not recommended
	Naproxen (Children 2 years or older)	10 mg/kg p.o. in 2 divided doses

Ibuprofen dosage: https://www.drugs.com/dosage/ibuprofen.html;
Naproxen dosage: https://www.drugs.com/dosage/naproxen.html#Usual_Pediatric_Dose_for_Juvenile_Rheum.atoid_Arthritis.

Glucocorticoids

Glucocorticoids are a group of drugs that reduces the activity of the immune system. Inside the cell, glucocorticoids attach to the appropriate cytoplasmic receptor (GR) and then pass the nuclear membrane as the glucocorticoid-GR complex. Inside the nucleus, the glucocorticoid-GR complex releases a specific molecule that binds to DNA. There are few steroid-responsive genes with glucocorticoid-responsive elements (GRE). The binding of the GR molecule to GRE may result in activation or repression of the gene (positive or negative GRE). The effects involve increasing the expression of anti-inflammatory proteins or decreasing pro-inflammatory proteins production (Rhen and Cidlowski, 2005). Some steroid-responsive genes do not express GRE itself, so the regulation is indirect via nuclear factor (NK)-κB, activating protein (AP)-1 or cAMP-responsive element-binding protein (CREB). The third mechanism of glucocorticoids' impact on the regulation of inflammatory protein synthesis is by boosting the transcription of particular ribonucleases, which degrade mRNA, decreasing its stability and shortening half-time of some pro-inflammatory cytokines (van der Velden, 1998).

In medicine, glucocorticoids are often used in the treatment of autoimmune diseases, allergies, and asthma. They are also used to reduce symptoms and sequelae of severe infections. For example, in bacterial meningitis, glucocorticoids may reduce associated cerebral edema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis, and neuronal injury by decreasing inflammatory response, but do not reverse the damage that occurred before treatment (Tunkel et al., 2004).

According to Cochrane Library, corticosteroids should be used in acute bacterial meningitis in children. Although they do not reduce the death rate, patients have significantly lower rates of hearing loss and other neurological sequelae. In children, the best effect was primarily observed in meningitis due to Gram-negative bacteria *Haemophilus influenzae* type b. However, these positive effects occurred only in high-income countries, and there were no significant beneficial effects in low-income countries. This phenomenon can be explained by the difference in patients' profiles on the example of African studies: usually, patients were admitted later, had many chronic conditions worsening the prognosis (malnutrition, HIV infection) or the antibiotics used in initial treatment (Brouwer et al., 2015). Nevertheless, glucocorticoids are routine adjunctive therapies to reduce the risk for neurologic sequelae. The recommended treatment according to IDSA is dexamethasone in a dose of 0.15 mg/kg IV every 6 h for 2–4 days (the first dose should be given 10–20 min before or with the first antibiotic dose) (IDSA Grade A-I). National Institute for Health and Care Excellence (NICE) recommends dexamethasone in infants and children beyond 3 months old with suspected or confirmed bacterial meningitis if lumbar puncture reveals any of the following:

1. frankly purulent cerebrospinal fluid,
2. elevated white blood cell count in cerebrospinal fluid with protein concentration above 1.0 g/L,
3. cerebrospinal fluid with white blood cell count above 1000/mcL or
4. bacteria on Gram stain.

Dexamethasone should be given within 4 h of starting antibiotics and should not be started if >12 h (NICE, n.d.).

Glucocorticoids are also mandatory adjunct therapy to antituberculous drugs in tuberculous meningitis, a severe neuroinfection causing death or severe neurologic deficits in more than half of those affected despite antituberculosis chemotherapy. A study performed in Vietnam provided clinical evidence that early treatment with dexamethasone and antituberculosis drugs improves survival among patients over 14 years of age with tuberculous meningitis, regardless of disease severity. However, dexamethasone probably does not prevent severe disability in the survivors (Thwaites et al., 2004). A Cochrane review of nine trials that included 1337 participants concluded that glucocorticoids reduce deaths by almost 25% in the short term, although they may have little or no effect on neurologic sequelae, the outcome that is less common than death. In addition, there was no difference between groups in adverse events, including gastrointestinal bleeding, invasive bacterial infections, hyperglycemia, and liver dysfunction. Thus, the possible harm is unlikely to be quantitatively important compared to the reduction in mortality (Prasad et al., 2016).

