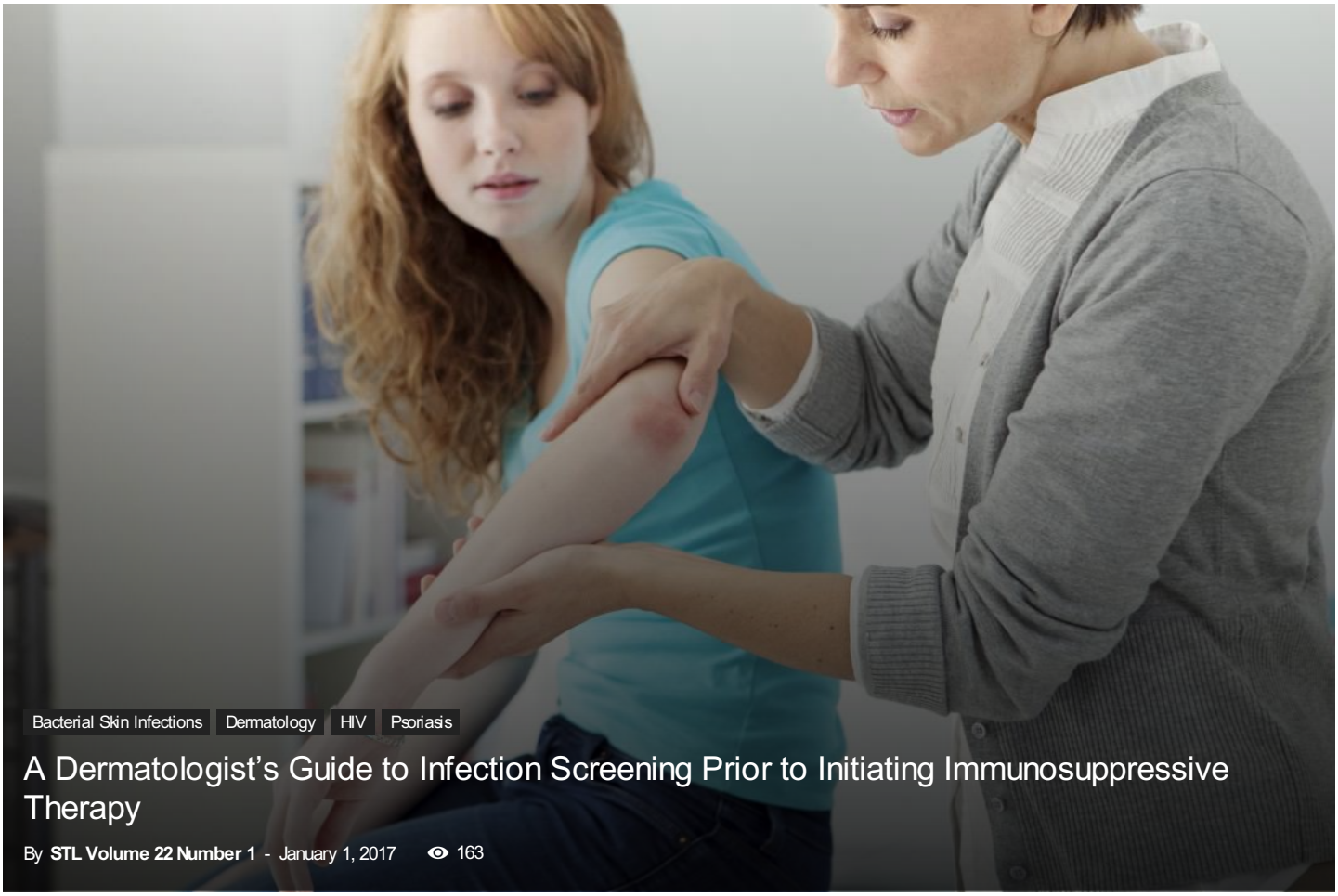

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ABSTRACT
Dermatologists have within their armamentarium numerous immunosuppressant agents, both traditional and new, that are useful in the treatment of chronic cutaneous disorders such as autoimmune bullous diseases and psoriasis. It is imperative that users of these agents are aware of potential sequelae from therapy, particularly infections. In this review, we summarize the most common immunosuppressant medications currently used in dermatology, and provide recommendations for infection screening prior to initiating treatment.

