

INFECTION PREVENTION IN SARCOIDOSIS: PROPOSAL FOR VACCINATION AND PROPHYLACTIC THERAPY

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ABSTRACT. Sarcoidosis is a systemic inflammatory disease characterized by granuloma formation in affected organs and caused by dysregulated immune response to an unknown antigen. Sarcoidosis patients receiving immunosuppressive medications are at increased risk of infection. Lymphopenia is also commonly seen among patient with sarcoidosis. In this review, risk of infections, including opportunistic infections, will be outlined. Recommendations for vaccinations and prophylactic therapy based on literature review will also be summarized. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (2): 87-98).

KEY WORDS: Sarcoidosis, infections, opportunistic infections, vaccinations, immunizations, prophylaxis, travel

Key points: Infections are common in patients with sarcoidosis receiving immunosuppressive therapy; Current guidelines for infection prevention and vaccination in sarcoidosis patients are lacking; Personalized approach is required when prescribing immunosuppressive therapy to sarcoidosis patients taking into consideration risk of infection and proper vaccination.

INTRODUCTION

Sarcoidosis is a systemic disorder that develops in response to an unknown antigen and is typically characterized by a heightened local inflammatory reaction characterized by granuloma formation and cytokine secretion in affected organs. Patients with sarcoidosis have been noted to have an increased risk of infection requiring hospitalization, especially pneumonia and some opportunistic infections^{1,2,3}. Although not fully elucidated, several mechanisms inherent to sarcoidosis and likely a result of the complex dysregulated immune response observed in

Received: 22 April 2020

Accepted after revision: 24 April 2020

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sarcoidosis (such as peripheral anergy as well as loss of local defenses when bronchiectasis and cavitations develop), contribute to this increased infectious susceptibility^{1,2,3}. Clinically significant peripheral lymphopenia and hypogammaglobulinemia are usually seen in association with immunosuppressive therapy, including corticosteroids. Additionally, patients with symptomatic disease are frequently treated with immunosuppressive medications which further disrupts inherent immunologic mechanisms.

As with other inflammatory diseases, on account of the immunosuppressive effects of the disease itself and the use of immunosuppressive medications, it is important to prevent infectious diseases and associated complications in sarcoidosis patients. Vaccination is generally regarded as a safe, efficacious and low-cost method that may reduce morbidity and mortality associated with sarcoidosis patients and prophylactic therapies may further be a safe and cost-effective manner of prevention^{4,5,6}. It is therefore imperative to ensure patients are properly vaccinated and placed on prophylactic therapy when indicated to prevent infections. However, it has been observed that lack of physician recommendation to do so is a predominant factor to the low rates of vaccination among immunosuppressed patients⁷. Specifically in sarcoidosis, and further contributing to low rates of vaccination and prophylaxis, we recognize that currently there are no guidelines on immunization or prophylaxis practices. Although data cannot be clearly extrapolated from other diseases, the recommendations for patients with autoimmune diseases and some forms of immunosuppression are likely applicable to sarcoidosis patients. In this review, we will outline the risk of infection in patients with sarcoidosis and immunosuppressive medications and recommendations for vaccinations and prophylactic therapy for sarcoidosis patients will be proposed.

IMMUNOSUPPRESSIVE THERAPY AND INFECTION RISK

Oral immunosuppressants commonly used in sarcoidosis

Of the oral immunosuppressant medications, glucocorticoids are found to be the highest risk for the development of infection. In a study done by Bernatsky, the relative risk of infections requiring hospitalization in those taking glucocorticoids was 2.56 (95% CI 2.29-2.85)⁸. Another study showed

the relative risk of infections from glucocorticoids was 1.6 (95% CI 1.3-1.9), and the rates of infection increased with higher doses⁹. However, patients taking less than 10mg of prednisone daily (or its equivalent) did not have higher infection rates compared to those not taking glucocorticoids¹⁰. Furthermore, risk of infection increased in patients taking combination therapy, either glucocorticoids plus a steroid-sparing agent or more than one steroid-sparing agent together.

Methotrexate can cause cytopenias in about 5.2% of patients, which can, in part, predispose patients to infections¹¹. However, a Cochrane review by Lopez-Olivo et al shows that the relative risk of serious adverse events in patients treated with methotrexate as compared to placebo is 1.44 (95% CI 0.36-5.74) and the relative risk of infection is 1.26 (95% CI 1.01-1.57)¹². A systematic review by Salliot et al showed that of patients who were on methotrexate for rheumatoid arthritis (RA) over a three year period, 8.3% developed infections¹¹.

