Considerations and clinical management of infections in sarcoidosis

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Purpose of review
To summarize data from recent reports about risks and outcomes of the infections most often reported in patients with sarcoidosis.

Recent findings
Rates of fungal infections and other severe infections are higher in patients with sarcoidosis compared to controls. Immunosuppression further increases the risk for an infection requiring hospitalization. In contrast, outcomes of coronavirus disease 2019 (COVID-19) are not worse unless lung impairment or other comorbidities are present.

Summary
Tuberculosis, fungal infections, and other severe infections requiring hospital admission are, fortunately, relatively rare in patients with sarcoidosis who live in nonendemic regions. However, ongoing vigilance is required when the course of sarcoidosis is atypical or inexplicably progressive, as costs are high when these infections are missed. In contrast, COVID-19 and other respiratory viral illnesses are common, including among patients with sarcoidosis. When organ impairment is minimal, an underlying diagnosis of sarcoidosis does not appear to increase the risk of severe COVID-19, but patients may have higher risks due to comorbidities, which are important factors to address in routine sarcoidosis care. The burden from respiratory viral events, including impacts on quality of life and life functionality including work capacity, is unknown and is important to measure.

Keywords
coronavirus disease 2019, infection, sarcoidosis, tuberculosis, viral infections

INTRODUCTION

Sarcoidosis is a lymphatic-based granulomatous disease which remains mysterious in terms of aetiology and diversity of the natural history. While the lungs and thoracic lymph nodes are the most common sites of disease, multiorgan involvement is common and nearly any organ in the body may be affected. Morbidity is related to the extent of local damage as well as burden of systemic symptoms such as fatigue. Many patients undergo spontaneous remission but a significant minority experience persistent inflammation with the attendant risk of fibrotic transformation.

The pathophysiology of sarcoidosis involves antigen-driven accumulation and activation of macrophages, which aggregate into granulomas [1]. Antigen deposition in tissue is a nidus for granuloma formation, while antigen delivery to regional lymph nodes serves to engage adaptive immune responses. Via chemokine recruitment, lymphocytes traffic to areas of antigen deposition in tissues, where they accumulate predominantly in the outer rim of granulomas. A range of cytokines, including tumour necrosis factor alpha (TNF-α), support the granulomatous response.

Persistent or progressive sarcoidosis, particularly affecting vulnerable organs, often requires treatment to control symptoms, improve organ function, or interrupt the process of fibrotic transformation [2]. To counter the pro-inflammatory cascade, down regulating lymphocyte or macrophage function directly or through blockade of cytokine signalling are goals of immunosuppressive treatments utilised

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KEY POINTS

- For COVID-19, comorbidity burdens and smoking status are associated with worse outcomes and should be actively managed in sarcoidosis care.
- Poly-immunosuppressive use contributes to the risk of severe infections in patients with sarcoidosis.
- Otherwise, currently available data do not support a strong need to reduce or stop sarcoidosis treatment for infection prevention purposes, if dosing is within a reasonable range.

for sarcoidosis. However, a main concern with systemic immunosuppression is infection risk.

The association between sarcoidosis and infections is multifaceted. Inflammatory or fibrotic lung damage can lead to a reduction in barrier function with impaired airway clearance, and/or to cystic parenchymal lesions with morphological and physiological changes which favour infection. It is unclear if cardiac involvement in sarcoidosis is a risk factor for worse outcomes from respiratory infections, similar to what is observed when cardiac impairment is present due to other causes, but for a variety of reasons patients with cardiac sarcoidosis may be especially medically vulnerable. Conversely, infections have been implicated as a possible cause or trigger of sarcoidosis [3]. We begin with a brief update on this consideration, followed by a review of recent reports of infections and their impacts in patients with sarcoidosis. We conclude with a summary of how recent data align with and can inform treatment guidelines.