Key Words:
immunosuppression, infection, TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, clinical protocol, drug therapy, skin diseases

Introduction

Psoriasis, connective tissue diseases, and autoimmune bullous diseases such as bullous pemphigoid and pemphigus are but a few examples of the dermatological indications for which immunomodulatory/immunosuppressive therapy may be indicated. Treating patients with these inflammatory cutaneous diseases often involves one or more immunosuppressive agents, either sequentially or in combination, which increases the risk of infection-related morbidity and mortality. One of the main safety concerns for the dermatologist prior to initiating therapy is the risk of infection. Risk factors for infection include age, medical comorbidities, travel history, location of residence, occupation, as well as the type, duration and extent of immunosuppression. Although pretreatment infection-testing guidelines exist for the disciplines of gastroenterology, hepatology, rheumatology, and transplant medicine, no specific guidelines have been developed for the dermatologist wishing to begin immunosuppressive therapy. This discussion is timely and of interest within the dermatology literature, as multiple publications have emerged within the last 5 years.[1-3] The dermatologist has a therapeutic armamentarium of immunosuppressive drugs including traditional therapies such as systemic corticosteroids, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil as well as novel therapeutics known as biologics. Within the last decade or so there has been an emergence of novel biologic therapeutics including inhibitors of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, CD20, p40 subunit of IL-12/23, and more recently IL-17. Herein, we discuss the current pre-treatment infection guidelines for the dermatologist prior to beginning immunosuppressive therapy.

Non-biologic immunosuppressive therapy

The non-biologic immunosuppressive therapies that will be discussed are corticosteroids, methotrexate, azathioprine, cyclosporine and mycophenolate mofetil (Table 1). Since their introduction in the 1950s, corticosteroids have revolutionized the management of inflammatory diseases.[4] Corticosteroids are among the oldest immunosuppressants; their mechanism of action is through inhibition of gene transcription and downregulation of secreted inflammatory cytokines.[5,6] The risk of infection with corticosteroid use depends upon the patient's underlying disease state, duration, dose and route of administration.[7] A lower dose of corticosteroids as well as a shorter duration are associated with a reduction in infectious complications.[8] Corticosteroid use in combination with other immunosuppressive agents, such as methotrexate or azathioprine, increases the risk of serious infections as evidenced in inflammatory bowel disease and rheumatoid arthritis.[9] However, given the short half-life of systemic corticosteroids (e.g., prednisone plasma half-life is 60 minutes, prednisolone plasma half-life is 115-212 minutes), it is reasonable to start these medications, if needed, while awaiting infection screening results.

Agent	Mechanism of Action	Immunosuppressive Effect
Azathioprine	Purine anti-metabolite	Apoptosis of T-cells
Corticosteroids	Inhibition of transcription of genes response for secretion of inflammatory cytokines	Multiple cytokine alterations; overall effects are decreased leukocyte migration and phagocytosis; decreased T-cell function

Cyclosporine	Inhibition of cytosolic enzyme calcineurin	Suppression of cell-mediated immunity
Methotrexate	Folic acid antagonist; inhibition of purine synthesis; JAK/STAT inhibitor	Mechanism for immunosuppression not fully elucidated
Mycophenolate mofetil	Inhibitor of purine biosynthesis	Decreased migration of inflammatory cells; decreased immunoglobulin production by B-cells

