Title
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Journal
Annals of the American Thoracic Society, 14(Supplement_6)

ISSN
2329-6933

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Publication Date
2017-12-01

DOI
10.1513/annalsats.201707-564ot

Peer reviewed

Disease Burden and Variability in Sarcoidosis

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Abstract

Sarcoidosis is a systemic inflammatory disease with substantial morbidity and increasing mortality. As part of the National Heart, Lung, and Blood Institute's workshop to better understand this disease and improve the outcomes of patients with sarcoidosis, we reviewed the available data on health care burden and outcomes of this disease in the United States. Disparities in outcomes exist by race, ethnicity, sex, and socioeconomic groups, with African Americans having disproportionately more severe disease. Mortality rates are highest in African Americans, but may be increasing in white individuals. The health care burden of sarcoidosis is defined not only by its somatic manifestations, but is also greatly impacted by psychosocial, economic, and comorbid conditions associated with this disease. Fatigue, depression, cognitive dysfunction, treatment side effects, and pain syndromes are highly prevalent in this population and contribute to poor outcomes. The direct and indirect economic costs to patients and society are likely also substantial, although not well defined. We recommend leveraging existing and future technology and infrastructure to more accurately define and monitor the overall total sarcoidosis-attributable health care burden and patient outcomes in the United States.

Keywords: sarcoidosis; disease burden; variability

(Received in original form July 18, 2017; accepted in final form September 21, 2017)

Supported, in part, by National Institutes of Health/National Heart, Lung, and Blood Institute grants K23HL114640-01 (A.K.G.), U01HL112696 (L.L.K.), and K01HL088709 (Y.C.C.), and by National Cancer Institute grants R01 CA058420 and UM1 CA164974 (Y.C.C.).

Author Contributions: All authors participated in concept, design, drafting of the manuscript, and critical review of the manuscript. All authors read and approved the manuscript.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 14, Supplement 6, pp S421–S428, Dec 2017

DOI: 10.1513/AnnalsATS.201707-564OT
Internet address: www.atsjournals.org

The health care burden of sarcoidosis is multifactorial, although the exact magnitude has not been well quantified. It includes the somatic manifestations of the disease itself, as well as psychosocial and economic contributors (Figure 1), and affects a sizeable portion of the U.S. population. The disease causes significant morbidity, not only directly but also from its treatment. Sarcoidosis-related mortality appears to be increasing over time; it is likely that the overall health impact is also increasing (1).

It is problematic to reliably assess the influence sarcoidosis has on health and health care for several reasons. First, there is no single diagnostic test for sarcoidosis. Diagnosis relies on specific pathologic and radiographic features in the setting of a compatible clinical presentation and exclusion of alternative diagnoses. Because it can be challenging to establish a definitive diagnosis, estimations of incidence and prevalence of sarcoidosis are difficult (2). This problem is further confounded by frequent, prolonged delay from symptom onset until secure diagnosis (3). Second, the manifestations of sarcoidosis extend to all organs, resulting in difficulties in extracting sarcoidosis health care data from a variety of medical subspecialty sources. Third, several manifestations of sarcoidosis are not organ-specific; these include sarcoidosis-related fatigue and pain syndromes (4, 5), manifestations that are often disabling yet problematic to document (6). Fourth, corticosteroids are widely used for the treatment of sarcoidosis, but are associated with morbidity that significantly impacts health care utilization and quality of life (7, 8). Finally, the concentration of sarcoidosis in economically disadvantaged populations in the United States, for which reliable data are extremely limited, may create issues of inadequate access to medical care. Thus, it is

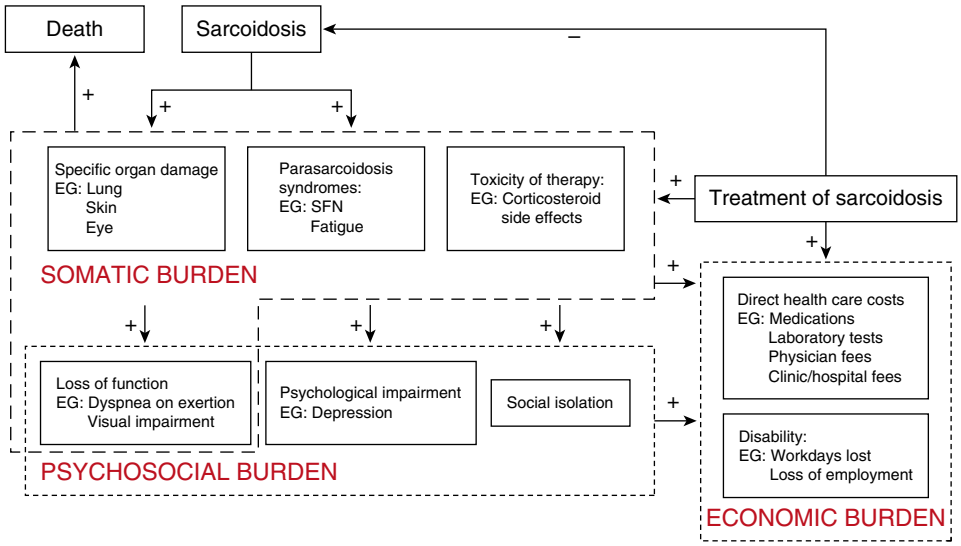

Figure 1. A conceptual framework of the health care burden of sarcoidosis and the integrated interaction of various components. *Arrows with a plus sign* indicate that these specific parameters augment the other parameters and outcomes. EG = for example; SFN = small-fiber neuropathy.

difficult to establish the full impact of sarcoidosis in terms of health care expenses and patient well-being.