Azathioprine, a purine analog, is converted to 6-mercaptopurine, then further degraded into its nontoxic metabolites by thiopurine methyltransferase. Azathioprine may cause myelosuppression, increasing its infectious risk profile. Those patients with a deficiency in thiopurine methyltransferase are at increased risk of azathioprine toxicity and lower doses of azathioprine should be used or avoided completely, and cell counts closely monitored¹³. A Cochran Review by Suarez-Alamazor et al shows the odds ratio of developing cytopenias with azathioprine as compared to placebo was 6.84 (95% CI 0.69-68.05)¹⁴. In a study completed by Bernatsky, the relative risk of infections requiring hospitalizations in patients taking azathioprine compared to placebo was 1.52 (95% CI 1.18-1.97)⁸.

Other oral disease modifying anti-sarcoid drugs (DMASD) are commonly used off-label in sarcoidosis patients. However the risk of significant immunosuppression with these agents is unknown¹⁵.

Significant immunosuppression with oral agents is considered to occur with > 2 weeks of prednisolone > 10mg/day (or its equivalent), methotrexate \geq 0.4mg/kg/week, and azathioprine \geq 3mg/kg/day⁷.

Biologic Therapy Commonly Used in Sarcoidosis

Biologic therapy carries an increased risk of numerous types of infections. In a study conducted

on 3,111 veteran patients with rheumatoid arthritis (RA), who had 4,158 treatment episodes with a biologic (defined as new biologic treatment, either abatacept, rituximab, or an anti-TNF agent), pneumonia was seen in 37%, cellulitis in 22%, urinary tract infections in 9% and bacteremia or sepsis in 7%. Hospitalized infection rates per 100 years were 4.4 (95% CI 3.1-6.4) for rituximab and 3.0 (95% CI 2.5-3.5) for anti-TNF agents¹⁶. In a study evaluating efficacy and safety of anti-TNF agents in sarcoidosis patients, Jamilloux et al found an infection rate of 36% among 132 patients¹⁷. In a systematic review and meta-analysis of small molecule JAK kinase inhibitors in RA patients, the incidence rate of serious infections among 5,888 patients taking tofacitinib 5mg twice daily was 1.97 (95% CI 1.41-2.68), and the incidence rate ratio when comparing to the placebo arm was 1.22 (95% CI 0.60-2.45)¹⁸.

Infection risk may also depend on dose of biologic therapy. A meta-analysis conducted by Leombruno et al reviewed 18 randomized trials with a total of 8808 patients with RA who were either randomized to anti-TNF agents (further divided into recommended dose vs high dose therapy), conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), or placebo. High dose therapy was defined as the following: adalimumab > 40mg every 2 weeks, etanercept > 50mg weekly, and infliximab > 8mg/kg every 8 weeks. Over an average follow-up of 0.8 years, the authors did not find a statistically significant increase in infections in the synthetic DMARDs or placebo group compared to the recommended dose anti-TNF group. However, the high dose anti-TNF group had a two-fold increased risk of infections¹⁹. This is of particular importance in sarcoidosis, as high dose therapy is often used, in the absence of prospective randomized data. Another systematic review and meta-analysis of anti-TNF use assessed the risk of infection in RA patients who were given standard dose anti-TNFs, high dose anti-TNFs, or control therapy. High dose anti-TNFs were defined as infliximab > 3mg/kg every 8 weeks and adalimumab > 40mg every other week. The authors found an OR of 2.3 (95% CI, 1.5-3.6) for the high-dose anti-TNF group compared to the control group and an OR of 1.8 (95% CI, 1.1-3.1) for the standard-dose group compared to the control group. However, when comparing the high-dose group to the standard-dose group, an OR of 1.4 was not found to be statistically significant (95% CI, 1.0-2.0, $P = 0.07$)²⁰.

Adelzadeh et al completed a meta-analysis that evaluated the risk of herpes zoster in patients taking different biologic therapy (infliximab, adalimumab, etanercept, and ustekinumab) and found slightly higher rates of zoster in patients taking infliximab. Data for the other biologics showed varying rates, making the results inconclusive²¹. In the aforementioned systematic review and meta-analysis evaluating infection risk with tofacitinib, the incidence rate for developing herpes zoster was 2.51 (95% CI 1.87-3.30), but the incidence ratio rate when comparing to the placebo arm was no longer significant (1.38 with 95% CI 0.66-2.88)¹⁸. In a retrospective review of Medicare patients with RA, older patients tended to be at high risk of developing zoster regardless of biologic used, but the highest adjusted hazard ratio was seen among patients taking oral corticosteroids (> 7.5mg daily of prednisone or its equivalent)²².