Cochrane Library also conducted a meta-analysis which suggests that the use of glucocorticoids in patients with sepsis results in a reduction in hospital or Intensive Care Unit (ICU) length of stay and probably reduces hospital mortality and mortality in 28-day and 90-day. The evidence for this statement is moderate-certain. Side effects of this therapy include increased risk of muscle weakness, hypernatremia (high-certainty evidence), and the potential risk of hyperglycemia (moderate-certainty evidence) (Annane et al., 2019). On the other hand, Surviving Sepsis Campaign does not support using corticosteroids intravenously to treat septic shock if it can be achieved by using adequate fluid therapy and vasopressors. In other cases, it is recommended to use hydrocortisone (Rhodes et al., 2017). In children, the guidelines do not indicate that using steroids is beneficial nor harmful—either hydrocortisone or no hydrocortisone may be used in case of lack of hemodynamic stability after adequate hydration and vasopressors were used (Weiss et al., 2020). Both in children and adults, the recommendations are classified as weak, with low quality of evidence.

Some studies also indicate the usefulness of glucocorticoids in reducing symptoms of viral infections. For example, steroid therapy may reduce the sore throat symptoms in infectious mononucleosis due to Epstein-Barr virus (EBV) infection (Rezk et al., 2015). However, the evidence to support this approach is low, and corticosteroids are not routinely recommended (Dunmire et al., 2018; Lennon et al., 2015; Luzuriaga and Sullivan, 2010). Since corticosteroids are not shown to provide substantial or sustained relief of symptoms associated with mononucleosis, they may be used based on clinical experience if concern for severe complications such as airway obstruction due to tonsils enlargement, hemolytic anemia, thrombocytopenia, mononucleosis-like aplastic anemia, or liver failure. No data is confirming the benefits of using steroids in these complications. There is no standard dosing, but

the common approach in adults is prednisone 40–60 mg/day orally for 1–3 days followed by taper over the next 7–14 days (Cohen, 2003). Reported adverse events include peritonsillar cellulitis, acute-onset diabetes mellitus, and neurologic sequelae.

Bell palsy is a subacute weakness of the facial nerve (the seventh cranial nerve), which may be idiopathic or secondary to herpes infections. In Bell's palsy complicating Herpes simplex virus (HSV) infection, steroids may shorten recovery time and increase recovery rates when added to antiviral treatment, but the difference does not seem statistically significant compared to antiviral treatment alone (Numthavaj et al., 2011). In idiopathic Bell palsy, corticosteroids are recommended by the American Academy of Neurology since they increase the likelihood of complete facial motor function recovery (Gronseth and Paduga, 2012) (Strong recommendation). Bell Palsy Working Group, Canadian Society of Otolaryngology—Head and Neck Surgery and Canadian Neurological Sciences Federation recommend using corticosteroids for all patients with Bell palsy (de Almeida et al., 2014). Various dosing regimens have been used, including prednisolone 25 mg twice daily for 10 days, prednisolone 60 mg orally once daily for 5 days, then tapered by 10 mg each day until day 10, prednisolone 1 mg/kg/day for 10 days in children (only use in children if complete palsy).

In upper respiratory tract infections, oral or intranasal glucocorticoids accelerate the resolution of otitis media with effusion (Hussein et al., 2017) but do not improve the quality of life (Francis et al., 2018). According to the American Academy of Otolaryngology-Head and Neck Surgery (2016), oral or intranasal steroids should not be used in otitis media cases with effusion as no data confirms long-term benefits from this approach (Rosenfeld et al., 2016). Intranasal steroids are commonly used to treat acute rhinosinusitis, chronic rhinosinusitis, and chronic rhinosinusitis with nasal polyps to reduce the severity of symptoms (Rot et al., 2020; Mullol et al., 2009; Head et al., 2016). The European Position Paper On Rhinosinusitis and Nasal Polyps (EPOS 2020) does not support using intranasal glucocorticoids in acute rhinosinusitis (common cold) in adults or children. However, some benefits can be achieved when using in the post-viral phase of acute rhinosinusitis (moderate quality of data, strong evidence). Systemic glucocorticosteroids should not be prescribed in this condition due to EPOS guidelines as they do not impact recovery in 7–14 days. In chronic rhinosinusitis (CRS), intranasal glucocorticoids remain the mainstay of the treatment, reducing symptoms and improving quality of life. When the nasal polyps occur in the course of the CRS, treatment with intranasal steroids reduces polyps' size and prevents polyps' recurrence after surgery (high-quality evidence). It is still under debate if there is strong evidence to support oral corticoids in chronic rhinosinusitis. EPOS guidelines advise using oral glucocorticoids in 1–2 short courses per year as an addition to intranasal treatment, which can help reduce symptoms and nasal polyp score. In children with CRS, although there is no evidence of the efficacy of this intervention. However, considering its safety profile, it is recommended to use intranasal steroids as part of the treatment (Fokkens et al., 2020).