As part of a larger National Heart, Lung, and Blood Institute (Bethesda, MD) workshop in August 2015, we reviewed available data on the health care burden of sarcoidosis in detail. We acknowledge that major knowledge and data gaps exist concerning this topic. Therefore, we not only describe the current, limited data and gaps in knowledge, but propose solutions to obtain this information in the future (Table 1). In the present era of acquisition and analysis of "big data," health care systems have been offered new tools to assess the human and economic costs of disease, improve efficiency, and optimize management. It is imperative that we leverage existing and future technologies and infrastructure to more accurately quantify and monitor the adverse health quality and cost implications of sarcoidosis, such that these data can be used to prioritize a research agenda and guide implementation of health care policies.

Epidemiology

Age, Sex, Race

Sarcoidosis occurs worldwide and affects men and women of all ages and races (9–13). The incidence of sarcoidosis varies by ethnicity and geography, with African American and Northern European white individuals having the highest rates (Table 2). Historically, sarcoidosis was thought to have a predilection for young adults, ranging from 30 to 50 years of age, with higher disease rates in both African American and white women (9, 12, 14). However, NHLBI-sponsored trials (ACCESS [A Case Control Etiologic Study of Sarcoidosis] and Nurses' Health Study) have demonstrated that a significant number of patients develop sarcoidosis after 50 years of age, consistent with previous observations that the incidence may be biphasic (10, 15–19). Similarly, a study within the Optum health care database in the United States reported that more than one-half of incident diagnoses were in patients over 55 years of age (9). Little is known about the phenotypic characteristics of older age groups; however, after accounting for comorbid conditions, the Black Women's Health Study indicated that sarcoidosis diagnosis was associated with a significantly higher mortality rate ratio for all age groups in U.S. African American women (20).

Disease patterns of sarcoidosis differ between white individuals and African Americans, with African Americans having a higher incidence than white individuals, presenting earlier in age, and being three times more likely to have familial disease (10, 11, 21, 22). Lifetime risk of sarcoidosis for the United States is estimated to be 2.4% for African Americans and 0.85% for white individuals (14). In addition, African Americans have more frequent treatment of lung disease, more organ involvement, and higher mortality rates than white individuals (23–25).

Mortality

Sarcoidosis can be a chronic, debilitating, and life-threatening disease (2, 25, 26). The age-adjusted (annual) rate of mortality due to sarcoidosis in U.S. death certificate data is 2.8 per million population for an underlying cause of sarcoidosis (27), and 4.32 per million for all causes of death among patients with sarcoidosis (1). Mortality is consistently highest in non-Hispanic African Americans, women, and those aged 55 years and older. The mortality rate ratio in African American women is estimated to be 2.44 for women with sarcoidosis compared with those without disease, with 25% of deaths directly attributed to sarcoidosis (28). Thus, the disease appears to be an important determinant of premature mortality.

Mortality in patients with sarcoidosis appears to be increasing over time, with the greatest absolute increase in death occurring among non-Hispanic African American women (1). In a separate study of death certificate data with sarcoidosis as the underlying cause, there was a statistically significant increase in the mortality rate in white individuals over the past decade (27), raising a question concerning whether the disease is changing.

Unresolved Issues

The impact of sarcoidosis on health care is likely underestimated. Large prospective cohorts (population-based and clinical) and disease registries that include environmental