PATHOGENIC ROLE OF INFECTIOUS AGENTS IN SARCOIDOSIS

Due to considerable clinical and histological similarities, a link between infection and sarcoidosis has frequently been considered. Histologically, focal areas of fibrinoid necrosis are often seen in sarcoidosis tissue samples, but necrotizing granulomatous inflammation, especially if a dominant feature, should raise concern for an alternative diagnosis [4–6]. Similarly, features of organizing pneumonia and fibroblastic foci indicative of a 'wound healing response' should prompt an investigation for other causes of lung injury including infection and autoimmunity [6–8]. Within the past 2 decades, the identification of microbial DNA and proteins in tissue samples renews interest for a potential role for a microbial exposure (most frequently mycobacterial) as a risk factor for developing sarcoidosis [9], and this interest is bolstered by the observation that immunological responses to mycobacterial antigens are demonstrable in a significant subset of sarcoidosis patients [10].

However, many studies have failed to demonstrate the presence of viable organisms in sarcoidosis samples, and, conversely, latent infections are not commonly observed in the vast majority of sarcoidosis patients treated with immunosuppression medications. Consistent with these observations, a multicenter trial concluded that treatment with a 5-drug antimycobacterial regimen (concomitant levofloxacin, ethambutol, azithromycin, and rifabutin, or CLEAR) did not provide any clinical benefit to patients with pulmonary sarcoidosis, confirming that active infections are not a major contributing factor for what we identify as sarcoidosis [11]. Interestingly, the study did find in vitro responses to mycobacterial antigens were down-regulated after treatment with the antimycobacterial regimen, supporting growing concern that host-microbiome interactions can modify systemic immune responses [12].

The possible exception linking pathogens to sarcoidosis are studies from Japan demonstrating the isolation of *Cutibacterium* (nee *Propionibacterium*) species from sarcoidosis tissue samples. However, even in this example, it is necessary to reconcile what host factors lead to sarcoidosis given that *Cutibacterium* is a commensal organism, widely isolated from 'normal' tissues. Studies with human cells and experiments with animals demonstrate that extracts of Cutibacterium elicit both adaptive and innate responses that are exaggerated in sarcoidosis patients compared to controls [13], suggesting that microbial exposures are complex and deposit both antigen and innate ligands, providing a substrate capable of inducing sarcoidosis in a susceptible host. Interestingly, a European study found that Cutibacterium was present in other lung diseases, suggesting that microbial exposure could act as an immunostimulatory adjuvant that unmasks an underlying (yet undefined genetic) predisposition for these diseases [14].

In this context, although treatment with antibiotics might not provide a 'cure' for sarcoidosis, these studies provide a possible explanation for how an exposure to pathogens could deposit molecules that initiate and perpetuate both adaptive and innate responses that support the development of sarcoidosis. The fact that molecular evidence of a past microbial exposure (otherwise eradicated; histologically absent and culture-negative) is found in sarcoidosis tissues posits that additional studies are needed to determine whether impaired antigen clearance or repeated exposures influence outcomes in sarcoidosis.

INFECTION RISK IN PATIENTS WITH ESTABLISHED SARCOIDOSIS

In light of anergic findings, infection concerns in sarcoidosis were historically focused on opportunistic infections. Ultimately, immunity in sarcoidosis has not been found to be intrinsically impaired in ways which confer an elevated risk of infection, opportunistic or otherwise. As a result, the impacts of immunosuppression and organ damage on risks and outcomes of infection have become the more predominant concerns in recent years.

Two recent studies identified an approximately 2-fold higher risk of severe infections (defined by hospitalization requirement) in patients with (non-phenotyped) sarcoidosis compared to controls [15,16]. Moreover, the risk for recurrent severe infections in the sarcoidosis group was higher still [15]. In these studies a range of infections were observed. Whether patients with sarcoidosis have an underlying higher risk of becoming infected, have a lower tolerance of infection-related physiological alterations, or are more likely to get severely ill from infections was not assessed. To understand the risks associated with specific infections, the course and impact of several infectious diseases are explored below.