Topical corticoids are helpful in the short-term treatment of conjunctivitis. However, according to most guidelines, their use should be limited to severe cases. In addition, side effects of the therapy are prolonging adenoviral infections, worsening of HSV infection course, increased intraocular pressure, glaucoma, or cataracts. Thus, the steroid choice should be carefully evaluated if the benefits of the therapy outweigh the risks (Holland et al., 2019).

Colchicine

Colchicine is a drug commonly used to treat gout and Behcet's disease. The primary anti-inflammatory mechanism of action is based on tubulin disruption, which causes the downregulation of multiple inflammatory pathways (Leung et al., 2015). In addition, colchicine inhibits the migration and activation of neutrophils and interrupts mast cells degranulation (Dalbeth et al., 2014).

Some studies show that the use of colchicine may be helpful in infections treatment. There is some evidence that colchicine is beneficial in managing viral liver diseases and may reduce time to deterioration, hospitalization time, and mortality in patients with COVID-19. Some studies indicate potential therapeutic utility in treating malaria, anogenital warts caused by human papilloma-virus (*condyloma accuminata*), common warts (verruca vulgaris), viral myocarditis, and *erythema nodosum leprosum*. Unfortunately, there is also an increased risk of pneumonia in patients using colchicine (McEwan and Robinson, 2021).

Anti-inflammatory therapy for COVID-19

In the course of COVID-19 infection, the three phases were described. In the first phase of early infection, the virus infiltrates lung parenchyma cells. In the second phase, lung tissue injuries occur because the host activates an immune response against the pathogen. The last phase, called the inflammatory cascade ("*cytokine storm*"), is caused by pathogen patterns exposed during viral replication. In this part, we notice an excessive inflammatory response to SARS-CoV-2 infection with viral load not correlated with the worsening of symptoms. Signals created by the SARS-CoV-2 virus cause the assembly of a pro-inflammatory protein complex, which converts the pro-IL-1β and pro-IL-18 to their active forms. IL-1β drives the synthesis of IL-6, which induces C reactive protein (CRP) and is considered a major pro-inflammatory factor in the COVID-19 cytokine storm. IL-1β and IL-6 activate neutrophils that infiltrate into the lungs and tissues of other organs. They degranulate and release more cytokines, chemokines, and proteases, causing inflammation of the affected organs, resulting in organ failure. Neutrophils also trigger events in arteries that promote thrombosis. Using anti-inflammatory drugs in the COVID-19 treatment is based on the idea to stop the activation of the cytokine storm (Reyes et al., 2021; The Recovery Collaborative Group, 2021).

Corticosteroids and immunomodulatory monoclonal antibodies are commonly used as anti-inflammatory drugs in the treatment of COVID-19 patients. In severely ill patients with COVID-19, systemic corticosteroids are strongly recommended because they result in lower mortality among patients receiving mechanical ventilation and among patients receiving oxygen

without mechanical ventilation. Patients without respiratory support did not benefit from taking corticosteroids (The Recovery Collaborative Group, 2021; Sterne et al., 2020). On the other hand, in adults with mild COVID-19, inhaled budesonide may lower the frequency of urgent care visits (Ramakrishnan et al., 2021). *Tocilizumab* is a monoclonal antibody blocking the interleukin-6 receptor. Studies have shown that in patients with severe COVID-19, tocilizumab improves survival (Abani et al., 2021; REMAP-CAP Investigators, 2021). Some studies also suggest that the use of colchicine may reduce the risk of hospitalization or death in patients with COVID-19 (Tardif et al., 2021).

Anti-inflammatory drugs are also used in Multisystem Inflammatory Syndrome in Children (MIS-C), a disease that is a complication following exposure to SARS-CoV-2 and had been announced first time by the Royal College of Pediatrics and Child Health (RCPCH) on May 1, 2020. This rare systemic inflammatory illness occurs mainly in children. It can lead to rapid multi-organ failure and the need for intensive care (Okarska-Napierała et al., 2020, 2021). In treating this disease, intravenous immunoglobulin, methylprednisolone, IL-1 antagonists, IL-6 receptor blockers, and anti-TNF agents are used (Harwood et al., 2021).

Conclusions

Anti-inflammatory medications are frequently used in infections to mitigate accompanying symptoms. They also act as host immune response modifiers and play an essential role in treating infections in selected groups of patients, e.g., with mucoviscidosis or COVID-19.

However, anti-inflammatory agents generally impair the immune system. NSAIDs inhibit granulocytes functions and enhance cytokines production, including TNF, and may contribute to the emergence of bacterial soft tissue infections or promote the development of the life-threatening disease from a minor infection, usually well-controlled by an immune system. Reducing infected patient's symptoms and signs of inflammation may provide a false sense of security and delay diagnosis of serious infections.

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