Table 1: Traditional immunosuppressive agents and their mechanism of action

Azathioprine and its derivative 6-mercatopurine are structurally similar to the endogenous purines adenine and guanine. The exact mechanism of action of this immunosuppressive agent is unknown, however it is thought that the structural similarity to endogenous purines allows it to be incorporated into DNA and RNA with subsequent inhibition of purine metabolism and cell division. Azathioprine use is associated with increased bacterial, fungal and viral infections.[10] Prior to initiating azathioprine, the dermatologist should ascertain whether the patient has been immunized or previously infected with varicella zoster virus and if not, immunization prior to commencing immunosuppression should be recommended.[10] Furthermore, azathioprine in combination with prednisolone is associated with an increased risk of infection which can be fatal in the elderly.[11]

Methotrexate is a potent competitive inhibitor of dihydrofolate reductase and a partially reversible inhibitor of thymidylate synthetase, which ultimately acts by inhibiting purine synthesis. However, the definitive mechanism of action of methotrexate is, to date, incompletely understood, as novel modes of action continue to be published; most recently its role as a Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway inhibitor has been described.[12] In patients receiving long-term treatment with methotrexate, hepatotoxicity is an important consideration and patients should be screened for hepatitis B and C infection prior to initiating treatment. In addition, untreated chronic tuberculosis and active tuberculosis infections are contraindications to treating with methotrexate.

Cyclosporine is postulated to act by inhibition of the intracellular enzyme calcineurin, resulting in reduced activity of the transcription factor nuclear factor of activated T-cells (NFAT-1). With decreased NFAT-1 activity, the transcription of a number of downstream cytokine genes, most notably IL-2, are suppressed. Furthermore, impaired production of IL-2 leads to a decline in the number of activated T-cells within the epidermis. Thus, cyclosporine results in decreased functional T-cell mediated immunity, leading to increased susceptibility to cytosolic microorganisms, including atypical *Mycobacterium*, and viruses.[13,14]

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase (IMPDH). Inhibition of this critical enzyme, IMPDH, subsequently deprives T- and B-cells of purine metabolites necessary for growth and replication. The net effect is selective immunosuppression. MMF is associated with an increased risk of infection especially when doses in excess of 2 g daily are used.[15,16] Serious

infections are most common in renal and cardiac (2%) and hepatic (5%) transplant patients at doses of 2-3 g daily. Viral (herpes zoster, herpes simplex), bacterial, atypical mycobacterial and fungal infections have been reported in the literature.[17-20]

Biologic Immunosuppressive Therapy

The biologics account for a relatively novel class of medications refered to as specialty drugs or specialty pharmaceuticals.[21] Biologics are derived from living cells and are administered by injection, infusion or oral route, and are used to treat a variety of rare conditions. Biologic immunosuppressive therapies include TNF-α inhibitors (infliximab, adalimumab, etanercept), IL-12/23 inhibitors (ustekinumab), CD20 inhibitors (rituximab) and most recently the IL-17 pathway inhibitors (secukinumab, ixekizumab, brodalumab) (Table 2). Given the relative success of TNF-α inhibitors and ustekinumab in the treatment of psoriasis, there has been an emergence of biologics targeting various other cytokines. Inhibitors of IL-17 are the latest wave of therapeutics developed for the treatment of psoriasis and psoriatic arthritis, which deplete the Th17 population of T-cells. Other types of IL-17 inhibitors are currently in various phases of clinical trials for psoriasis and psoriatic arthritis.[22] The clinical trials for these agents are currently ongoing and data pertaining to incidence and type of infections have not yet been published.

