DECISIONS

Reducing the risk of infection in a 74-year-old man who is to receive prednisone

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A 74-year-old man presents with a one-month history of cutaneous bullae. Skin biopsy confirms a diagnosis of bullous pemphigoid. His dermatologist plans to start treatment with prednisone (40 mg/d for four weeks followed by a tapering regimen) and considers potential infectious complications of the therapy and ways to screen for and prevent them.

Should this patient be screened for latent tuberculosis?

A retrospective case–control study in the United Kingdom involving 497 patients with tuberculosis (TB) who had no history of HIV infection or cancer reported an odds ratio of 7.7 (95% confidence interval [CI] 2.8–21.4) for TB developing in patients taking 15 mg or more of prednisone per day (or equivalent).[1] Citing this study, the Canadian Thoracic Society advises that patients receiving glucocorticoid therapy at a dose equivalent to 15 mg or more of prednisone per day for one month or more are at moderate risk of reactivation of TB and recommends screening with a tuberculin skin test (sensitivity 90%, specificity > 95%, false-positive rate ≤ 5%) or an interferon-gamma release assay (sensitivity 80%–90%, specificity > 95%, false-positive rate ≤ 5%).[2] However, a cost-effectiveness analysis found that screening for latent TB was cost-effective only if the risk of disease was high.[3] Therefore, it is reasonable to screen patients prescribed 15 mg or more of prednisone per day for one month or more who are at high risk of latent TB (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.131430/-/DC1). Patients with a positive test result should receive treatment.[2]

Does this patient require screening for chronic hepatitis B virus infection?

Patients receiving 7.5 mg or more of prednisone per day should be screened for hepatitis B virus (HBV) infection. Manifestations of HBV reactivation range from asymptomatic elevations in HBV DNA viral load and alanine aminotransferase level to acute hepatic failure. The risk of HBV reactivation appears to be minimal in patients receiving less than 7.5 mg of prednisone per day, because there are no published reports of HBV reactivation at this dosage.[4] Reactivation has occurred in patients with rheumatic diseases who received lower doses of steroids in combination with other immunosuppressive medications.[4]

Most of the literature regarding HBV reactivation in patients receiving immunosuppressive therapies is based on studies involving oncology patients; less is known about patients being treated for other conditions. In a retrospective cohort study that included more than 10 000 patients undergoing chemotherapy, HBV reactivation occurred in 23% of patients with a positive result for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc).[5] All-cause mortality was significantly lower among patients who received HBV prophylaxis (22%) than among those who did not (71%).

Canadian guidelines recommend using the HBsAg test to screen for chronic HBV infection in all patients receiving immunosuppressive therapies.[6] American guidelines recommend using both the HBsAg and anti-HBc tests.[7] However, a cost-effectiveness analysis found that universal screening for HBV using both tests in patients with nonhematopoietic solid tumours was not cost-effective.[8] It is therefore reasonable to screen all patients receiving 7.5 mg or more of prednisone per day with the HBsAg test alone and to add screening for anti-HBc in patients who will receive multiple immunosuppressants.

Patients with positive test results for HBsAg should be referred to a specialist for measurement of their HBV DNA viral load and antiviral prophylaxis, ideally before the start of immunosuppressive therapy (Appendix 1).[8]

Should this patient be screened for infection with *Strongyloides stercoralis*?

Strongyloides stercoralis is a nematode endemic to many tropical and subtropical regions. Screening for *S. stercoralis* infection is recommended for all

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patients prescribed immunosuppressive therapies who have lived in or travelled to an endemic area, regardless of the time lapsed or the anticipated duration of glucocorticoid therapy (Appendix 1). Strongyloides hyperinfection syndrome has a mortality approaching 100% and has been associated with short courses of glucocorticoid therapy in patients who are infected.[9] In a retrospective case–control study, glucocorticoid use was associated with a relative risk of 3.28 (95% CI 1.24–10.43) for disseminated strongyloidiasis.[10] Stool microscopy is the most specific test, but it has poor sensitivity. Serologic testing has a high negative predictive value, making it useful for ruling out infection (Appendix 1).[9] Patients with positive test results should be treated with ivermectin in consultation with an infectious disease specialist.

Should this patient receive prophylaxis against *Pneumocystis jirovecii* pneumonia?

Prophylaxis with trimethoprim–sulfamethoxazole should be considered for patients receiving the equivalent of 20 mg or more of prednisone per day for four to eight weeks, based on expert opinion.[11] In a retrospective analysis of 116 HIV-negative patients with a first episode of *Pneumocystis jirovecii* pneumonia, 90.5% of the patients had received glucocorticoid therapy during the month before onset. One-quarter received as little as 16 mg of prednisone per day, and one-quarter received less than eight weeks of therapy.[11] There are no guidelines for prophylaxis against *P. jirovecii* pneumonia in patients with dermatologic or rheumatologic conditions who are receiving glucocorticoid therapy. However, a systematic review and meta-analysis of 12 randomized controlled trials involving immunocompromised patients who were HIV-negative reported a 91% reduction in the occurrence of *P. jirovecii* pneumonia when trimethoprim–sulfamethoxazole was administered (relative risk 0.09, 95% CI 0.02–0.32).[12] Adverse events that necessitated discontinuation of the trimethoprim–sulfamethoxazole occurred in 3.1% of adults and resolved after the treatment was stopped. Atovaquone or dapsone may be used in patients who cannot tolerate trimethoprim–sulfamethoxazole.[12]

Is this patient at risk of other infections related to glucocorticoid therapy?

Patients receiving glucocorticoid therapy are at increased risk of infection with viral, bacterial and fungal pathogens. The Canadian National Advisory Committee on Immunization recommends administration of all age-appropriate vaccines and boosters before initiation of immunosuppressive therapy.[13] Although recommendations for reducing the risk of infection rely on the best available evidence, there still is a need for high-quality data showing the efficacy and safety of these recommendations in these populations. If febrile illness develops during treatment, an infectious cause should be strongly suspected.

Case revisited

Further inquiry showed that the patient had lived in China for two years 20 years ago. Before the prednisone treatment is started, a tuberculin skin test is performed. Testing for HBsAg is also requested, as well as serology and stool microscopy for *S. stercoralis* infection.

The results of the tuberculin skin test and the tests for *S. stercoralis* infection are negative. The HBsAg test result is positive. The patient is referred to a specialist in liver diseases, who prescribes lamivudine for prophylaxis against HBV reactivation. Because the patient will receive more than 20 mg of prednisone per day for at least one month, prophylaxis for *P. jirovecii* pneumonia will be considered at the one-month follow-up visit.

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