Fungal infections

Granulomas are often observed in tissue samples from sites of fungal infections. Case reports continue to be published on the finding of fungal infections in patients suspected of having sarcoidosis [17], and the consideration of sarcoidosis *versus* fungal infection is common during the initial evaluation of granulomatous inflammation. However, the consideration of sarcoidosis *and* fungal infection also becomes relevant for a subset of patients. While overall rates are low, patients with the high-risk phenotype of fibrocystic pulmonary sarcoidosis are substantially more vulnerable to develop chronic pulmonary aspergillosis (CPA), which portends a poor prognosis. In a recent case series of patients with sarcoidosis who developed CPA, 27% died within 5 years of follow-up [18]. However, death was most often the result of progressive impairments from underlying sarcoidosis (including pulmonary hypertension effects); haemoptysis and other direct effects of infection were less commonly the cause of death, and these complications may be increasingly better managed with utilization of interventional radiology and surgical manoeuvres.

Sarcoidosis also has been associated with an increased risk of cryptococcal infections, particularly cryptococcal meningitis. This association was recognized decades ago, yet it is not a condition of the past: ongoing case reports [19,20] serve as a reminder that infection needs to be assessed for and ruled out in all sarcoidosis presentations and may need to be considered again during the follow-up period, particularly if signs or symptoms are not readily attributed to underlying sarcoidosis.

Tuberculosis

In a recent report highlighting the potential co-existence of sarcoidosis and tuberculosis (TB), the majority of patients had emergence of clinical TB within a year of their sarcoidosis diagnosis [21]. This timeline suggests that the diagnosis of TB was initially mislabelled as sarcoidosis in at least some patients. In contrast, for patients with TB who were later diagnosed with sarcoidosis, the average time between diagnoses was several years, suggesting that (particularly for TB treated patients) sterile granulomatous inflammation due to sarcoidosis is a real phenomenon in at least a subset of patients. Thus, even in highly endemic TB areas, sarcoidosis exists and should be considered when comprehensive testing is negative for mycobacterial presence, particularly when clinical features are not compelling for TB. Indeed, a recent report highlighted the presence of sarcoidosis in South Africa, an area highly endemic for TB [22]. As diagnostic tools for TB continue to be developed [23] we anticipate the recognition of more cases of sarcoidosis in such areas, contributing to the notion that sarcoidosis is, truly, a global disease.

Coronavirus disease 2019

A report published during the height of the pandemic found higher rates of COVID-19 among patients with sarcoidosis compared to those with cancer [24]. Such rates are influenced by social contact dynamics which, during lockdown times, varied according to socio-economic status [25], and controlling for these factors is important in incidence studies for respiratory infections. Indeed, in a multisite community survey of patients with sarcoidosis, those who developed COVID-19 were substantially more likely (with an odds ratio of 27) to have contact with an infected roommate compared to patients not reporting an infection [26].

Several studies have evaluated the clinical course of COVID-19 in sarcoidosis. Of 7337 patients with COVID-19 and presenting to hospitals in the New York City region in the first year of the pandemic, outcomes (admission, intubation with mechanical ventilation, and mortality) were not worse for those with sarcoidosis after adjusting for a range of covariates [27]. However, in the sub-group

analysis, sarcoidosis patients with moderate to severe lung function impairment had higher rates of a severe outcome (death or need for mechanical ventilation) compared to those with more preserved lung function. The high mortality rate of 16% in the sarcoidosis group was influenced by the study design of limiting enrolment (only) to patients sick enough to present to hospital. Mortality rates were much lower in a larger study derived from the retrospective extraction of data from a clinical database. In that study, sarcoidosis was again not found to a be a risk factor for poor outcomes: rates of admission and intubation with mechanical ventilation among 954 patients with sarcoidosis and a coded diagnosis of COVID-19 were not significantly different, after propensity score matching, to those of COVID-19 patients without sarcoidosis [28▪].

While admission rates have been a proxy for severe infection in several recent studies [15,16,29], it is not clear that for COVID-19 hospital admission was equated with severe illness, at least early in the pandemic where thresholds for admission could have been influenced by the reported concern that patients with sarcoidosis may be at heightened risk of severe infection [30]. In two studies which specifically reported hospital admission rates for community dwelling patients who developed COVID-19, rates varied from 16% to 31%; in contrast, overall intensive care unit rates were similar at approximately 5% for each study [26,31].