Biologic Class	Generic Name/Trade Name	Monoclonal Ab vs. Receptor	Mechanism of Action
TNF-α inhibitors	Infliximab (Remicade®)	Monoclonal Ab (chimeric), IgG1κ	Binds TNF-α only, inhibits binding to soluble and transmembrane TNF receptor
	Adalimumab (Humira®)	Monoclonal Ab (fully human), IgG1	Binds TNF-α only, inhibits TNF binding to p55 and p75 transmembrane TNF receptor
	Etanercept (Enbrel®)	Receptor, dimeric fusion protein, p75 TNF receptor linked to Fc IgG1	Binds to both TNF-α and TNF-β; binding to soluble and membrane bound TNF-α
IL-12/23 inhibitor	Ustekinumab (Stelara®)		

	Monoclonal Ab (fully human), IgG1	Binds the common p40 subunit of IL-12 and IL-23 preventing interaction with IL-12Rβ1; decreased Th1 and Th17 signalling
IL-17 pathway inhibitors		
Secukinumab (Cosentyx®)	Monoclonal Ab (fully human), IgG1κ	Neutralizes IL-17A; decreased IL-23 signalling pathway downstream of Th17 cells
Ixekizumab (Talz®)	Monoclonal Ab (fully human), IgG4	Neutralizes IL-17A; decreased IL-23 signalling pathway downstream of Th17 cells
CD20 inhibitor		
Rituximab (Rituxan®)	Monoclonal Ab (chimeric), IgG1κ	Binds CD20 surface molecule on B-cells

Table 2: Biologic immunosuppressive therapy. Ab = antibody; IgG = immunoglobulin G antibody; Th = T helper cells

Rituximab, a biologic that targets the B-cell surface antigen CD20, can be used in several dermatologic conditions including pemphigus vulgaris. Rituximab became the first monoclonal antibody approved by the US FDA for the treatment of cancer. Since rituximab depletes CD20+ B-cells, it should not be administered to patients with active infections. Live vaccines should not be given to patients taking rituximab, and recombinant or killed vaccines should be given at least 4 weeks prior to initiating treatment. Patients should undergo screening for active and latent infections. Rituximab has been associated in particular with reactivation of hepatitis B virus (HBV).[23] The time from last rituximab dose to reactivation of HBV was 3 months, although 29% occurred >6 months after last rituximab. Patients with previous exposure to HBV should be screened prior to initiating rituximab. Carriers should be closely monitored for clinical and laboratory signs of infection as reactivation may lead to liver failure and death in the months following therapy. There is an argument for the consideration of prophylactic treatment in selected patients.[24] Reactivation of the JC virus (a type of human polyomavirus), leading to progressive multifocal leukoencephalopathy (PML) has also been associated with rituximab treatment.[25] Among human immunodeficiency virus (HIV)-negative patients, the median time to diagnosis of PML was 5.5 months following the last dose of rituximab and a 90% fatality was reported. These data warrant vigilant monitoring for new onset neurologic findings during and after the course of treatment.

Pretreatment Infection Workup

Recent publications within the dermatology literature have provided recommendations for an infection workup for the dermatologist prior to initiating immunosuppressive agents.[2,3] In general, the suggested steps apply to all immunosuppressants, whether non-biologic or biologic. Table 3 provides a summary of these and our

recommendations.

Although the morbidity and mortality from infectious complications can be significant, careful patient selection and monitoring can mitigate risk and reduce potential harm. General recommendations include conducting a thorough history and physical exam, with particular focus on country of birth and residence, travel history, sexual and social risk factors and exposure to sick contacts. Vaccination records should be reviewed and, if feasible, age-appropriate vaccinations should be updated prior to initiating immunosuppressive therapy. Patients should be educated on the importance of general hygiene (i.e., handwashing), signs and symptoms of early infection and when they should seek urgent medical care. Likewise, the dermatologist should be vigilant for early signs and symptoms of infection, and have a low threshold to treat bacterial, fungal and viral illness. Physicians should assess patients at each visit for impetiginization and treat appropriately.

