Review Article

Pediatric Rheumatic Diseases: A Systematic Review of the Saudi Population

Muhammad Helyel Alharbi[1*], Abdulaziz Muhammad Alrowais[1]
[1]Department of Pediatric Rheumatology, Prince Sultan Military Medical City, Saudi Arabia.

Abstract

One of the important methods of improving medical care is the population's awareness of common diseases, within their respective communities. This is also relevant in diseases where early management can prevent major morbidities and expected mortality. Major rheumatologic diseases are seen in higher prevalence in our region and for such a delicate population like pediatrics, proper knowledge about them is necessary to the child and adolescent well-being. We aim to present the latest information about the situation of the most common rheumatic diseases within the sociodemographic context of Saudi Arabia, along with the latest updates in management. PubMed database was used for article selection and the following keys were used in the mesh ("[epidemiology] and [pathophysiology] and [clinical features] and [diagnosis] and [management]) including the selected diseases. Rheumatological diseases pose significant clinical challenges not only to the patients and community but also to physicians due to a variety of possible clinical presentations. Moreover, these diseases cause a major load on the medical staff, community, and financial aspect, with their morbidity and even mortality. Thus, having a clear idea about these diseases is vital for all clinicians to spread awareness to the patients and thus, the community since some of them can even be preventable. However, our local awareness, understanding, and even prevalence of these diseases in Saudi Arabia still needs many studies to establish a clear idea about the society and not just based on a few studies.

Keywords: Saudi Arabia, Systemic lupus erythematosus, Juvenile idiopathic arthritis, Kawasaki disease, Rheumatic fever

Introduction

Generally, one of the most important disregarded aspects of medical care is the general population's awareness of diseases, especially in our community in Saudi Arabia [1]. This important factor is vital to seek the correct medical care, and choose the appropriate setting for the patient (primary health care unit or hospital) which is more significant in vulnerable populations like children. Moreover, the early diagnosis and treatment of these diseases usually prevent major complications and thus is an integral part to lessen these consequences on the community and help these patients. This is more impeccable in the vulnerable pediatric population and in rheumatological diseases which are usually a huge clinical challenge to diagnose for clinicians [1, 2]. Thus, in this paper, we will be discussing some of the most important rheumatologic diseases with the highest prevalence, morbidity, mortality rates seen in Saudi Arabia and the world, focusing on their diagnosis, management, and prevention if possible.

Materials and Methods

The PubMed database was used for article selection, papers were obtained and reviewed. This database was used for article selection, and the following key terms, epidemiology, pathophysiology, clinical features, diagnosis, and management. Regarding the inclusion criteria, the articles were selected based on the inclusion of one of the following topics, epidemiology, diagnosis, management, complications, and prevention. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Results and Discussion

Unfortunately, studies assessing public knowledge about rheumatologic diseases are scarce in Saudi Arabia and the Middle East region, so we included the common diseases in clinical practice as relevant to the aforementioned population. We will be reviewing the most common diseases seen in clinical practice through our experience and the relevant literature.

Systemic Lupus Erythematosus (SLE)

Address for correspondence: Muhammad Helyel Alharbi, Department of Pediatric Rheumatology, Prince Sultan Military Medical City, Saudi.
ca-baha@hotmail.com

How to cite this article: Alharbi MH, Alrowais AM. Pediatric Rheumatic Diseases: A Systematic Review of the Saudi Population. Arch Pharm Pract. 2023;14(S):A06231535.

Systemic lupus erythematosus is the first disease we gonna discuss, it is a chronic autoimmune disease that is systemic with diverse clinical symptoms and manifestations. Due to this fact, it is difficult for some physicians to suspect such diseases and connect what looks like random complaints. Thus, SLE remains one of the most underdiagnosed diseases in clinical practice. Generally, there is a notable difference in the epidemiological numbers worldwide between different age, gender, and ethnic groups [2, 3]. As a result, classification and diagnostic criteria were developed and they became a vital tool when approaching such cases. Unfortunately, managing these diseases is not any simpler, usually, it involves complex treatment modalities and enough experience and knowledge to apply them in the clinic [4].