Rituximab is also associated with increased infections, with serious infections encountered at rate of 3.76 per 100 patient years, although not all analyses reported an increased risk^{1,23,24,25,26}. Because of its suppression of immunoglobulin production, there is an overall increased risk for viral infections. Rituximab has been shown to cause reactivation of herpes simplex virus, herpes zoster virus, and hepatitis B^{27,28}. However, prolonged use of rituximab can lead to IgG depletion and neutropenia, and monitoring IgG levels on a regular basis is recommended. Immunoglobulin replacement therapy can be effective in reducing risk of infections in patients on prolonged rituximab therapy, but there are currently no guidelines on when and in which patients this should be done^{29,30,31,32,33,34,35}.

Infections in Sarcoidosis

In sarcoidosis patients specifically, various infections have been described while on immunosuppressive therapies. Dureault et al examined infection rates in 585 patients, and reported 22 episodes of severe non-mycobacterial infections among 16 patients, and 14 mycobacterial infections among 14 patients². Patients with severe infections were more likely to have been treated with ≥ 3 immunosuppressive agents. Although limited, current data suggests patients with sarcoidosis are at increased risk of infection regardless of immunosuppressant therapy. A retrospective review by Ungprasert et al found that patients with sarcoidosis had an increased incidence of community acquired infection requiring

hospitalization compared to age- and sex-matched healthy controls (HR 2.00, 95% CI 1.14-2.84). Less than half of this cohort was on immunosuppressive therapy. Risk factors for infections included baseline diffusing capacity of the lung for carbon monoxide (DLCO) and baseline forced vital capacity (FVC), with a steady increase in infection rates with decreases in DLCO and FVC¹. Further study is needed to further delineate infection risk in treatment-naïve sarcoid.

Opportunistic infections

Due to inherent and medication-induced immunosuppression, sarcoidosis patients have been shown to be at increased risk for opportunistic infections, albeit infrequently. Reported infections include *Pneumocystis jirovecii* pneumonia (PJP), Mycobacterial infection, *Cryptococcus neoformans*, and aspergillosis. Epidemiologic and geographic factors, as well as presence of parenchymal fibrosis, also play a part. Opportunistic infections have been observed in other autoimmune diseases in conjuncture with initiation of immunosuppressive medications. A large retrospective review identified opportunistic infections at an incidence rate of 0.045% , among patients who were newly started on either biologic or immunosuppressive therapy. Of the patients newly started on biologic therapy, the most commonly occurring infections were PJP (20%), nocardiosis (15%), tuberculosis (12.5%), histoplasmosis and non-tuberculosis mycobacteria (11.3% each), and salmonellosis (10%). The other opportunistic infections reported occurred in $\leq 5\%$ of the cases³⁶.

PJP is a commonly known opportunistic infection that affects HIV-positive patients as well as non-HIV, immunocompromised patients. In those without HIV, it tends to have a more severe course with rapidly progressive and fatal disease³⁷. Several studies have reported the prevalence of PJP among patients with autoimmune disease to range from 0.18% to 1.2%, with the highest risk being among those on corticosteroid therapy, especially at doses $> 20\text{mg/day}$ ^{38,39,40,41,42}. Other risk factors include older age and co-existing pulmonary disease⁴⁰. PJP has been infrequently reported in sarcoidosis.

Mycobacterial infection has not often been reported in patients with sarcoidosis. As mycobacterial infection, especially tuberculosis, can present as

granulomatous disease, it should be on the differential when assessing for sarcoidosis. There have been 27 reported cases of tuberculosis among sarcoidosis patients between 1976 and 2013, of which 74% were in patients being treated with corticosteroids.⁴³ Fourteen non-tuberculosis mycobacterium cases were reported between 1977 and 2010, of which 71% were receiving corticosteroid therapy. A greater risk for tuberculosis than sarcoidosis itself is TNF-alpha inhibitors, which are frequently used to treat sarcoidosis. This increased risk has been observed more commonly with infliximab and adalimumab than with etanercept^{44,45,46}. Furthermore, TNF-alpha has been shown to play a part in the host defense against tuberculosis, and blockade of TNF-alpha can lead to reactivation of latent tuberculosis. A meta-analysis of 29 randomized clinical trials evaluating incidence of tuberculosis in patients on anti-TNF therapy identified 45 patients (0.57%) on anti-TNF therapy who developed tuberculosis, compared to only 3 of 3967 control patients who developed tuberculosis ($p = 0.02$)⁴⁷. A systematic review of 40 randomized controlled trials with a total of 14,683 patients found an odds ratio of 24.8 for developing TB while on anti-TNF therapy (95% CI 2.4-133). When anti-TNF agents were combined with other immunosuppressive agents (methotrexate or azathioprine), the odds ratio increased to 54 (95% CI 5.3-88)⁴⁸.