1. Screen patient for risk factors of infection:

- Comorbid medical conditions (i.e., organ/hematopoietic transplant, active malignancy, renal or liver failure, diabetes mellitus etc.)
- Age
- Occupation
- History of travel to areas of endemic disease
- History of high risk sexual activity, drug abuse
- History of exposure to tuberculosis
- History of blood transfusion

2. On a case by case basis, consider laboratory screening for patients at risk:

- Hepatitis B (HBsAg, anti-HBc, IgM anti-HBc, anti-HBs)
- Hepatitis C (HCV enzyme immunoassay)
- HIV (HIV ELISA)
- *Strongyloides* (stool culture for ova and parasites; Strongyloides ELISA)
- Tuberculosis (PPD tests; interferon-gamma release assay; chest x-ray, for patients with a positive PPD test from previous Bacillus Calmette-GuÃ©rin vaccination)
- Systemic fungal infections, such as cryptococcosis, histoplasmosis, coccidiomycosis, blastomycosis, and paracoccidioidomycosis (serum and/or urine test; chest x-ray)
- Consider pneumocystis pneumonia prophylaxis

3. Ensure immunizations are up-to-date according to latest recommendations (www.cdc.gov/vaccines/schedules/)

- Seasonal influenza vaccination (non-live vaccine; avoid live vaccine after immunosuppressive therapies have been initiated)
- *Pneumococcus* vaccination (non-live vaccine)
- Herpes zoster vaccination (live vaccine; initiate prior to starting immunosuppressive therapy)
- Tetanus/diphtheria vaccination (non-live vaccine)

4. Patient education in regards to:

- Frequent handwashing
- Avoiding high-risk infectious exposures if possible (i.e., over-crowded areas, child care centres, nursing homes, farms, compost, travel to countries where aforementioned diseases are endemic)
- Early signs and symptoms of infection (e.g., including impetiginization, and systemic bacterial, fungal and viral infections)

Table 3: A dermatologist's checklist to infection screening prior to initiating immunosuppressive therapy (adapted from Lehman JS et al.[2])
Anti-HBc = hepatitis B virus core antibody; anti-HBs= hepatitis B virus surface antibody; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B virus
surface antigen; HCV = hepatitis C virus; PPD = purified protein derivative

All patients should undergo HIV, HBV, and hepatitis C virus (HCV) testing. Furthermore, testing and diagnosis of tuberculosis should be undertaken as per Centers for Disease Control and Prevention (CDC) and Health Canada recommendations (Health Canada: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbcanada-7/tb-standards-tb-normes-ch3-eng.php and CDC: http://www.cdc.gov/tb/topic/testing/).
Testing for parasitic infections, particularly *Strongyloides stercoralis (S. stercoralis)* should be considered and done on an individualized basis. Infection with *S. stercoralis* is usually chronic and asymptomatic in immunocompetent patients and may persist undetected for many years. In immunosuppressed patients, strongyloidiasis can cause hyperinfection and dessimination and carries a high mortality rate. It is reasonable to screen those who have resided in an endemic area for a prolonged period even if it was in the distant past (i.e., southeastern United States and subtropical areas, Europe) and those who possess other risk factors (i.e., occupation, activities). Unexplained hypereosinophilia should also trigger the physician to screen for *Strongyloides*. Conversely, the physician should be mindful that prolonged corticosteroid use can suppress hypereosinophilia. Stool microscopy for ova and parasites is currently the gold standard for diagnosis, however, up to seven collections may be required in order to reach a sensitivity of 100%.[26] A single stool sample collection has a low sensitivity of 30-75%.[27,28] Sensitivity for the enzyme-linked immunosorbent assay (ELISA) for *S. stercoralis* serology is 83-93% with 95-97% specificity.[29]

Conclusion

We have provided an overview of some of the major immunosuppressant drugs used in dermatology and have presented a summary of recommendations prior to initiating these medications (Table 3). Regardless of the immunosuppressive agent used, the type of infections that the dermatologist needs to screen for and prevent are similar. Overall, the risk of infection is likely to be directly proportional to the dose and duration of immunosuppressant therapy.