Among studies assessing COVID-19 outcomes in patients with sarcoidosis, two did not assess the association of treatment status [27,28▪], while for two that did [26,31] outcomes were not worse for patients on immunosuppression, with the exception of rituximab use in one [26].

For outcomes studies which included data on smoking histories [32,33], smoking rates in sarcoidosis groups were not only higher than rates in control groups, but also were high (positive histories in up to 43% of patients) relative to the generally low rates of smoking observed in sarcoidosis cohorts [34]. Thus, while patients with a history of smoking generally comprise a minority of patients in sarcoidosis cohorts, they may be at particularly higher risk of poor outcomes from respiratory infections such as COVID-19. Rates of several comorbidities also were higher in the sarcoidosis groups, although there were discrepancies for specific diagnoses: diabetes, hypertension, and ischemic heart disease were higher in one [28▪] but not another study [27].

Several case reports / series have reported the occurrence of sarcoidosis discovered post-COVID-19 or following COVID-19 vaccination. Given the common observation of intense inflammatory side effects and non-specific peripheral adenopathy induced by COVID-19 vaccination in otherwise healthy individuals, more work is needed to understand how inflammatory events during COVID-19 may precipitate or accentuate sarcoidosis activity. We agree that caution is indicated in 'attributing the development of sarcoidosis to. . .severe acute respiratory syndrome-CoV-2' [35]: while the association may be causal in some cases, the overall risk of infection-induced sarcoidosis appears exceptionally low among the vast number of patients to date with a history of COVID-19, suggesting that multiple risk factors may be involved in the relatively few cases that develop.

Other respiratory viral infections

The epidemiology of respiratory viral infections in sarcoidosis is largely speculative or abstracted. Due to their ubiquitous, transient, and often (but not always) benign nature, these infections and their associated outcomes have not been systematically measured and analysed among patients with sarcoidosis. However, the SARCOVID study, which captured all respiratory viral events over a 3-year period, recently completed data collection with results expected in the near future [36].

CLINICAL MANAGEMENT: MINIMIZING THE BURDEN OF INFECTIONS IN PATIENTS WITH SARCOIDOSIS

Informed by the data reviewed above, recommendations for clinical management are provided and summarized in Table 1. Concern regarding immuno-suppression use became particularly pressing for many patients during the COVID-19 pandemic. It is a concern that we anticipate may endure, as a range of respiratory viruses continue to circulate and evolve. The recommendation to reduce treatment(s) to the lowest possible dose (or dosing interval) [30] is sage and applies broadly to all patients at all times. However, whether treatment regimens should be adjusted to possibly reduce respiratory viral infection risk in ways which, in turn, risk triggering recurrent sarcoidosis activity can be a difficult decision which is best informed by consideration of the nature of the infectious agent(s), the underlying phenotype of sarcoidosis and effects of recurrent activity, and other health factors which mediate infection risk.

Patient preference is critical in treatment decisions; clinical discussions benefit from and should lead with an active exploration of patient priorities and concerns. These discussions also should be informed by available data from sarcoidosis and auto-immune cohort studies which, while still

Table 1. Clinical management considerations for infections in patients with sarcoidosis.

Infectious condition	Factors which increase risk	Recommendations
Aspergillosis	Presence of fibrotic pulmonary sarcoidosis	Consider infection if subjective / objective lung function is declining Multidisciplinary care with infectious disease team While lung transplant options are limited with active infection, antifungal treatments can successfully eradicate disease in some patients
Other pulmonary fungal infections	Time spent in endemic areas	As patients have diverse geographic backgrounds, awareness of fungal disease features and diagnostic modalities are important in the work-up of possible sarcoidosis
Tuberculosis	Travel to / contact with travellers from TB endemic areas	A TB evaluation should be pursued when clinical features suggest super-imposed infection Sterile granulomas are not enough to rule out TB; a range of histopathological and clinical features help distinguish TB from sarcoidosis If any TB concern, close follow-up warranted in patients diagnosed (sometimes provisionally) with sarcoidosis; repeat biopsy may be needed if diagnosis remains unclear
COVID-19 and other respiratory infections	Lung impairment: moderate to severe impairment associated with worse COVID-19 outcomes	No clear data that sarcoidosis alone increases risk of severe disease in most patients High rates of comorbidities in sarcoidosis are risk factors for poor infection outcomes Targeting comorbidities (with recognition that sarcoidosis treatments may contribute to them) is an important yet under-emphasized element of clinical care Reducing immunosuppression in most cases for the purpose of reducing infection risk is not supported by the limited available data
Infections requiring hospitalization	Systemic corticosteroid use, especially for doses > 10 mg / day prednisone equivalent Poly-immunosuppression use	Avoid multiple immunosuppressive medications when possible