Fungal infections in patients with sarcoidosis has been sparsely reported. Baughman's study found 7 cases of fungal infection among 753 cases of sarcoidosis⁴⁹. CrypOsarc, a study completed by Bernard et al, identified 18 patients with cryptococcal infection and sarcoidosis and found that sarcoidosis accounted for 2.6% of the non-HIV associated cryptococcal infections⁵⁰. One third of the identified patients were not on corticosteroids at the time of diagnosed infection, though presence of other immunosuppressants is not mentioned. Increased rates of aspergillosis have been documented among patients with chronic pulmonary fibrotic disease, and have been noted to occur more frequently in sarcoidosis than in other interstitial lung diseases³. Again, corticosteroids play an important role as a risk factor for development of aspergillosis as does mold exposure².

Progressive multifocal leukoencephalopathy (PML) is more likely to occur in immunocompromised patients but has been reported in sarcoidosis

patients not on immunosuppression. There are case reports of symptoms and magnetic resonance imaging (MRI) findings mistakenly attributed to neurosarcoidosis, leading to increased immunosuppression and worsening of symptoms^{17,51,52}. The presentation of sarcoidosis-associated PML differs from neurosarcoidosis. In PML, cerebrospinal fluid (CSF) is typically normal and MRI brain shows multifocal asymmetrical subcortical white matter lesions that are hypointense on T1, hyperintense on T2, and non-enhancing with contrast. In neurosarcoidosis, CSF frequently has pleocytosis and elevated protein but can be normal. MRI of the brain typically shows meningeal or parenchymal lesions with contrast enhancement. Definitive diagnosis requires JC virus DNA detection in the CSF by polymerase chain reaction or brain biopsy. JC virus may not be detected in CSF in early disease so it may require repeat lumbar puncture to diagnose. Brain biopsy can be considered if suspicion remains high^{17,43}.

Herpes zoster is reported infrequently in patients with sarcoidosis, and likely occurs at the same rate as the general population^{53,54}. There are reports of sarcoid granulomas occurring at the sites of healed zoster lesions^{55,56,57}.

RECOMMENDATIONS FOR VACCINATIONS

As described, the dysregulated immune response underlying granuloma formation in sarcoidosis along with use of immunosuppressive therapies contributes to overall immune dysfunction. Despite the infection risk, there are no current guidelines on immunization practices in sarcoidosis patients. Although data describing infection risk in sarcoidosis is lacking, the recommendations for vaccinations in immunosuppressed patients are likely applicable to sarcoidosis patients. As sarcoidosis most commonly affects the lungs, vaccination should be considered in alignment with recommendations for chronic lung disease. Special consideration for vaccination should be taken in regards to use of immunosuppressive therapy and type of vaccine. Discussion with patients should also include possibly vaccinating household members and those who are regularly in close contact with the patient.

All new patients should be screened for their vaccination status and administer any appropriate immunizations prior to the start of immunosuppressive therapy⁷. Though patients with immune-mediated

disease have been shown to have a comparable serologic response to vaccinations as those in the general population, immunosuppressive therapy can interfere with the immune response. This is most concerning with biologic therapy, especially rituximab, a B cell depletion therapy⁵⁸. Patients treated with rituximab have been shown to have lower probability of immune response to various vaccines and absent antibody titers to influenza vaccines and pneumococcal vaccines^{58,59,60}. In order to allow an adequate immune response, it would be best to wait two weeks after vaccinations to start immunosuppressive therapy⁷. If a patient is already receiving immunosuppressive therapy, therapy need not be held to administer inactivated vaccines. Though immunogenicity may be lower, there is still a protective response from the vaccinations.

However, when considering live vaccinations for patients on immunosuppressive medications, there should be careful thought to ensure benefits outweigh the risks. If possible, immunosuppressive therapy should be held 2-4 weeks prior to the administration of live vaccines, and the length of viremia should help determine when to restart immunosuppressive therapy. Special consideration should be given to patients receiving live vaccines while on rituximab; vaccinations should not be given until at least 5 months after the last dose of rituximab, and rituximab should not be re-dosed for at least one month after vaccinations⁷.

