Infectious Diseases Risk While on Chronic, High-Dose Corticosteroids

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Abstract

While the definition of high-dose corticosteroids depends on the indication, it is typically defined as greater than 15–20 mg for greater than 2–4 weeks. Corticosteroids have a variety of indications such as autoimmune, gastrointestinal, rheumatologic, respiratory, and hematologic conditions and after organ or hematopoietic stem cell transplantation. They can predispose these patients to infections such as pneumococcal pneumonia, *Pneumocystis jirovecii* (carinii) pneumonia (PJP), hepatitis B reactivation, active tuberculosis, and disseminated strongyloides infection. This article outlines ways to modify these risks in these patients. Prophylaxis is of utmost importance to those at risk for PJP with trimethoprim/sulfamethoxazole, lamivudine for those at risk of hepatitis B reactivation, isoniazid (INH) for latent tuberculosis and ivermectin for those with positive strongyloides serology. Equally important in mitigating disease risk is the appropriate timing of vaccines to elicit an adequate immune response as well as offering additional vaccines such as the pneumococcal vaccine.

Résumé

La notion de dose élevée de corticostéroïdes varie selon les indications, mais elle est généralement définie comme correspondant à plus de 15-20 mg sur une période de plus de deux à quatre semaines. Les corticostéroïdes sont indiqués dans nombre de conditions auto-immunes, gastro-intestinales, rhumatologiques, respiratoires et hématologiques, ainsi qu'à la suite d'une transplantation d'organe ou de cellules souches hématopoïétiques. Ils peuvent toutefois prédisposer les patients à diverses infections comme la pneumonie pneumococcique et la pneumonie à *Pneumocystis jirovecii* (carinii) ou PCP, à une réactivation de l'hépatite B, à une tuberculose active et à une strongyloïdose disséminée. Le présent article passe en revue différentes façons de réduire ces risques chez les patients concernés. Voici des mesures de prophylaxie qui s'avèrent être de la plus haute importance pour les personnes à risque : le triméthoprim ou le sulfaméthoxazole pour celles à risque de PCP; la lamivudine pour celles à risque de réactivation de l'hépatite B; l'isoniazide (INH) dans les cas de tuberculose latente; et l'ivermectine pour les personnes montrant une sérologie positive aux strongyloïdes. De plus, pour réduire le risque de maladie, un calendrier de vaccination approprié est tout aussi important, en vue de susciter une réponse immunitaire adéquate et de pouvoir offrir d'autres vaccins comme le vaccin antipneumococcique.

Corticosteroids were first used in clinical practice in 1949 for rheumatoid arthritis.¹ The number of patients on high-dose corticosteroids is not well known but the use of corticosteroids is becoming increasingly common for a number of indications: An estimated 1% of the general population in the UK is treated with corticosteroids, and this rate increases with age to almost 2.5% in those aged 70–79.⁴

“High-dose corticosteroids” as a risk factor for infections is typically defined as greater than 15–20 mg of prednisone (or its equivalent) for greater than 2–4 weeks, although this definition does vary slightly depending on the infection considered. Notably, this definition is different from the standard definition of high-dose corticosteroids for treatment purposes used in the literature – which is usually defined as greater than 30 mg but less than 100 mg/day – as this dose results in almost complete cytosolic receptor saturation.²

Corticosteroids are used commonly for their anti-inflammatory effects in many conditions with an element of autoimmune disease. The mechanism is to induce transient lymphocytopenia by altering lymphocyte circulation, inducing lymphocyte death and inhibiting cytokines to prevent T-cell activation.³ For example, they are used to induce remission in inflammatory bowel disease (IBD) or to maintain symptom control in rheumatologic diseases like polymyalgia rheumatica. They are also used to prevent organ rejection in solid organ transplantation. Other indications include autoimmune hepatitis, other rheumatologic diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis, respiratory conditions such as interstitial lung disease, sarcoidosis, hematologic disorders such as lymphoma, leukemia, idiopathic thrombocytopenic purpura, hemolytic anemia), endocrine disorders like Graves disease to prevent ophthalmopathy and other conditions like multiple sclerosis.

The relative risk of bacterial infections was found to be 5-fold higher in IBD patients on corticosteroids alone, 4-fold higher for other infections like strongyloides and tuberculosis, and only 1.5 fold higher for viral infections.⁵ However, the absolute individual risk of infectious complications from corticosteroid use remains fairly small. Nevertheless, the burden is significant at a population level due to the high frequency of corticosteroid use.⁴ Thus, most practitioners eventually come across these complications during their career.

Vaccinations

One of the first considerations in patients on high-dose corticosteroids is the timing of the administration of vaccines to be given to these patients. Immunizations with inactivated vaccines can be given up to 2 weeks before high-dose corticosteroids are initiated, whereas live vaccines need to be given 4 weeks before

the high-dose corticosteroids are begun. If the vaccines cannot be given prior to the start of a corticosteroid treatment, both live and inactivated vaccines must wait for 4 weeks after the steroids are completed to elicit an adequate immune response and prevent infectious complications with live vaccines.⁶

Equally important to the timing of the vaccines, patients on high-dose corticosteroids (defined as anyone receiving ≥ 20 mg/day for 14 days or more) should receive additional vaccines. A single dose of an inactivated pneumococcal conjugate vaccine (Pneumovax), at least one year after any previous dose of pneumococcal vaccine polyvalent (Pneumovax), followed by a single dose of Pneumovax 8 weeks later with a booster of Pneumovax 5 years later is recommended for those on high-dose corticosteroids.^{7,8}