In terms of epidemiology in our community, some studies done recently showed in general a point prevalence of 19.28 cases per 100,000 people which is comparable to some other regions in Europe (Denmark has a 21.7 per 100,000), however, it is not reported as common as places with higher diagnosis rates (some regions in the US report as high as 372 per 100,000). This can be a result of genetic factors in our community being less likely to develop the diseases or can be attributed to the low suspicion and diagnosis in medical settings. Moreover, this condition is reported more in females in terms of gender, and Asians and Hispanics in terms of ethnicity in comparison with Caucasians. In addition, some studies reported high prevalence in African and Native Americans with high mortality rates, thus in our region numbers can vary mainly due to lack of sufficient studies [1-4].

Generally, the SLE pathogenesis pathway is not fully understood and is still thought to involve complex factors and processes. Multiple studies have shown overwhelming evidence regarding the role of genetic factors in the development of this disease among other autoimmune disorders. SLE was estimated to occur in around 5.87% with first-degree relative history, however, high heritability rates were seen (up to 43.9%) [5-7]. Moreover, multiple environmental factors have been linked with potential association with SLE pathogenicity exogenously and indigenously. Some of the exogenous factors to this disease included; pesticides, solvents, UV radiation, and certain drugs that also induced SLE in rare cases. On the other hand, intrinsic factors such as a patient's reproductive history (especially in females) and latent infections such as Epstein-Barr virus infection have been suggested to have links as well. The effect of these environmental factors has been shown to lead to the activation of self-reactive lymphocytes and certain innate immune cells [7, 8].

The course, severity, and progression of systemic lupus erythematosus are dependent upon systemic involvement. Skin, musculoskeletal, cardiac, hematologic, renal, reproductive, and neuropsychiatric systems are typically among them [9-11]. As a result, the clinical signs of SLE vary greatly and its course remains uncertain. To diagnose these patients, early clinical and laboratory evaluation must be performed as soon as the disease is suspected and compared against diagnostic criteria **(Table 1)**. Three organizations developed diagnosis criteria used by clinicians, and they are the American College of Rheumatology (ACR), the Systemic Lupus International Collaborating Clinics (SLICC), and the European League Against Rheumatism (ACR/EULAR). While SLICC classification criteria produced superior results in terms of patient specificity in 2012, ACR classification criteria performed better in terms of sensitivity than specificity. However, in 2017, a new classification with a specificity of up to 97% and a sensitivity of 96 to 98% was given as a result of collaborative efforts between ACR and EULAR (called EULAR/ACR criteria) [12, 13].

Thus, in 2019, EULAR/ACR was adapted as a new classification criterion. This criterion added non-infectious fever as a new point in the assessment of early stages of SLE and ANA antinuclear antibodies which are crucial criteria. Additionally, it made identifying and diagnosing the SLE based on a points system with 10 points sufficient to diagnose; however, reaching 6 points is significant to maintain EULAR classification. ACR classification depends on detecting 4 out of the 11 ACR criteria. On th other hand, SLICC structured their criteria mainly on histological findings compatible with lupus nephritis and anti-dsDNA or high ANA titers or any 4 out of the 17 features (and must have one immunological criterion at least) [11, 13, 14].

Table 1. Diagnosis of SLE in three classifications Involving SLICC, ACR, and new EULAR/ACR 2019 Criteria [11, 12, 14]

Systems	SLICC	ACR	EULAR/ACR2019
Skin	-- Subacute or acute cutaneous lupus - Chronic cutaneous lupus - Oral and nasal ulcers - Non-scarring alopecia	- Malar(Butterfly) facial rash - Discoid rash - Oral and nasal ulcers - Photosensitivity	--Acute cutaneous lupus (6 points) -Subacute lupus (4 points) -Discoid lupus (4 points) - Non-scarring alopecia (2 points) - oral and nasal ulcers (2 points)
Immunologic	--ANA Positive results, antiphospholipid antibodies or anti-	--ANA Positive results	-ANA (entry criterion) - low complements: C3 OR C4 (3 points) C3 AND C4 (4 points)