Table 1 summarizes the list of vaccinations and Table 2 proposes the use of these vaccinations in patients with sarcoidosis.

Influenza

In sarcoidosis, as is the case with many other diseases, the presence of chronic pulmonary disease and impaired immune function likely predisposes to higher risk of complications, increased severity of disease and death from influenza⁶¹. The protective effect rendered by vaccination with modern influenza vaccines results from induction of antibody production against hemagglutinin (HA) or neuroaminidase antigens⁶².

Currently, the CDC recommends that any person 6 months of age or older should receive an influenza vaccination unless contraindicated because of severe allergy or other special considerations (e.g.:

Table 1. Recommendations for vaccinations in immunosuppressed patients.

Vaccination	Age	Frequency	Special Considerations
Influenza, inactivated or recombinant	6 months an older	Annually	
Pneumococcal PCV13 (Pneumovax) PPSV23 (Pneumovax)	≥ 19 years	Once See Figure 1	To be given no sooner than 1 year after PPSV23 To be given no sooner than 8 weeks after PCV13
Zoster (recombinant)	≥ 50 years	2 doses 2-6 month apart	
HPV	11-26 years (women) 11-21 years (men)	3 doses at months 0, 1-2, and 6	
HepA 2 dose series HepA 3 dose series HepA/B		2 doses 6-18 months apart 3 doses at 0, 1, and 6 months	Risk factors for HepA: • chronic liver disease • clotting factor disorders • men who have sex with men • drug use (including non-injection) • homelessness • working with hepatitis A in research labs • close interaction with international adoptee within 60 days of arrival • travel to country with endemic rates
HepB 2 dose HepB 3 dose HepB 3 dose HepA/B		2 doses > 4 weeks apart 3 doses at 1, 2, and 6 months 3 doses at 1, 2, and 6 months	Risk factors for HepB: • hepC Infection • chronic liver disease • infection with HIV • sexual exposure risk • current or recent injection drug use • percutaneous or mucosal risk of exposure to blood (including dialysis patients) • travel to country with endemic rates
Tdap If received childhood series If did not receive childhood series		Every 10 years 3 doses at 0, 1 and 6-12 months, then every 10 years	

PCV13 – 13-valent pneumococcal conjugate vaccine. PPSV23 – 23-valent polysaccharide vaccine. HPV – human papilloma virus. HepA – Hepatitis A. HepB – Hepatitis B. Tdap – tetanus toxoids, diphtheria, and acellular pertussis vaccine.

Table 2. Proposed use of vaccines in patients with sarcoidosis

	Killed vaccines			Live attenuated vaccine
	Pneumococcal 1	Influenza 2	Hepatitis B 3	Herpes zoster
Before initiating therapy				
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Recommended ⁴
Non-TNF biologics	Recommended	Recommended	Recommended	Recommended ⁴
While already taking therapy				
DMARD monotherapy	Recommended	Recommended	Recommended	Recommended
Combination DMARD	Recommended	Recommended	Recommended	Recommended
TNFi biologics	Recommended	Recommended	Recommended	Not recommended
Non-TNF biologics	Recommended	Recommended	Recommended	Not recommended

DMARD – disease-modifying anti-rheumatic drugs. TNFi – tumor-necrosis factor inhibitor.

patients who are unlikely to respond or who have received anti-B-cell antibodies within 6 months). Expressly, the CDC recommends that among the various types of influenza vaccines, adults 18 years of age and older receive 0.5mL of an age appropriate inactivated vaccine (trivalent or quadrivalent) or, alternatively, a recombinant quadrivalent vaccine. Notably, avoidance of live attenuated influenza vaccines in the immunocompromised individual is emphasized because of the risk of adverse events, though this is a weak recommendation with low quality of evidence^{63,64}. Additionally, attention is brought to those patients 65 years of age and older given the decreased immune response to standard influenza vaccines as compared to healthy adults because of cellular senescence, and a recommendation is made which allows these individuals to receive a high-dose influenza vaccine which may provide greater immunogenicity^{64,65}.