Pneumocystis jiroveci infection

The following patient groups are considered to be at higher risk for *Pneumocystis jiroveci* pneumonia (PJP; formerly known as *Pneumocystis carinii* pneumonia [PCP]) if exposed to prednisone at doses as low as 20 mg/day for at least 4 weeks⁹: patients with an underlying immunosuppressive disorder (including autologous HSCT and malignancy), or those with chronic obstructive pulmonary disease and interstitial lung disease secondary to polymyositis/dermatomyositis. Also, patients receiving the same dose of prednisone plus TNF-alpha inhibitors, cyclophosphamide, methotrexate, or temsirolimus should also receive PJP prophylaxis. The first-line agent for prophylaxis is trimethoprim/sulfamethoxazole 80/400 mg (single strength) daily or 160/800 mg (double strength) three times per week (e.g., Monday/Wednesday/Friday). While adverse events are rare on such low doses, thrombocytopenia is possible given that this is an idiosyncratic reaction but pancytopenia is usually observed at much higher (i.e., treatment) doses. Also possible are hyperkalemia, increased serum creatinine and aseptic meningitis. A more rare but devastating adverse event is Stevens-Johnson syndrome. A second line agent for PJP prophylaxis is dapsone but this requires glucose-6-phosphate dehydrogenase (G6PD) testing first, as those who are deficient in this erythrocytic enzyme show a two-fold higher predisposition to dapsone-induced hemolytic anemia. Other alternatives for PJP prophylaxis are atovaquone 1500 mg daily, but this is a costly option, or inhaled pentamidine via a nebulizer at 300 mg every month. Correct administration of inhaled pentamidine is crucial and due to the route of administration, disseminated PCP disease is still possible.⁹

Hepatitis B Reactivation

Furthermore, patients on corticosteroids of at least 20 mg/day for at least 4 weeks, have an 11–20% chance of reactivation if

they are hepatitis B surface Ag carriers. An inactive carrier is hepatitis B surface antigen positive for greater than 6 months without detectable hepatitis B e antigen (HBeAg), presence of anti-hepatitis B e antibodies (anti-HBe), and undetectable or low levels of hepatitis B DNA, repeatedly normal ALT levels, and no or minimal liver fibrosis. Inactive carriers comprise the largest group of chronic hepatitis B infected individuals with an estimated 250 million people worldwide and can convert to active disease under such immunosuppression.

Therefore, it is prudent to prescribe hepatitis B prophylaxis to these patients although no high-level evidence supporting this approach is available.¹¹ Lamivudine is considered first choice for these patients if they do not otherwise meet treatment criteria for hepatitis B. Tenofovir is considered first line in areas highly prevalent for resistance to lamivudine, which tends to occur with prolonged lamivudine exposure. For example, lamivudine resistance develops in up to 90% of HBV-HIV co-infected individuals after 4 years of lamivudine therapy.¹²

In the setting of isolated anti-Hb-core antibody positivity, prophylaxis is not recommended given that the rate of reactivation is less than 1%.¹⁰ Instead, patients should have serial measurements of liver function, hepatitis B serology and hepatitis B DNA every 1–3 months during the period of immunosuppressive treatment and if there is any elevation in these markers, antiviral prophylaxis or treatment (depending on the results) should be offered.

So, when assessing patients for the need for PCP or hepatitis B prophylaxis, both the intended duration as well as the dose of the corticosteroids need to be considered.

Strongyloides stercoralis Infection

Strongyloides stercoralis can persist for several decades and can reactivate with glucocorticoid exposure causing a severe and sometimes fatal disseminated infection. Strongyloides infection can be asymptomatic and can be acquired walking barefoot on soil in the developing world.¹³ Strongyloides serology is therefore recommended for refugees from low-income countries in Southeast Asia and Africa where strongyloides is endemic before starting high-dose corticosteroid treatment.¹⁴ If positive, patients should be treated with 2 doses of ivermectin to prevent the development of hyperinfection.

Tuberculosis

Patients with latent tuberculosis on higher dose and/or longer duration of glucocorticoid use are also at risk of conversion to active disease. A one-step tuberculin skin test (TST) ≥ 5 mm is considered positive when a patient is on prednisone doses ≥ 15 mg/day for one month or more. First-line treatment for latent tuberculosis is isoniazid over 9 months. Patients should

begin therapy ideally at least 4 weeks before starting such immunosuppression to prevent conversion to active disease.^{15,16} If this is not possible, the recommendation is to start isoniazid and the corticosteroids at the same time.

Conclusions

Serious and potentially fatal infections are just one of the many potential complications of being on high-dose corticosteroids for a long period of time – others include diabetes, hypertension, psychosis, osteoporosis, adrenal insufficiency and the development of cushingoid features.¹⁷ Infectious diseases that are either latent or inactive may reactivate under high-dose corticosteroids including tuberculosis, *pneumocystis jirovecii* pneumonia, *Strongyloides stercoralis*, and hepatitis B. Screening and treatment for such conditions prior to starting high-dose corticosteroids, or at least once the corticosteroids are started, can prevent these complications. Furthermore, the timing of both inactivated and live vaccines is crucial for the patients' ability to mount an appropriate immune response and to avoid complications from live vaccines. Finally, patients on high-dose corticosteroids are at higher risk for illnesses that may require additional vaccinations not otherwise given to such individuals – for example the pneumococcal vaccine.

Disclosure

There are no conflicts of interest for either author on this manuscript.

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Mission Statement

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