	Sm, anti-dsDNA, low complement (C3, C4, CH50), - direct Coombs test (Hemolytic anemia)	-Elevated antiphospholipid antibodies or anti-Sm, anti-dsDNA	-antiphospholipid (2 points) -Anti-dsDNA and Anti-Sm (6 points) - Coombs+ hemolytic anemia (4 points)
Musculoskeletal	Synovitis in 2 or more joints(effusion or swelling)morning stiffness for 30 minutes	Arthritis in 2 or more joints	Arthritis (6 points)
Renal	Urinary Creatinine >500mg or red cell casts/24 hours	Persistent proteinuria or red cell cast	- Persistent proteinuria or red cell cast - Proteinuria (4 points) -Lupus nephritis Classes: II/V (8 points) III/IV (10 points)
Hematologic	Leukopenia <4000 cell/mm^3more than once or lymphopenia <1500cell/mm^3 Hemolytic anemia, Thrombocytopenia< 100,000 cells/mm^3	Leukopenia <4000 cell/mm^3 and lymphopenia <1500cell/mm^3 Hemolytic anemia, Thrombocytopenia< 100,000 cells/mm^3	-Leukopenia (3 points) - Hemolytic anemia, Thrombocytopenia< 100,000 cells/mm^3 (4 points)
Neuropsychiatric	.Mononeuritis complex, psychosis Seizures, cranial or peripheral neuropathy, myelitis	Psychosis or seizures	-Delirium (2 points) -Psychosis (3 points) -Seizures (5 points)
Cardiopulmonary	,Serositis (involves pleurisy pericardial and pleural effusion and (pericarditis	Pleurisy and pericarditis	-Effusion (5 points) -Pericarditis (6 points)

Unfortunately, diagnosis of SLE does not only rely upon achieving these classification criteria alone but rather depends on the physician's approach to an SLE patient and his clinical sense [10, 12].

In general, early detection of SLE complications and any co-morbidities are the cornerstone of management. The approach to this disease involves many modalities of treatment that often require a team from different specialties to manage these cases. The general management depends on the severity of the case, and if there has been any improvement or no response to medications. As a first line, hydroxychloroquine or chloroquine is usually started with steroidal anti-inflammatory drugs and/or glucocorticoids given as well if indicated. In patients who are not responding well to treatment, it is recommended to start them on azathioprine, mycophenolate mofetil, or methotrexate this is also applicable if we cannot reduce the dose of glucocorticoids to less than 7.5 mg in the long run. In cases with positive SLE autoantibody, with high activity of the diseases despite the treatment, the clinician shall introduce belimumab as an adjacent therapy. The management of severe organ involvement SLE is more aggressive with an induction and maintenance (after response to the induction therapy) phase. Hydroxychloroquine is still used in these cases, moreover, induction therapy is a combination of glucocorticoids with one of the following; cyclophosphamide (IV and low dose), azathioprine, and mycophenolate mofetil. Maintenance therapy is a low dose of glucocorticoids with either azathioprine or mycophenolate mofetil. In refractory cases or when the medications are contraindicated, considerations to treat with calcineurin inhibitors (tacrolimus, cyclosporine A), and Rituximab are to be taken [13-15].

As a clinician, patients with SLE and/or their guardians must receive intense educational guidance and supportive sessions to understand the nature of this disease and the treatment plan. Changing lifestyle is important in these cases to avoid future complications, and these can start with simple regular exercising, sunscreens, and a balanced diet. Moreover, these patients must be aware of the drugs that they should avoid, and ascertain to them that they can only take medications after a clinician's approval. Moreover, we must educate patients' guardians about the possible long-term cardiovascular and renal complications, the importance of regular follow-up, and possible opportunistic infections (e.g. pneumonia) [11, 12, 15].

SLE comorbidities are associated highly with many modifiable life-threatening risks, especially in patients with cardiovascular and renal involvement. About 50% of patients present with renal injury known as Lupus nephritis. In elderly individuals, and 15% of patients overall, they present with homocysteinemia, along with lupus nephritis, which are considered risk factors for myocardial infarction and thrombosis in patients with lupus [11, 15].