In sarcoidosis, specifically, there is paucity of data evaluating the degree of susceptibility to influenza, predisposition to disease flare after administration of influenza vaccine, and the robustness of antibody production to preventative levels against influenza after vaccination. A small prospective case-control study evaluated the serological response to influenza vaccination, and found no difference in serologic response to influenza vaccines, but interestingly, patients with sarcoidosis demonstrated a higher protection rate against the influenza B antigen after vaccination. Moreover, no signs of disease flares or major adverse events were observed in the sarcoidosis group after 6 months of follow-up⁶⁶.

At the present, we recommend that immunosuppressive therapy should only be held if the risks do not outweigh the benefits. All patients without to vaccination should receive inactivated seasonal influenza vaccination yearly regardless of their therapy with a consideration for high-dose vaccination in those over 65 years of age.

Pneumococcus

Pneumococcal vaccines are typically indicated in adults over the age of 65. However, in immunocompromised patients, the CDC recommends vaccinations start at 19 years old⁶⁷.

Regardless of age, patients should receive the 13-valent pneumococcal conjugate vaccine (PCV13 or Prevnar) vaccine first followed by the 23-valent polysaccharide vaccine (PPSV23 or Pneumovax) vaccine at least eight weeks later. Patients older than 65 years old should receive each vaccine only once (PCV13 and PPSV23). Patients less than 65 years old should have up to three PPSV23 vaccines no less than 5 years apart, with only one dose being given after a patient turns 65 years old^{7,67}.

If the patient has already received PPSV23 first, the PCV13 should be given no sooner than one year after the PPSV23 vaccine. See Figure 1.

Tetanus, diphtheria, and pertussis (Tdap)

Tdap is typically completed as a series in childhood, and then is recommended every 10 years throughout adulthood. If a patient has not received any childhood Tdap vaccines, they should receive Tdap at 0, 1, and 6-12 months, and then a booster every 10 years⁶⁷.

Zoster

The live zoster vaccine is not recommended in anyone who is immunosuppressed. As of 2020, the CDC does not yet have a recommendation regarding recombinant zoster vaccination (Shingrix) in immunocompromised adults⁶⁸. The recombinant vaccine is given as a two-vaccine series, 2-6 months apart. If the second vaccine in the series is given too soon, it is recommended to repeat the dose at the appropriate interval. If the second vaccine is given too late, it is recommended to start over with the two-vaccine series^{7,67}.

Patients who have already had a shingles infection or received the live zoster vaccine are still advised to get the recombinant zoster vaccine series⁶⁷. Additionally, the recombinant vaccine is preferred over the live attenuated vaccine for all populations.

Hepatitis A and B

Hepatitis A (HepA) and hepatitis B (HepB) vaccines are recommended for those individuals at risk for exposure to the virus, but should also be given routinely for those who want protection. Risk factors for HepA include chronic liver disease, clotting

