Sarcoidosis was first identified by English physician, Johnathan Hutchinson in 1877. More than a hundred years have passed, but it still remains an enigma. In India, the first case was reported by Ghosh and Chakraborty in 1956.[1] Sarcoidosis is a multi-systemic granulomatous disease that affects both sexes across all ages and races worldwide. The first international statement was published in 1999 by the American Thoracic Society, European Thoracic Society and World Association of Sarcoidosis and Other Granulomatous Diseases (AATS/ERS/WSOAG) jointly, which was later updated in 2014.[2] The recent guidelines published by ATS (2020) and ERS (2021) have further advanced our understanding of the disease but some questions still remain unanswered.[3-4] The aetiology is uncertain, diagnostic criteria are not standardised and dosing and duration of drugs remain to be researched and finalised. Sarcoidosis has a waxing and waning course with variable outcomes which makes the management even more challenging.

The recent evidence indicated that worldwide prevalence and mortality (2.4 times) associated with the disease is higher than previously reported figures.[3] The exact prevalence in India is not known. Previous studies from respiratory units of hospitals at Kolkata and Delhi reported annual sarcoidosis cases in the frequency of 10–12 per thousand and 61.2 per lakh new registrations, respectively.[1] In view of the lack of standardised criteria, the diagnosis of sarcoidosis is never fully secure. Furthermore, tuberculosis (TB) closely mimics sarcoidosis on epidemiological, clinical and radiological grounds. There is a high possibility of labelling a patient with sarcoidosis as tuberculosis, especially in TB endemic countries. Furthermore, sarcoidosis is a diagnosis of exclusion. It is imperative to rule out an exhaustive list of granulomatous diseases before labelling a patient as sarcoidosis posing a further challenge in resource-limited countries. All these factors may account for the under-reporting of sarcoidosis, especially in our country.

Traditionally, diagnosis has been based on three major criteria, which include compatible clinical presentation, non-caseating granulomas in one or more tissue samples and exclusion of other causes of granulomatous diseases.[3] Recently, ATS made 15 recommendations targeting diagnosis and detection of sarcoidosis based on available evidence. Out of 15 recommendations, only 1 is strong (SR), 13 are conditional (CR) and 1 is a best practice statement.[3] Clinical features have been arranged on the basis of high and low probability for sarcoidosis, and out of all, only Lofgren syndrome, lupus pernio and Heerfordt syndrome have been declared diagnostic. The choices for sampling techniques for extra-pulmonary involvement have been placed clearly too. Endo-bronchial ultrasonography (EBUS) is preferred over mediastinoscopy as an initial sampling procedure for thoracic lymphadenopathy. It is further advocated that sampling of hilar lymph nodes can be left to the physician’s discretion if the patient is asymptomatic. Magnetic resonance imaging is preferred over positron emission tomography/trans-thoracic echocardiography (TTE) to ascertain cardiac involvement and initial TTE followed by right heart catheterisation when pulmonary hypertension is suspected. It is strongly recommended to carry out baseline serum calcium testing in order to screen abnormal calcium metabolism. Conditional recommendations for baseline screening for the extra-pulmonary disease are as follows: ocular examination, serum creatinine, alkaline phosphatase, 25-hydroxy vitamin D and 1,25 di-hydroxy vitamin D levels, complete blood count and ECG. Blood urea nitrogen and serum transaminases estimation is not considered essential for screening of asymptomatic renal and hepatic sarcoidosis. More than 20% of patients with sarcoidosis develop new disease manifestations within 3 years of baseline evaluation. Therefore, annual estimation of serum calcium, creatinine and alkaline phosphatase levels is recommended to detect clinically silent cases. An exhaustive evaluation of ocular and cardiac sarcoidosis in asymptomatic patients has been abandoned as it is neither feasible nor practical.[3]

In 2021, the multi-disciplinary ERS task force developed eight clinical questions on PICO (Patients, Intervention, Comparison, Outcomes) format targeting treatment of sarcoidosis and made recommendations based on GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The committee reviewed treatment for pulmonary, cutaneous, cardiac and neurologic manifestations along with associated fatigue and small fibre neuropathy. No recommendations were made for other organ involvement including ocular sarcoidosis in view of the lack of sufficient evidence. The analysis was restricted to anti-inflammatory treatments. Glucocorticoids remained the first choice of treatment (starting with lowest possible dose) in pulmonary (SR), cutaneous (CR), cardiac (SR) and neurological (SR) involvement depending on the risk for death or organ failure and impairment of quality of life. In case of glucocorticoid toxicity, continued disease and/or relapse, other agents recommended are methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporine and infliximab. No specific conclusions were made regarding dosing, monitoring and duration of treatment for any form of
diagnosis. Fatigue is often under-reported and had been neglected all these years. It was proposed that pulmonary rehabilitation or inspiratory strengthening should be initiated in all sarcoidosis patients suffering from troublesome fatigue (CR). Furthermore, neuro-stimulants such as armodafanil (150 mg OD for 4 weeks followed by 250 mg OD for 4 weeks) and D-methylphenidate can be tried for 8 weeks if the problem persists (CR). No statements have been made on small fibre neuropathy because of a lack of evidence. Symptomatic treatment with pain killers (tramadol), gamma-aminobutyric acid analogues, anti-depressants and anti-convulsants (lamotrigine, carbamazepine) is suggested. The guidelines do not mention alternative potential treatment strategies like oxygen supplementation and organ transplantation. [4]