Rheumatic Fever

Overall, cardiovascular diseases are the main cause of premature death worldwide, thus diseases with such complications are to be taken more seriously. Rheumatic heart disease is one of the most diagnosed reasons for such patients in our pediatric population. This is more relevant in our community since the highest reported cases of mortality

are in middle and low-income countries. Globally, around 250,000 deaths per year are due to RHD with a total of 15 million reported cases around the world and around 282,000 new patients yearly [16]. Unfortunately, it is considered an endemic disease in Saudi Arabia with studies reporting a sum of 3.1 cases per 1000 people. This is even with the lack of a high number of studies about epidemiology, but still, all are indicating that the Saudi rate of cases is higher than the global one. Another unique aspect of the disease is that even though females are less likely to have a recurring attack, they are more likely to get acute rheumatic fever [17, 18]. Due to the relapsing nature of RF a lot of cases are reported to be relapse cases, studies in Saudi Arabia showed that up to 32% of cases are relapsing ones. Moreover, the aspect of chronicity of this disease and causing long-term morbidity and mortality risk is still considerable for this population. HEARTS registry reported more than RHD patients developed acute heart failure, among other valvular issues which are even more common, mostly affecting the mitral valve [16, 18].

As a disease, it has only been around 150 years since an association between sore throat and heart disease has been established. This disease is a sequelae of infection by group A Streptococcus pyogenes which usually starts as a throat infection, then resulting in valvular damage. Moreover, it can still affect the skin, and the focal sensory system, but this disease is almost a preventable one. Rheumatic coronary illness (RHD) is the most widely recognized cardiovascular sickness overall in those under 25 years old and it is believed to be a late sequela of gathering a streptococcal disease of the throat, the rheumatic fever (RF) influences the focal sensory system, skin, and heart. RF nearly is a preventive sickness [19, 20].

The pathophysiology behind this disease is believed to mainly involve certain reactions between the M protein found in Group A β-hemolytic streptococcal (GAS -mainly streptococcus pyogenes-) and the cardiac myosin and laminin, and the main characteristic pathological finding is aschoff knob. Unfortunately, these parts can be scattered in all layers of the heart (Myocardium, Epicardium, and Endocardium) and all of them might get affected [19].

One of the most challenging aspects of this disease is diagnosing it. This is because this disease is mainly a clinical one and the known Jones criteria developed in 1944 had a lot of issues and the clinicians were stuck in either under or over-diagnosing cases. This also can be attributed to the lack of any specific laboratory or definite clinical findings in these patients. Multiple revisions by the American Heart Association (AHA) were done both in 1992 and 2015 trying to create a balance in the diagnosis approach. In the latest update, cases were subdivided into two main categories depending on the risk stratification (Low, and moderate to high risk). This division is based on the incidence of the disease in the area. Generally, a country/community with incidence of less than 2 per 100,000 in a year or with chronic rheumatic carditis cases less than one in a thousand in a year is considered as a low risk. Moderate to high risk, are children (aged 4 to 15 years) living in a population with 2 cases or more of RF per 100,000 in a year or when chronic rheumatic carditis is seen in more than one case in a thousand per year. Unfortunately, Saudi Arabia is considered a moderate to high-risk area [20, 21].

Moreover, subclinical carditis has been added to the criteria, and monoarthritis was added as a musculoskeletal feature. Nevertheless, the core five diagnostic criteria (carditis, arthritis, chorea, erythema marginatum, and subcutaneous nodules) were kept and considered major. Subsequently, minor criteria are there and include clinical features (arthralgia, hyperpyrexia) and laboratory/ECG findings (high erythrocyte sedimentation rate (ESR), high C reactive protein (CRP), and prolonged PR interval). The diagnosis is made when two major or one major and two minor criteria are met with evidence of a recent GAS infection. This infection can be proven with either a positive throat culture or a positive rapid group A streptococcal carbohydrate antigen test. Regarding throat culture, multiple anti-streptolysin O titer (ASO) readings trending up are preferred when deciding that a culture is positive rather than a single titer result. There are multiple differences in the two main populations of the diagnosis (low and moderate to high risk) when categorizing our patients based on all aspects of diagnoses highlighted in the table below **(table 2)**. These new changes lead to an international increase in diagnosed cases, especially in moderate and high-risk areas [21, 22].