Table 1. Sarcoidosis outcome domains: knowledge gaps and future directions

Epidemiology
Knowledge gaps ● Prevalence, incidence, and mortality of sarcoidosis in the general population and by specific phenotypes are not well understood, due to limitations of current studies, including varying case definitions, regional differences, and population sampling variability ● It is unclear whether mortality in sarcoidosis is changing over time ● Reasons contributing to racial and sex differences in sarcoidosis severity and outcomes are not well understood ● Emerging evidence indicates that sarcoidosis may be of higher prevalence and increasing morbidity in older patients, emphasizing the importance of the particular needs of sarcoidosis in the aging population
Future directions ● Establish larger prospective cohorts of all phenotypes; this can be accomplished by collaborative epidemiologic cohorts and registries ● Integrate large networks of health care electronic medical records systems to study the epidemiology of sarcoidosis ● Leverage existing epidemiologic cohorts to study sarcoidosis, such as the Black Women's Health Study (20), Nurses' Health Studies (17), and others ● Assess the contribution of disease complications, treatments, aging, and comorbid conditions to long-term morbidity and mortality in sarcoidosis
Somatic Burden
Knowledge gaps ● The impact of sarcoidosis on physical impairment, loss of function, and lost productivity is unknown ● Current objective measurements of pulmonary function and organ involvement do not correlate with dyspnea; the field lacks current quantifiable outcome measures for life impairment and symptoms ● Outcome measurements reflecting extrapulmonary organ-specific impairment are lacking ● Although becoming increasingly recognized, severe pain, cognitive dysfunction, and disabling fatigue syndromes ("parasarcoidosis") are not well understood mechanistically, and there are no current methods of quantifying these aspects ● Current outcome measures do not account for toxicity and comorbidity due to immunosuppressive therapy ● It is unclear whether treatment with immunosuppressives leads to improvements in how patients feel, function, or survive ● Frequency and types of testing (imaging, pulmonary function) used to quantify sarcoidosis severity and monitor the clinical care of patients with sarcoidosis are established by convention and expert opinion, rather than clinical studies
Future directions ● Establish validated outcome measures that accurately reflect patient-centered outcomes and impact of sarcoidosis on health care ● Establish organ-specific measures of dysfunction that accurately measure health and life impairment in patients with sarcoidosis ● Establish care algorithms for types and frequency of diagnostic tests and treatment that best reflect improved health and outcomes ● Interrogate "big data" sources, such as payer databases or large health care systems, to establish the overall impact of being diagnosed with sarcoidosis on "downstream" health care utilization
Economic Burden
Knowledge gaps ● The societal impact of sarcoidosis, due to lost productivity, stress, and disability, is likely high but not well documented ● The reasons for racial disparities in cost (both direct and indirect) are unclear ● Cost-effectiveness studies regarding diagnostic tests and treatments are sparse in sarcoidosis ● It is not known how monetary savings in direct costs will correlate with health and quality of life for patients with sarcoidosis
Future directions ● Establish systems to access new health care databases that will allow more accurate assessment of costs ● Consider integrating larger health care collaborations and e-health technologies that may set the stage for pragmatic clinical trials ● Assess patient-centered outcomes and how they relate to cost in order to define standards of care
Psychosocial Burden
Knowledge gaps ● Psychosocial well-being, including pain, depression, cognitive dysfunction, and fatigue, are not incorporated into current phenotyping ● There are few validated instruments to help quantify and assess change in psychosocial domains for patients with sarcoidosis
Future directions ● Study psychosocial disability within the phenotyping schema, including physical (deconditioning, disabilities) and neuropsychiatric health ● Develop and validate survey instruments that are relevant, short, easy to complete, and target appropriate components of psychosocial burden ● Analyze the effect of pain, fatigue, depression, and cognitive dysfunction on economic cost and health. Research that employs data extraction and analysis of electronic medical records could be one strategy to collect data related to these symptoms ● Develop therapeutic interventions, such as exercise therapies, for psychosocial comorbidity
Health Care Systems
Knowledge gaps ● The impact of geography, nationality, and varied health care systems on outcomes in sarcoidosis is currently not known
Future directions ● Analyze effects of the emerging U.S. health care system, as well as other global health care systems, on sarcoidosis outcomes in order to standardize efficient care practices ● Develop sound methodology to improve physician competence in the treatment of sarcoidosis

Table 2. Global incidence and prevalence of sarcoidosis: per 100,000 per year

Country/Study	Incidence (*per 100,000*)	Prevalence (*per 100,000*)
U.S. Optum Database (9)	7.6–8.4	59.0–60.1
African American	17.8	141.4
White	8.1	49.8
Hispanic	4.3	21.7
Asian	3.2	18.9
U.S. Black Women's Health Study Cohort (20)	71	2,000
Detroit, Michigan: 1990–1994 (14)	10.9	
White	35.5	
African American		
Franklin County, Ohio: 2010 (70)		48
Sweden (71)	24	64
Finland (72)	11.4	28.2
Norway (71)	14–15	27
U.S. Nurses' Health Study II (17)		
White	11	92
African American	43	519
Other	6	69
Hispanic	5	
Denmark (16)	7.2	
South Africa (73)	3.7	6
White	23.2	27
Black	11.6	17
Colored		
United Kingdom (74)	5	
London 1977–1978 (75)	19.8	
Black	16.8	
Asian	1.5	
White		
Rochester, Minnesota (76)	6.1	
Australia (77)	4.4–6.3	
Moravia and Silesia (78)	3.3–4.4	41.3–63.1
Greece (79)	1.07	5.89
Japan (18)	1.01	
Hokkaido, Japan (72)	1	3.7
Singapore (15)	0.56	
Spain (80)	0.42	
Israel (19)	0.2–2	

and behavioral risk factors are essential to examine exposures and risks before diagnosis, as well as phenotyping after diagnosis. Leveraging existing epidemiologic cohorts developed for other diseases may also be useful.

It remains unknown whether racial differences are due to genetics and/or socioeconomic/environmental factors. African Americans have higher granuloma density compared with other races despite similar stages of disease, suggesting that differing outcomes in African Americans may be reflective of increased predisposition for severe disease (29). African Americans are diagnosed approximately 10 years earlier than white individuals, due to earlier onset of symptoms, whereas race is not associated with longer time to diagnosis from onset of symptoms (24). Independently, socioeconomic status has been strongly associated with disease severity; therefore, race may be a confounding variable in this complex interaction: both must be taken into account in future studies (30). The question of whether treatment responses differ by race is also unknown.

Another question is whether mortality is truly increasing and why. Potentially, improvements in diagnosis may result in increased recognition of sarcoidosis, accounting for the higher incidence and increased attributed mortality (31). Comorbid illness may be associated with mortality in older age groups, and expanded use of (off-label) treatments (e.g., antirheumatic agents, antimetabolite immunosuppressants, biologics) in patients with sarcoidosis may contribute to lethal toxicities (26, 32, 33). Last, sarcoidosis has been associated with other diseases, such as cancer, pulmonary hypertension, and pulmonary embolism, which can contribute to mortality (27, 34–36). However, "cause of death" studies in the United States are limited to retrospective analyses, including autopsy studies, death certificates, and small cohorts. Larger prospective cohorts, studied by standardized approaches, will be necessary to establish the contribution of sarcoidosis to mortality in a more granular manner.