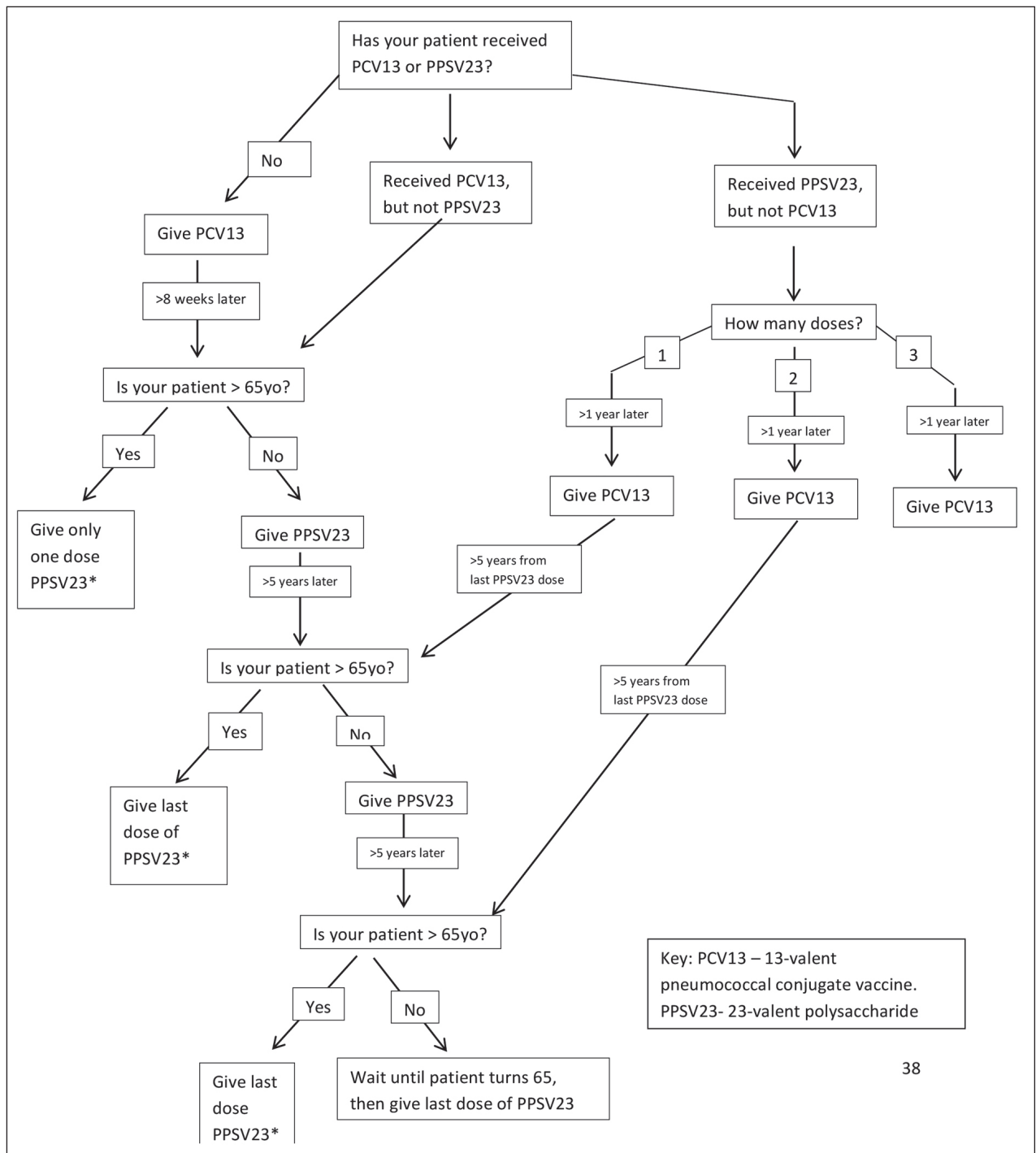


Fig. 1. Algorithm for Pneumococcal vaccine administration.

factor disorders, men who have sex with men, drug use (including non-injection), homelessness, working with hepatitis A in research labs, close interaction with international adoptee within 60 days of arrival,

and travel to country with endemic rates. Risk factors for HepB include hepatitis C Infection, chronic liver disease, infection with HIV, sexual exposure risk, current or prior injection drug use, percutaneous or

mucosal risk of exposure to blood (including dialysis patients), and travel to countries with high endemic rates. Each vaccine is given as 2-3 dose series, depending on the vaccine⁶⁷.

Other vaccinations

Vaccination for Measles / Mumps / Rubella (MMR), Yellow Fever and HPV should be followed per CDC guidelines. As the MMR vaccine is typically given to patients between the ages of 12 months and 12 years old, an adult patient should be considered vaccinated if there is presumptive evidence against immunity. This evidence includes written documentation of adequate vaccination, laboratory evidence of immunity, laboratory confirmation of measles, or birth before 1957. In those without presumptive evidence against immunity, measles immunoglobulin G (IgG) levels should be obtained. If the results are negative or equivocal, then the patient should be vaccinated or re-vaccinated. If vaccination is not possible, then the patient should be sent for second line diagnostic testing at the local health department⁶⁹.

PREVENTIVE THERAPY FOR OPPORTUNISTIC INFECTIONS:

Tuberculosis

As TNF-alpha inhibitors can lead to reactivation of latent tuberculosis, it is recommended to screen all patients for tuberculosis exposure prior to initiation of biologics. This can be done either with a tuberculin skin test (TST) or with an interferon gamma release assay (IGRA). TST studies are less sensitive but highly specific (97.6%) for the diagnosis of tuberculosis among sarcoidosis patients⁷⁰. However, as sarcoidosis has been associated with anergy, it is difficult to say if a negative TST in a sarcoidosis patient is a true negative. Therefore, IGRA may be more helpful. In a study by Gupta et al, patients with biopsy-proven sarcoidosis, pulmonary tuberculosis, and extra-pulmonary tuberculosis, as well as healthy controls, were prospectively enrolled to receive TST and IGRA. Patients with sarcoidosis reacted to the IGRA test more frequently than the TST, and not significantly less than in healthy controls⁷¹. As IGRA continues to be positive in sarcoidosis patients, it may be a better diagnostic tool for tuberculosis.