Newer guidelines are certainly a big leap forward but still far from perfection. Sarcoidosis continues to be a diagnostic challenge, and with pulmonary involvement being the most common presentation, the onus shifts on to pulmonologist. It is imperative that the clinician looks for multi-systemic involvement both initially and over time. Also, one should be aware that recurrence is common if treatment is withdrawn too soon. Formulating clear guidelines on dosing and duration of treatment is the need of the hour. Measurement of response to treatment needs to be standardised. Composite scores may be more effective than single endpoints. More randomised controlled trials are required in future to evaluate the role of immune-suppressants, anti-fibrotics (nintedanib, pirfenidone), rituximab, repository corticotropin injection, anti-tumour necrosis factor agents etc., and precisely compare treatment options in terms of efficacy, safety and cost-efficiency. The evolution of guidelines with future research areas has been summarised in Table 1.

An Indian perspective
As discussed above, TB mimics sarcoidosis and there is a high likelihood of confusing sarcoidosis for tuberculosis in sputum negative cases, especially in TB endemic countries like India. In a study by Kumar et al.,[9] 29.5% of patients had been misdiagnosed as TB and had a history of anti-tubercular treatment intake. Another study by Kashyap et al.[9] showed similar findings. Distinguishing sarcoidosis from TB is pertinent as corticosteroids, which is the mainstay therapy for sarcoidosis that can flare up TB with catastrophic consequences, including failure of national programmes intended for elimination of TB. According to the Global TB report 2020, India had already estimated 2.64 million cases in 2019, which accounts for 26% and 27% of the drug-sensitive and drug-resistant global burden, respectively.[7]

Moreover, there are ethnic and racial variations in clinical presentations. A review of the literature has shown that Indian patients have older age of onset with no gender predominance when compared to those from Japan, Europe and North America where bimodal age distribution is described with earlier onset in males. Radiologically, the most common finding on chest radiography (CXR) is Stage II involvement as opposed to Stage I in the Western population.[5,8] However, the latest study by Madan et al.[9] reported contradictory findings and its results corroborated with the Western studies. Atypical presentations of sarcoidosis are not so rare. In a study, necrotic lymph nodes were found on computed tomography of 5.9% of sarcoidosis patients resembling TB.[9] Likewise, different patterns of granulomas do not differentiate sarcoidosis from TB.[10] Also, the possibility of the coexistence of both diseases in the same patient cannot be ruled out given the close clinico-radiological resemblance between these two diseases. Miliary sarcoidosis, although rarely reported in sarcoidosis, was reported in 9.6% of patients in a study by Kumar et al.[9] Tuberculin skin test (TST) negativity has high specificity but poor sensitivity for TB. Cutaneous sarcoidosis in India is 10%; however, ACCESS study in the USA reported a higher prevalence of 15.9%. Lofgren and Heerfordt syndromes are considered diagnostic for TB with catastrophic consequences, including failure of anti-tubercular treatment intake. Another study by Kashyap et al.[9] showed similar findings. Distinguishing sarcoidosis from TB is pertinent as corticosteroids, which is the mainstay therapy for sarcoidosis that can flare up TB with catastrophic consequences, including failure of national programmes intended for elimination of TB. According to the Global TB report 2020, India had already estimated 2.64 million cases in 2019, which accounts for 26% and 27% of the drug-sensitive and drug-resistant global burden, respectively.[7]
sarcardiosis (ATS guidelines 2020) but these were not seen in any of the patients in a study in India and none had parotid involvement.

More studies are required to validate the findings with respect to racial and ethnic considerations. It is time to raise awareness regarding this disease through multi-disciplinary participation. Sarcardiosis registry should be maintained and difficult to treat cases should be discussed on national forums. With improved diagnostic techniques like EBUS and endoscopic ultrasound, the chances of confident diagnosis become high. National guidelines should be developed to cater to diagnostic and treatment concerns from an Indian perspective, which are likely to differ from American and European standards.

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