Somatic Burden

Sarcoidosis affects many aspects of health, including survival, daily function, and quality of life. In addition to possible increases in death rates from sarcoidosis, the degree of morbidity and impairment of quality of life is substantial (37). Another important feature that impacts health outcomes is that the age of affected individuals is young—mainly adults during their prime working and family years. There are few data on the effects of sarcoidosis on physical function, productivity, or effects on life roles.

Organ impairment in sarcoidosis, a possible surrogate for functional impairment, is poorly characterized. In one Japanese center, 9% of patients developed organ impairment sufficiently severe that assistance was required for activities of daily living (38). Disabling organ impairment tended to occur more quickly after sarcoidosis onset in those with neurologic, cardiac, or ocular disease than in those with pulmonary or hepatic sarcoidosis (38). Severe organ disease was more common when multiple organs were involved. Whether these data can be extrapolated to U.S. populations remains to be determined. The higher frequency of multiorgan involvement in African Americans may account for the clinical observation that somatic disease burden is greater in African Americans than in white individuals (39).

Dyspnea and low exercise tolerance are common symptoms in sarcoidosis (40). Causes include pulmonary restriction, obstruction, pulmonary vascular disease, myopathy, weight gain from steroids, and cardiac disease (41). Static lung function values, such as FVC, and chest radiographic stage correlate poorly with symptoms such as dyspnea (42, 43). Rather, markers of exercise capacity, including 6-minute-walk distance, have been shown to correlate with reduced physical function and quality of life (6). Six-minute-walk distance was reduced

in more than one-half of patients in one prospective sarcoidosis cohort, suggesting a high prevalence of functional limitation; distance walked correlated poorly with FVC (44). Furthermore, even in patients with modest impairment of pulmonary function, maximal oxygen consumption, a measure of functional capacity, may be impaired (39). The impact of pulmonary sarcoidosis on quality of life is likely comparable to that of other chronic diseases such as chronic obstructive pulmonary disease, acquired immune deficiency syndrome, and end-stage renal disease (42, 44–47).

There are limited data regarding the effect of sarcoidosis on other organ impairment. Ocular involvement is seen in 15–20% of patients with sarcoidosis and is associated with reduced long-term visual acuity in approximately one-half of those affected, and with bilateral legal blindness in 5% (48, 49). Cardiac sarcoidosis may lead to sudden cardiac death, heart failure, and/or persistent dysrhythmias in up to 65% of affected patients (50). Neurologic sarcoidosis (5–10% of sarcoidosis cases) is often nonresolving, with death or progressive neurologic impairment occurring in more than one-third of affected individuals (51). Other organ involvement, including liver, skin, bone, and muscle, may lead to bothersome symptoms or impaired organ function (52). However, other than mortality from cardiac disease, there are few data linking organ involvement to short- or long-term outcomes. Thus, there is a need for disease-specific outcome measures that closely relate to or reflect function or quality of life for each involved organ. The development of novel disease severity tools, or the adaptation of existing instruments to sarcoidosis (such as the Multiple Sclerosis Functional Composite Instrument for neurosarcoidosis), would be a substantial advance for sarcoidosis clinical research and to understand disease impairment.

Historically unrecognized consequences of sarcoidosis, termed the "sarcoidosis penumbra" or "parasarcoidosis," occur in more than one-half of patients if searched for carefully. These include fatigue (70–80%), small-fiber neuropathy (30%), and cognitive impairment (35%) (53–56). Sarcoidosis-associated fatigue may persist despite apparent resolution of sarcoidosis (57); its impact on quality of life is profound and is not related to response to treatment (58). Small-fiber neuropathy, characterized by loss of unmyelinated nerve fibers, leads to severe neuropathic pain and/or dysautonomia that may be disabling (59). Despite the high prevalence of these parasarcoidosis syndromes, there has been little research regarding their effect on quality of life, employment, family relationships, and avocations. A systematic assessment of how parasarcoidosis syndromes impact quality of life and function, and the interventions that are useful to treat these symptoms, is needed to more accurately assess the impact in terms of disability and medical costs.

Immunosuppressive therapy for sarcoidosis may also affect disease outcomes as a result of toxicities. Use of corticosteroids, after adjusting for baseline demographic variables and disease severity, has been associated with impairment of quality of life, regardless of sex, age, or ethnicity (42). Specifically, fatigue, daily activities, and satisfaction are lower in patients receiving higher cumulative corticosteroid doses (7). Although sarcoidosis therapy may improve metrics of lung function, the patient may feel worse, or in the extreme case, may die or lose organ function(s) because of treatment-related toxicities. Because current outcome measures fail to account for toxicity of therapy, future research should address whether treatments lead to improvements in how patients feel, function, and/or survive.

Going forward, the somatic burden of sarcoidosis could be explored by using claims data from large insurers, analyzing patterns of postdiagnosis medication use, comorbidity, and health care utilization. With the advent of accountable care organizations, such data may be captured and analyzed as health systems attempt to maximize efficiency. Using diagnostic testing and referral patterns as a means to "phenotype" patients could also help to determine outcomes related to economic and longer-term health concerns.