Table 2. Rheumatic Fever Diagnosis Criteria [20-22]

Major Criteria in Low-Risk Population	-Major Criteria in Moderate to high-risk Population
Carditis (subclinical or clinical)	Carditis (subclinical or clinical)
polyarthritis	Polyarthritis + polyarthralgia, and/or monoarthritis
Chorea	Chorea
Erythema Marginatum	Erythema Marginatum
Subcutaneous Nodule	Subcutaneous Nodule
Minor Criteria in Low-Risk Population	**Minor Criteria in Moderate- to high-risk Population**
Polyarthralgia	Polyarthralgia
Prolonged PR interval (only (if there is no carditis	Prolonged PR interval (only if there is (no carditis
Fever (More than or equal to 38.0 °C)	Fever (More than or equal to 38.5 °C)
Elevation of ESR (equal to or more than 60 mm in the 1st	Elevation of ESR (equal to or more than 30 mm in the 1st hour and/or CRP equal to or more than 3 mg/dL)

hour and/or CRP equal to or more than 3 mg/dL)

Regarding these symptoms, the most common clinically seen symptom globally is carditis, followed by arthritis. Chorea is mostly seen in females (ranging from 10 to 30% of cases) the other two (subcutaneous nodules and erythema marginatum) are rare but highly specific to RF. However, in Saudi Arabia, a 2009 study reported that arthritis is more commonly seen in RF patients, and high ESR was mostly seen from the minor criteria followed by fever. One important aspect of diagnosis is the new recommendation of using echocardiography with Doppler when assessing for carditis. This is due to its high sensitivity and better in assessing any valvular issues and can be repeated when uncertain. Subclinical carditis is diagnosed through this when there are positive valvitis findings (either mitral or aortic) with no murmur or other clinical signs. Carditis is diagnosed when there is either mitral or aortic valve regurgitation or with pan systolic or pan diastolic murmurs respectively [21-23].

Treating cases of acute rheumatic fever revolves around two goals, eliminating the bacterial (GAS) infection via antibiotics, and treating the existing clinical signs (carditis, arthritis, and chorea). The drug of choice when treating bacterial pharyngitis in these cases is oral phenoxymethylpenicillin (known as penicillin V). In children weighing less than 27 kg, the dosage is 250mg twice or three times a day for 10 days and it is 500mg twice or three times a day in children weighing more than 27 kg. Amoxicillin can be used orally for 10 days as well, given as a 50mg per kg maximum dosage of 1000 mg every 8 hours. If the patient is hospitalized benzylpenicillin (known as penicillin G) can be used and is administered intramuscularly as a single dose, 600,000 IU when weighing less than 27 kg or younger than 6 years, and 1.2 MIU when older than 6 years or weighing more than 27 kg. The American Heart Association guidelines recommend starting penicillin as soon as possible to prevent the progression of rheumatic fever up till the ninth day of onset. If the patient is allergic to penicillin, multiple options are there, preferably a narrow-spectrum cephalosporin can be started orally for 10 days (e.g. cefadroxil or cefalexin). Another option in cases with immediate-type hypersensitivity macrolides can be started which can be clarithromycin (twice a day, 15 mg per kg in a day -maximum 250 mg per dose-), clindamycin (three times a day, 20 mg per kg in a day -maximum 1800 mg per dose-) orally for ten days, or azithromycin (once a day, 12 mg per kg in a day -maximum 500 mg per day-) for 5 days. However, clinicians should keep in mind that resistance is common in GAS infections with some studies reporting resistance rates up to 46% (against tetracyclines) [24, 25].

Regarding clinical symptoms, treating them individually is the preferred approach. Aspirin however is unique and can be started in both arthritis and mild carditis in a dose of 100 mg per kg a day for 2 to 3 weeks, when the patient improves the dose is tapered down between 60 and 70 mg per kg a day. If the patient cannot tolerate aspirin, then naproxen shall be in a dose between 10 to 20 mg per kg in a day divided into two doses. In arthritis, nonsteroidal anti-inflammatory drugs can be used. In moderate or severe cases of carditis, oral prednisone is used with a dose of 2mg per kg in a day with a maximum of 80 mg but shall be tapered down over the next two to four weeks lowering it every three days by 2.5 to 5mg. Moreover, an aspirin dosage of 50 to 75 mg per kg in a day shall be taken simultaneously and continued for 3 months. In mild chorea, usually, a sedative is given (diazepam or phenobarbitone). If there is no improvement then haloperidol or valproic acid is administered for 3 months or 2 to 4 weeks if there is clinical improvement, however, clinical shall be aware of possible extrapyramidal syndrome when using haloperidol (especially at high doses) and replace it with valproic acid [25, 26].