In patients with a positive TST or IGRA, TNF-inhibitor therapy should only be started one month after initiation of prophylactic therapy (in cases of latent tuberculosis) or after the completion of therapy (in cases of active tuberculosis)⁷². Special consideration for anti-tuberculosis therapy should be given to patients with hepatic sarcoidosis or those on hepatotoxic DMASD therapy.

Pneumocystis pneumonia (PJP)

As rates of PJP among non-HIV immunocompromised patients are low, there is no consistent data to help guide prophylaxis. A retrospective review evaluating patients on high dose corticosteroid therapy (defined as prednisolone \geq 30mg/day or its equivalent) with and without prophylactic therapy identified 30 cases of PJP, 29 of which were not receiving PJP prophylaxis⁷³. Furthermore, a 2014 Cochrane review found a significantly reduced incidence of PJP in patients with acute leukemia or solid organ transplant who received prophylaxis by 85%. Trimethoprim-sulfamethoxazole was given thrice weekly or as a single daily dose, and the number needed to treat was 19⁷⁴. Patients with risk factors (age older than 65 years, co-existing pulmonary disease, on corticosteroids) may benefit from prophylaxis⁴⁰. The American Thoracic Society recommends considering prophylactic therapy for any patient who is receiving prednisone \geq 20mg/day for \geq 8 weeks, has an internal derangement of their immune system due to their disease, or is on a cytotoxic agent such as methotrexate or TNF-inhibitors⁷⁵. Different regimens for prophylaxis are available (Table 3). Trimethoprim should be avoided in patients taking methotrexate as it may increase blood levels of methotrexate.

Herpes Simplex and Herpes Zoster

In patients who have a history of previous herpes simplex or zoster infection, consideration should be given for prophylactic therapy in order to prevent a flare precipitated by the initiation of DMASDs. In a Cochrane review of randomized clinical trials evaluating the efficacy of anti-virals in preventing herpes simplex infections in patients receiving cancer therapy, acyclovir was shown to be effective, with a risk ratio of 0.16 (95% CI 0.08-0.31) when

Table 3. Regimens for PJP Prophylaxis

Drug	Dosing	Comments
Dapsone	50mg BID or 100mg daily	Rule out G6PD deficiency
Dapsone/ Pyrimethamine/Leucovorin	50mg daily/50mg weekly/25mg/weekly	
Dapsone/ Pyrimethamine/Leucovorin	200mg weekly/50mg weekly/25mg/weekly	
Atovaquone (liquid)	1500mg daily	Take with food
Pentamidine (aerosolized)	300mg monthly	

compared to placebo. Further, valacyclovir was not found to be more efficacious than acyclovir⁷⁶. According to guidelines put forth by the American Society of Clinical Oncology and the Infectious Diseases Society of America, prophylaxis with acyclovir should be considered in patients with profound neutropenia (defined as < 100 neutrophils per microliter) and seropositivity for herpes simplex⁷⁷.

CONCLUSION

Infection prevention and vaccination in patients with sarcoidosis are of crucial importance. There is increased risk of infection associated with the use of immunomodulatory drugs used to treat sarcoidosis. Therefore the vaccination status should be evaluated in the initial patient workup. We propose that vaccination strategies should be implemented during stable disease and reassessed periodically during regular follow up.

The immune response to various vaccines in sarcoidosis patients is not well defined. Furthermore, the effectiveness of vaccines in patients with sarcoidosis to prevent life threatening infection requires additional research. In this review, we summarized the existing literature regarding infections in sarcoidosis patients. Furthermore we propose considering vaccination in this patient population, building on the experience from patients with other autoimmune diseases

Future collaborative multi-center studies should help better understand the safety and efficacy of various vaccines in patients with sarcoidosis with and without immunomodulatory therapy. Even though the preliminary evidence is reassuring on the safety of vaccination in patients with sarcoidosis, there is a need for further studies regarding optimal vaccination strategies.

More longitudinal data is needed including large scale epidemiological studies in regard to the prevalence of various infections in sarcoidosis and the role of prophylactic therapy and vaccination in preventing such infections.

Efforts should be made to educate practicing physicians taking care of sarcoidosis patients, as well as patients, to pay special attention to infection prevention and vaccination. A personalized approach to infection prevention and vaccination would serve patients best.

This paper was reviewed and approved by the World Association of Sarcoidosis and Other Granulomatous disease (WASOG) executive committee.

There are no financial disclosures or conflicts of interest for any of the listed authors.

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