Economic Burden

Few published studies address the economic implications of sarcoidosis. With the highest prevalence reported in African American women, the cost impact may be most severe within this group (20). Furthermore, up to 25–40% of patients with sarcoidosis will have a chronic, protracted course requiring years of health care use, with highest costs involving inpatient care, office visits, and pharmacy (9).

Perceived economic effects of sarcoidosis vary by stakeholder: patients, caregivers, insurance companies, governmental organizations, and employers. Advanced imaging and steroid-sparing immunosuppressives have likely driven up direct costs. More than 80,000 patients were hospitalized in 2011, twice the admissions compared with 1998, although reasons for this increase are unclear. The primary payers for these hospitalizations were Medicare (foremost), followed by private insurance and Medicaid (60). Trends analyses confirm increased hospitalization rates in all age groups, both sexes, and all races, but the highest rate increases are in African Americans, elderly patients, and women (61). Corticosteroid treatment is associated with higher emergency department use, which may reflect a selection bias for more severe disease or side effects of corticosteroids (8).

Indirect costs include lost work capacity, income, productivity, and premature death. In the WISE (Worldwide Sarcoidosis Research) study, an international longitudinal registry of patients with sarcoidosis, 27% of 898 respondents reported a delay in seeking care due to cost, and 27% applied for disability (62). In addition, delayed diagnosis may contribute to increased health care costs. One-third of patients in the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study had more than 6 months of symptoms before diagnosis, and 25% waited more than 6 months from their first physician visit before diagnosis (3). In a Midwestern U.S. insurance cohort, patients incurred more antibiotics, corticosteroids, imaging tests, and doctor visits in the year before diagnosis compared with patients with asthma, chronic obstructive pulmonary disease, or pneumonia (63).

Future cost-effectiveness studies will be essential as diagnostic technologies and treatments improve and become more expensive. Cost-efficient care must correlate with quality and improved outcomes, both short and long term. "Optimal" outcomes may vary by stakeholder. The advent of larger, integrated health care systems and databases will allow improved quantification of economic costs, as well as methods to sustain cost improvements over time. Researchers must then bridge the gap between cost and patient outcomes to establish standardized care algorithms.

Psychosocial Burden

Psychologic/Psychiatric

Sarcoidosis is associated with psychological and psychiatric disorders. This relationship may be due to the fact that sarcoidosis, like most chronic diseases, is associated with long-term symptoms and disabilities. It is also possible that specific inflammatory mediators directly or indirectly induce psychological or psychiatric effects in the brain. Being diagnosed with sarcoidosis may also lead to social isolation because of physical limitations and lack of public knowledge of the disease, further impacting psychiatric and psychological domains.

Depression is frequently identified among both African American and white individuals with chronic sarcoidosis, with a prevalence of 23–66% depending on the cohort (42, 43, 64, 65). Predictors of depression include female sex, decreased access to medical care, and dyspnea (64). Depression is less frequent in patients with sarcoidosis with a new diagnosis (within 6 mo) than in patients with extended disease manifestations, suggesting that longer duration of illness increases the likelihood of developing depression (43, 64).

The severity of disease, as reflected by number of organs involved, has been associated with higher levels of anxiety and depression compared with disease involving fewer organs (66). In addition, comorbid diseases have a larger impact on depression than does specific organ involvement, with sleep apnea showing the largest consequence on both anxiety and depression (66). In other studies, dyspnea has the largest impact on depression (accounting for age, sex, organs, comorbidities), and reduced lung function has also been correlated with reduced quality of life (64, 67). Symptoms of fatigue are present in depressed patients, and depression is more common in patients with "all day fatigue" compared with milder forms (68). Depressed patients perceive more serious consequences of sarcoidosis than those who are not depressed (65). Future research should focus on whether targeted evaluation and treatment of depression leads to improved health and quality of life, including fatigue.

Cognitive Impairment

The impact of systemic sarcoidosis on cognitive function is increasingly documented, but not well understood. Patients with sarcoidosis have a higher frequency of cognitive failure than do control subjects (35 vs. 14.3%), and treatment with anti–tumor necrosis factor agents may be beneficial in improving cognition (an effect not observed for prednisone or methotrexate) (55). These data suggest that neurocognitive assessments and appropriate referrals should be an integral part of initial and follow-up sarcoidosis care. However, routine neuropsychological testing is time-consuming and expensive. Validated instruments for assessment of cognition have been utilized for multiple sclerosis and may be useful in the evaluation of sarcoidosis. The Multiple Sclerosis Neuropsychological Screening tool (69) administered to a University of California San Francisco sarcoidosis cohort showed that 28% were cognitively impaired compared with 7% of healthy control subjects (personal communication, L.L.K.). However, not all aspects of currently available instruments may be applicable for the evaluation of patients with sarcoidosis (e.g., aphasia). The future design of instruments should reflect clinically relevant aspects of sarcoidosis.

Perceptions Regarding Health Care Delivery and Burden of Sarcoidosis around the World

Health care systems involve a complex interplay of resources, organizations, and regulations among local communities, municipalities, provinces, states, and nations. These systems vary widely throughout the world, as does the effect they have on sarcoidosis care, management, and related costs. Defining the effect of varying global health care systems on the management of sarcoidosis may guide future implementation of successful health care delivery strategies in the United States. Smaller countries than the United States may be able to more easily establish sarcoidosis centers/institutes. Strategically placed, experienced sarcoidosis physicians could directly care for, or perform consultation services for, a majority of patients with sarcoidosis in a sizable portion of the country. Payment models other than fee-for-service may stimulate early referral of patients to established sarcoidosis centers in non-U.S. countries.