Luckily, this disease is preventable in multiple ways (primordial, primary, and secondary). Thus, prevention especially in its acute phase is important and ranges from simply improving the community living conditions by sanitation, to providing antibiotics for pharyngitis caused by streptococci. due to the transmission of this bacteria usually via close contact (of patients), raising public knowledge about not ignoring sore throat when affected. Moreover, advising seeking medical attention, awareness about transmission, and management among the general population is crucial. Nevertheless, controlling all modifiable risk factors will help control the incidence of this disease. Secondary prevention can be achieved by continuous antibiotic therapy when trying to eliminate recurrence chances in diagnosed patients. This is important because relapsing episodes usually cause a worsening of cardiac condition. Prophylaxis can be achieved by giving penicillin G intramuscularly once every 28 days or 21 days in high-risk cases in similar doses to treatment ones. Alternatively, penicillin V can be given as an oral medication (250 mg twice a day). The duration of prophylaxis ranges from 5 years minimum to lifetime depending on recurrence status and cardiac complications [24, 25, 27].

In Saudi Arabia, a study is showing a decrease in the total new hospital admissions due to acute rheumatic fever lately, but another study is reporting an increase in recurrence due to poor compliance with prophylaxis medications. Unfortunately, multiple studies are showing a low level of awareness, knowledge, and understanding of RF in the population, which would have been an ideal solution for managing and preventing this disease [17, 18].

Kawasaki Disease

Lastly, Kawasaki disease (KD) is one of the rheumatological diseases that is multi-systemic and can be an acute febrile illness, usually present in the pediatric population. The most affected age group is between six months to five years, and it is very rare to affect children older than nine years old (<1%). The incidence of Kawasaki is abundant throughout the globe,

but the incidence ranges between 9 and 20 per 100,000, with some geographical areas having higher prevalence. The highest prevalence of this disease is seen in Japan and Asian countries, moreover, males have a higher risk compared to females (1.5 to 1). In Saudi Arabia, multiple studies reported an incidence rate of 7.4 cases per 100,000 children (below the age of five), nevertheless, a definitive overall incidence is not available due to the lack of studies and bigger data samples [28-30].

This disease was thought of as one of the mucocutaneous-ocular syndrome subtypes, however, in 1967, Dr. Tomisaku Kawasaki first reported the unique presentations in fifty cases. Afterward, this disease was named after him to this day. Multiple etiologies have been suggested to cause the inflammatory reaction seen in KD from infections to autoimmune factors, nevertheless, the definitive factor remains unknown. However, multiple recent studies have shown that certain individuals are at higher risk simply due to their genetic susceptibility. The pathophysiology of this disease revolves around inflammation of the medium-sized muscular arteries. There are multiple findings in KD pathologically, where there is a T cell activation by an antigen, also there have been recorded high levels of IL-17 in these patients. Antigen activation has been important with concurrent infections seen in many patients raising the possibility of having a part in etiology. This has been studied in immunohistochemistry analyses that showed infiltration of IgA cells with cytoplasmic antigen in macrophages, and bronchial and vascular endothelial cells [31, 32].

Diagnosis is clinically done with fever which is persistent for more than five days as the central criteria. In addition, there needs to be at least four of the following criteria; bilateral conjunctivitis (non-purulent) sparing the limbus, oropharyngeal mucosal changes (e.g. cracked red lips), diffuse erythematous oropharynx or strawberry-like tongue, swelling and erythema of the extremities, nonspecific generalized rash, and unilateral cervical lymphadenopathy. Nevertheless, we have incomplete Kawasaki cases which are more seen in a third of patients and mostly older children and that is when there are less than four criteria but with high clinical suspicion and more than five days of persistent fever. This suspicion can be based on some atypical findings of Kawasaki, these include; erythema, oral mucosa involvement and/or lips, extremity changes (usually as an edema with erythema of soles and palms which desquamate in 2 to 3 weeks and seen in subacute phase). Due to these facts, incomplete cases present a difficult challenge to clinicians and they are usually diagnosed late which increases possible side effects. Echocardiography is important and yields some findings that can help in diagnosis and recognizing any complications and shall be done in these patients [33, 34].