COVID-19, coronavirus disease 2019; TB, tuberculosis.

somewhat limited, do not indicate in aggregate that immuno-suppression is a risk for poor outcomes from *respiratory viral infections*. In contrast, immunosuppression use has been associated with increased risk of severe infections in general, with particular concern raised for patients on multiple immunosuppressive therapies [37]. We note that systemic corticosteroid dosing for sarcoidosis is recommended, in most cases, to not exceed a daily equivalent of 30 to 40 mg of prednisone [38,39]; while outcomes from viral infections for patients maintained within recommended dosing ranges have not been shown to be worse, this finding may not apply to patients managed with higher and potentially more dangerous dosing regimens.

As other considerations, whether the circulating lymphopenia commonly observed in patients with sarcoidosis represents a risk for reduced lymphocyte potency at sites of infection has not been determined and, in our assessment, is an important unknown that we hope is addressed by future research. Fortunately, sarcoidosis has not been identified as a high-risk condition for *Pneumocystis jiroveci* pneumonia [40] in spite of long-term systemic corticosteroid use in many patients; prophylactic antimicrobials to prevent pneumocystis (and herpes zoster) infections continue to be recommended, including in a recent review of pulmonary sarcoidosis [41].

The complexity of assessing the risk of immunosuppression for patients with sarcoidosis was addressed in a recent editorial [42]. Beyond systemic corticosteroids, a recent study evaluated infection risk associated with second and third-line treatments, finding no difference in rates of infection (specific types not emphasized) in patients with sarcoidosis treated with methotrexate versus azathioprine [43].

Finally, prophylactic vaccination is highly recommended for patients with sarcoidosis [44]. While sarcoidosis may not, overall, increase the risk of adverse outcomes from respiratory infections, the burden of super-imposed infectious events may be higher for patients with sarcoidosis who often have reduced physiologic reserve and/or quality of life impairments. The results of recent research highlight the importance of sleep quantity in contributing to vaccine efficacy for the COVID-19 vaccine,

with the evolving understanding that sleep acts as a 'natural adjuvant' to enhance short-term immune responses and long-term immune memory [45–48,49▪▪,50]. As patients with sarcoidosis have increased risk of impaired sleep [51,52] counselling patients on sleep practices during the pre and post vaccination weeks may be especially beneficial. While not as cutting edge as the development of novel therapeutics, the data supporting this recommendation are highly robust, and the inclusion of sleep counselling with vaccine planning is low-hanging, unpicked fruit.

CONCLUSION

Sarcoidosis alone is not correlated with worse outcomes from COVID-19. However, in addition to pulmonary impairment, comorbidity burdens and smoking status are associated with worse outcomes and should be considered in the clinical management of sarcoidosis aimed at maximal reduction of infection risk. Patients with sarcoidosis do appear to have a higher risk of (non-COVID-19) infections requiring hospital-level care compared to patients without sarcoidosis. Although overall rates of these severe infections are low, immunosuppression augments this risk. The impact of immunosuppression use in respiratory viral infections outcomes is less clear, and ongoing research which controls for underlying lung function and overall clinical status is needed to delineate the risks associated with treatment in sarcoidosis. Finally, the burden from non-COVID-19 viral infections, known to impair quality of life in their own right, warrant assessment in sarcoidosis: while most individual infections are not severe enough to require hospitalization, they are more frequent and often recurrent, and the cumulative toll may be substantial.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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