In contrast, although the United States may incur higher rates of health care utilization because of a comparatively higher prevalence of patients with more severe, chronic disease (9, 20), the United States possesses several potential advantages in providing outstanding care. First, because of the high prevalence in the United States, physicians may develop more familiarity and expertise than in countries where sarcoidosis is less common. Second, the United States and other modern nations also have economic advantages. Third, a high density of subspecialists and technologies in the United States allows for potential easy access for effective multidisciplinary care. Last, theoretically, the United States has telemedicine systems that may be able to overcome geographic issues of access to centers in proximity to patients.

A brief survey concerning sarcoidosis-related health systems was administered to sarcoidosis experts in the United States and internationally (*see* the online supplement). The survey was administered on the WASOG (World Association of Sarcoidosis and Other Granulomatous Disorders) website, as well as to all invited participants in this workshop. There were 86 responses, 30 from the United States and 56 from other countries, demonstrating that perceptions concerning several aspects of health care delivery are similar between the United States and other nations. Both U.S. and international experts believe that (*1*) less than one-half of patients with sarcoidosis receive care or are consulted by a sarcoidosis expert; (*2*) more than three-quarters of patients can obtain methotrexate, azathioprine, or an antimalarial drug if required; (*3*) less than one-half can obtain a biological drug such as a tumor necrosis factor antagonist if required; (*4*) one-half or less of the patients receive adequate care of their disease; and (*5*) most patients have access to an ophthalmologist, cardiologist, or another subspecialist for complex sarcoidosis issues. Surprisingly, 87% of U.S. sarcoidosis experts stated that there were established sarcoidosis institutes, centers of excellence, or specialty centers. Up until recently, there was no official designation of such centers in the United States. Thus, we interpreted the U.S. responses to reflect that most clinicians believe that they are functioning as, or have access to, experts in sarcoidosis. Of note, developing countries were underrepresented in this survey. In summary, the survey responses suggest that access to sarcoidosis-specific care exists, although there are no standardized

definitions of centers of excellence. However, a significant proportion of patients may not be utilizing these services, thereby impacting burden of disease.

Conclusion

The various components contributing to the burden of sarcoidosis in the United States would suggest the impact on patients and society is substantial. There is an urgent need for future studies to granularly quantify each type of burden, identify at-risk subgroups, and establish coordinated health care systems that mitigate these issues. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank their patients; study participants who have enrolled in sarcoidosis-related research studies; the many organizations that have supported the sarcoidosis community and its research mission; Drs. Jerry Eu, George Mensah, Lora Reineck, and Antonello Punturieri, and the National Heart, Lung, and Blood Institute; and other Institutes/Centers of the National Institutes of Health for the support of this workshop. The authors also thank the remainder of the workshop participants for thoughtful discussions that led to the development of these recommendations, and Megan Marchant for assistance with editing and formatting the manuscript.