References

1. Keith PJ, Wetter DA, Wilson JW, et al. Evidence-based guidelines for laboratory screening for infectious diseases before initiation of systemic immunosuppressive agents in patients with autoimmune bullous dermatoses. *Br J Dermatol.* 2014 Dec;171(6):1307-17.
2. Lehman JS, Wetter DA, Davis MD, et al. Anticipating and preventing infection in patients treated with immunosuppressive medications for dermatologic indications: a dermatologist's checklist. *J Am Acad Dermatol.*

2014 Oct; 71(4):e125-6.
3. Lehman JS, Murrell DF, Camilleri MJ, et al. Infection and infection prevention in patients treated with immunosuppressive medications for autoimmune bullous disorders. *Dermatol Clin.* 2011 Oct;29(4):591-8.
4. Hench PS, Kendall EC, Slocumb CH, et al. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. *Arch Intern Med (Chic).* 1950 Apr;85(4):545-666.
5. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. *N Engl J Med.* 2005 Oct 20;353(16):1711-23.
6. Buttgereit F, Straub RH, Wehling M, et al. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. *Arthritis Rheum.* 2004 Nov;50(11):3408-17.
7. Cutolo M, Seriolo B, Pizzorni C, et al. Use of glucocorticoids and risk of infections. *Autoimmun Rev.* 2008 Dec;8(2):153-5.
8. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis.* 1989 Nov-Dec;11(6):954-63.
9. Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. *Drug Saf.* 2000 Nov;23(5):429-48.
10. Meggitt SJ, Anstey AV, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol.* 2011 Oct;165(4):711-34.
11. Wojnarowska F, Kirtschig G, Highet AS, et al. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol.* 2002 Aug;147(2):214-21.
12. Thomas S, Fisher KH, Snowden JA, et al. Methotrexate Is a JAK/STAT Pathway Inhibitor. *PLoS One.* 2015 Jul 1;10(7):e0130078.
13. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010 Dec;63(6):925-46; quiz 47-8.
14. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol.* 2010 Dec;63(6):949-72; quiz 73-4.
15. Beissert S, Mimouni D, Kanwar AJ, et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebocontrolled trial. *J Invest Dermatol.* 2010 Aug;130(8):2041-8.
16. Powell AM, Albert S, Al Fares S, et al. An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol.* 2003 Jul;149(1):138-45.
17. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol.* 2007 Jan;32(1):23-7.
18. Benez A, Fierlbeck G. Successful long-term treatment of severe atopic dermatitis with mycophenolate mofetil. *Br J Dermatol.* 2001 Mar;144(3):638-9.
19. Rowin J, Amato AA, Deisher N, et al. Mycophenolate mofetil in dermatomyositis: is it safe? Neurology. 2006 Apr 25;66(8):1245-7.
20. Saha M, Black MM, Groves RW. Risk of herpes zoster infection in patients with pemphigus on mycophenolate mofetil. *Br J Dermatol.* 2008 Nov;159(5):1212-3.
21. Gleason PP, Alexander GC, Starner CI, et al. Health plan utilization and costs of specialty drugs within 4 chronic conditions. *J Manag Care Pharm.* 2013 Sep;19(7):542-8.
22. Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. *Curr Opin Rheumatol.* 2015 Mar;27(2):127-33.
23. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol.* 2011 May;22(5):1170-80.
24. Leung C, Tsoi E, Burns G, et al. An argument for the universal prophylaxis of hepatitis B infection in patients receiving rituximab: a 7-year institutional experience of hepatitis screening. *Oncologist.* 2011;16(5):579-84.
25. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood.* 2009 May 14;113(20):4834-40.
26. Sarubbi FA. Hyperinfection with Strongyloides during treatment of pemphigus vulgaris. *Arch Dermatol.* 1987

Jul;123(7):864-5.
27. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. *Clin Infect Dis.* 2001 Oct 1;33(7):1040-7.
28. Cartwright CP. Utility of multiple-stool-specimen ova and parasite examinations in a high-prevalence setting. *J Clin Microbiol.* 1999 Aug;37(8):2408-11.
29. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep.* 2000 Oct;49(RR-10):1-125, CE1-7.

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