References

1 Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, *et al*. Sarcoidosis-related mortality in the United States from 1988 to 2007. *Am J Respir Crit Care Med* 2011;183:1524–1530.
2 Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, *et al*. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders: statement on sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:149–173.
3 Judson MA, Thompson BW, Rabin DL, Steimel J, Knattereud GL, Lackland DT, *et al*.; ACCESS Research Group. The diagnostic pathway to sarcoidosis. *Chest* 2003;123:406–412.
4 Bakkers M, Faber CG, Drent M, Hermans MC, van Nes SI, *et al*. Pain and autonomic dysfunction in patients with sarcoidosis and small fibre neuropathy. *J Neurol* 2010;257:2086–2090.
5 de Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009; 15:499–506.
6 Drent M, Marcellis R, Lenssen A, De Vries J. Association between physical functions and quality of life in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31:117–128.
7 Judson MA, Chaudhry H, Louis A, Lee K, Yucel R. The effect of corticosteroids on quality of life in a sarcoidosis clinic: the results of a propensity analysis. *Respir Med* 2015;109:526–531.
8 Ligon CB, Judson MA. Impact of systemic corticosteroids on healthcare utilization in patients with sarcoidosis. *Am J Med Sci* 2011;341:196–201.
9 Baughman RP, Field S, Costabel U, Crystal RG, Culver DA, Drent M, *et al*. Sarcoidosis in America: analysis based on health care use. *Ann Am Thorac Soc* 2016;13:1244–1252.
10 Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, *et al*.; Case Control Etiologic Study of Sarcoidosis (ACCESS) Research Group. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164:1885–1889.
11 Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev* 1983;5:124–156.
12 Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336: 1224–1234.
13 Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, Iannuzzi MC. Epidemiology, demographics, and genetics of sarcoidosis. *Semin Respir Infect* 1998;13:166–173.
14 Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234–241.
15 Anantham D, Ong SJ, Chuah KL, Fook-Chong S, Hsu A, Eng P. Sarcoidosis in Singapore: epidemiology, clinical presentation and ethnic differences. *Respirology* 2007;12:355–360.
16 Byg KE, Milman N, Hansen S. Sarcoidosis in Denmark 1980–1994: a registry-based incidence study comprising 5536 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:46–52.
17 Dumas O, Abramovitz L, Wiley AS, Cozier YC, Camargo CA Jr. Epidemiology of sarcoidosis in a prospective cohort study of U.S. women. *Ann Am Thorac Soc* 2016;13:67–71.
18 Morimoto T, Azuma A, Abe S, Usuki J, Kudoh S, Sugisaki K, *et al*. Epidemiology of sarcoidosis in Japan. *Eur Respir J* 2008;31: 372–379.
19 Yigla M, Badarna-Abu-Ria N, Goralnik L, Rubin AH, Weiler-Ravell D. Sarcoidosis in residents of northern Israel of Arabic and Jewish origin: a comparative study. *Respirology* 2006;11:586–591.
20 Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg L. Sarcoidosis in black women in the United States: data from the Black Women's Health Study. *Chest* 2011;139:144–150.
21 Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, *et al*.; ACCESS Research Group. Familial aggregation of sarcoidosis: A Case–Control Etiologic Study of Sarcoidosis (ACCESS). *Am J Respir Crit Care Med* 2001;164: 2085–2091.
22 Rybicki BA, Kirkey KL, Major M, Maliarik MJ, Popovich J Jr, Chase GA, *et al*. Familial risk ratio of sarcoidosis in African-American sibs and parents. *Am J Epidemiol* 2001;153:188–193.
23 Gideon NM, Mannino DM. Sarcoidosis mortality in the United States 1979–1991: an analysis of multiple-cause mortality data. *Am J Med* 1996;100:423–427.
24 Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis* 2012; 29:119–127.
25 Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. *Chest* 2002;121:32–39.
26 Gerke AK. Morbidity and mortality in sarcoidosis. *Curr Opin Pulm Med* 2014;20:472–478.
27 Mirsaeidi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. *Chest* 2015;147:438–449.
28 Tukey MH, Berman JS, Boggs DA, White LF, Rosenberg L, Cozier YC. Mortality among African American women with sarcoidosis: data from the Black Women's Health Study. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30:128–133.
29 Burke RR, Stone CH, Havstad S, Rybicki BA. Racial differences in sarcoidosis granuloma density. *Lung* 2009;187:1–7.
30 Rabin DL, Richardson MS, Stein SR, Yeager H Jr. Sarcoidosis severity and socioeconomic status. *Eur Respir J* 2001;18:499–506.
31 Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, *et al*. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* 2015;131: 624–632.
32 Baughman RP, Lower EE. Fungal infections as a complication of therapy for sarcoidosis. *QJM* 2005;98:451–456.
33 Vorselaars AD, van Moorsel CH, Deneer VH, Grutters JC. Current therapy in sarcoidosis, the role of existing drugs and future medicine. *Inflamm Allergy Drug Targets* 2013;12:369–377.
34 Ji J, Shu X, Li X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalized sarcoidosis patients: a follow-up study in Sweden. *Ann Oncol* 2009;20:1121–1126.
35 Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. *Eur Respir J* 2005;25:783–788.

36 Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon JJ, Sprunger D, *et al*. Increased risk of pulmonary embolism among US decedents with sarcoidosis from 1988 to 2007. *Chest* 2011;140: 1261–1266.
37 Lazar CA, Culver DA. Treatment of sarcoidosis. *Semin Respir Crit Care Med* 2010;31:501–518.
38 Takada K, Ina Y, Noda M, Sato T, Yamamoto M, Morishita M. The clinical course and prognosis of patients with severe, moderate or mild sarcoidosis. *J Clin Epidemiol* 1993;46:359–366.
39 Baughman RP, Judson MA, Teirstein A, Yeager H, Rossman M, Knatterud GL, *et al*. Presenting characteristics as predictors of duration of treatment in sarcoidosis. *QJM* 2006;99:307–315.
40 Lopes AJ, de Menezes SL, Dias CM, de Oliveira JF, Mainenti MR, Guimarães FS. Comparison between cardiopulmonary exercise testing parameters and computed tomography findings in patients with thoracic sarcoidosis. *Lung* 2011;189:425–431.
41 Marcellis RG, Lenssen AF, Elfferich MD, De Vries J, Kassim S, Foerster K, *et al*. Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011;38:628–634.
42 Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. *Chest* 2004;125: 997–1004.
43 Yeager H, Rossman MD, Baughman RP, Teirstein AS, Judson MA, Rabin DL, *et al*.; ACCESS Research Group. Pulmonary and psychosocial findings at enrollment in the ACCESS study. *Sarcoidosis Vasc Diffuse Lung Dis* 2005;22:147–153.
44 Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007;132:207–213.
45 Bing EG, Hays RD, Jacobson LP, Chen B, Gange SJ, Kass NE, *et al*. Health-related quality of life among people with HIV disease: results from the Multicenter AIDS Cohort Study. *Qual Life Res* 2000;9:55–63.
46 Spencer S, Calverley PM, Sherwood Burge P, Jones PW; ISOLDE Study Group. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:122–128.
47 Tsuji-Hayashi Y, Sizer Fitts S, Takai I, Nakai S, Shinzato T, Miwa M, *et al*. Health-related quality of life among dialysis patients in Seattle and Aichi. *Am J Kidney Dis* 2001;37:987–996.
48 Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Prognosticators for visual outcome in sarcoid uveitis. *Ophthalmology* 1996;103:1846–1853.
49 Edelsten C, Pearson A, Joynes E, Stanford MR, Graham EM. The ocular and systemic prognosis of patients presenting with sarcoid uveitis. *Eye* (*Lond*) 1999;13:748–753.
50 Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. *Am Heart J* 2009;157:9–21.
51 Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. *Acta Neurol Scand* 1986;73:283–290.
52 Culver DA. Sarcoidosis. *Immunol Allergy Clin North Am* 2012;32: 487–511.
53 Bakkers M, Merkies IS, Lauria G, Devigili G, Penza P, Lombardi R, *et al*. Intraepidermal nerve fiber density and its application in sarcoidosis. *Neurology* 2009;73:1142–1148.
54 de Kleijn WP, Elfferich MD, De Vries J, Jonker GJ, Lower EE, Baughman RP, *et al*. Fatigue in sarcoidosis: American versus Dutch patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2009;26:92–97.
55 Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti–TNF-α treatment. *Respiration* 2010;80:212–219.
56 Hinz A, Fleischer M, Brähler E, Wirtz H, Bosse-Henck A. Fatigue in patients with sarcoidosis, compared with the general population. *Gen Hosp Psychiatry* 2011;33:462–468.
57 Korenromp IHE, Heijnen CJ, Vogels OJM, van den Bosch JMM, Grutters JC. Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. *Chest* 2011;140:441–447.
58 Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. *Chest* 2006; 130:989–994.
59 Tavee J, Culver D. Sarcoidosis and small-fiber neuropathy. *Curr Pain Headache Rep* 2011;15:201–206.
60 Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP): Overview of the National (Nationwide) Inpatient Sample (NIS). Rockville, MD: Agency for Healthcare Research and Quality; 1998–2011 [accessed 2015 Oct 15]. Available from: https://www.hcup-us.ahrq.gov/nisoverview.jsp.
61 Gerke AK, Yang M, Tang F, Cavanaugh JE, Polgreen PM. Increased hospitalizations among sarcoidosis patients from 1998 to 2008: a population-based cohort study. *BMC Pulm Med* 2012;12:19.
62 Gerke AKYM, Tang F, Cavanaugh JE, Polgreen PM. A web-based registry for patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2017;34:26–34.
63 Gerke AK, Tang F, Pendergast J, Cavanaugh JE, Polgreen PM. The high frequency of healthcare use in patients one year prior to a sarcoidosis diagnosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31: 256–261.
64 Chang B, Steimel J, Moller DR, Baughman RP, Judson MA, Yeager H Jr, *et al*. Depression in sarcoidosis. *Am J Respir Crit Care Med* 2001;163: 329–334.
65 Ireland J, Wilsher M. Perceptions and beliefs in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2010;27:36–42.
66 Hinz A, Brähler E, Möde R, Wirtz H, Bosse-Henck A. Anxiety and depression in sarcoidosis: the influence of age, gender, affected organs, concomitant diseases and dyspnea. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:139–146.
67 de Boer S, Kolbe J, Wilsher ML. The relationships among dyspnoea, health-related quality of life and psychological factors in sarcoidosis. *Respirology* 2014;19:1019–1024.
68 de Kleijn WP, Drent M, De Vries J. Nature of fatigue moderates depressive symptoms and anxiety in sarcoidosis. *Br J Health Psychol* 2013;18:439–452.
69 Benedict RH, Munschauer F, Linn R, Miller C, Murphy E, Foley F, *et al*. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Mult Scler* 2003;9:95–101.
70 Erdal BS, Clymer BD, Yildiz VO, Julian MW, Crouser ED. Unexpectedly high prevalence of sarcoidosis in a representative U.S. metropolitan population. *Respir Med* 2012;106:893–899.
71 Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950–1982: epidemiology and clinical picture. *Sarcoidosis* 1990;7: 50–57.
72 Pietinalho A, Hiraga Y, Hosoda Y, Löfroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan: a comparative epidemiological study. *Sarcoidosis* 1995;12:61–67.
73 Benatar SR. Sarcoidosis in South Africa: a comparative study in whites, blacks and coloureds. *S Afr Med J* 1977;52:602–606.
74 Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006;61:980–985.
75 Edmondstone WM, Wilson AG. Sarcoidosis in Caucasians, blacks and Asians in London. *Br J Dis Chest* 1985;79:27–36.
76 Henke CE, Henke G, Elveback LR, Beard CM, Ballard DJ, Kurland LT. The epidemiology of sarcoidosis in Rochester, Minnesota: a population-based study of incidence and survival. *Am J Epidemiol* 1986;123:840–845.
77 Gillman A, Steinfort C. Sarcoidosis in Australia. *Intern Med J* 2007;37: 356–359.
78 Kolek V. Epidemiological study on sarcoidosis in Moravia and Silesia. *Sarcoidosis* 1994;11:110–112.
79 Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopoulou A, *et al*.; Hellenic Interstitial Lung Diseases Group. Epidemiology of interstitial lung diseases in Greece. *Respir Med* 2009;103:1122–1129.
80 López-Campos JL, Rodríguez-Becerra E; Neumosur Task Group; Registry of Interstitial Lung Diseases. Incidence of interstitial lung diseases in the south of Spain 1998–2000: the RENIA study. *Eur J Epidemiol* 2004;19:155–161.