Regarding treatment, generally, cases are resolved in an average of 12 days with no treatment, however, complications may still occur. Similar to RHD, cardiac complications are the most feared ones, with coronary artery aneurysm as the most concerning one. Moreover, coronary artery lesions (CALs) can occur as sequelae as well and may lead to myocardial infarction and death. Another rare but significant complication is Kawasaki disease shock syndrome (KDSS), and seen when patients develop either hypotension (with a 20% decrease in systolic pressure) or any signs of hypoperfusion. These cases have a higher risk of developing further cardiovascular complications and usually very high inflammatory markers are found. Treatment of KDDS is oriented around immunomodulatory and immunosuppressive agents, mainly Intravenous immunoglobulin (IVIG) [35, 36]. Its mechanism of action is controversial, but recent studies suggest that the anti-inflammatory effect of IVIG is mediated by the up-regulation of T-regulatory cells and the downregulation of Th17 signaling pathways. IVIG was able to shorten the duration of the disease and prevent coronary artery aneurysm. Therefore, early detection and treatment of KD are crucial to achieve the best outcomes. The American Heart Association (AHA) recommends starting IVIG treatment within 10 days of disease onset, ideally within seven days. If diagnosis is delayed beyond 10 days, treatment should only be started with fever or aneurysms with laboratory evidence of active inflammation present. In several patients and even at late presentation, there was still a persistent fever and evidence of early coronary artery changes (detected by echocardiography) [37, 38]. Patients with KDSS have an even greater risk of developing dilatation of the coronary arteries. Unfortunately, cases that develop neurological manifestations usually have a higher resistance to IVIG treatment. and thus requiring an extra dosage of IVIG. In patients showing resistance to IVIG, corticosteroids may be an adequate replacement or used in combination with it, especially in poor prognosis. Pulse therapy is usually initiated (with high doses) which can change the size of the coronary artery aneurysm. Another medicine that has been suggested if cases are still resistant is tumor necrotic factors (e.g. infliximab), nevertheless, these cases have very bad prognosis. Aspirin has a role in KD cases with its anti-inflammatory effect in suppression of fever (with high doses), and as an antiplatelet till the patient recovers from CAL [38-41].

Conclusion

The rheumatological disease poses big clinical difficulties not only for the patients and community but also for physicians due to a variety of possible clinical presentations. Moreover, these diseases cause a major load on the medical staff, community, and financial aspect, with their morbidity and even mortality. These can be avoided or at least delayed in many cases when an early diagnosis is made, raising the importance of early referrals to rheumatologists and seeking their consultations in such vague cases. Thus, having a clear idea about these diseases is vital for all clinicians in order to spread awareness to the patients and thus community since some of them can even be preventable. Management of cases is still a topic with many updates and many breakthroughs can

be achieved in the near future. However, our local awareness, understanding, and even prevalence of these diseases in Saudi Arabia still need many studies to establish a clear idea about the society and not just based on a few small studies.

ACKNOWLEDGMENTS: None
CONFLICT OF INTEREST: None
FINANCIAL SUPPORT: None
ETHICS STATEMENT: None

References

1. Al-Arfaj AS, Al-Balla SR, Al-Dalaan AN, Al-Saleh SS, Bahabri SA, Mousa MM, et al. Prevalence of systemic lupus erythematosus in central Saudi Arabia. Saudi Med J. 2002;23(1):87-9.
2. Alballa SR. Systemic lupus erythematosus in Saudi patients. Clin Rheumatol. 1995;14(3):342-6.
3. Al Nahdi MS, Al Mohaya S, Al Fadel Saleh M, Al Awamy BH, Abdulrahman IS. Clinical presentation of systemic lupus erythematosus in Saudi patients. Trop Geogr Med. 1987;39(2):187-90.
4. Hochberg MC. The epidemiology of systemic lupus erythematosus. In: Wallace DI, Hahn BH, editors. Dubois' Lupus Erythematosus. 5th ed. Baltimore (MD): Williams & Wilkins; 1997: p. 49-65.
5. Almaghlouth IA, Hassen LM, Alahmari HS, Bedaiwi A, Albarrak R, Daghestani M, et al. National systemic lupus erythematosus prospective cohort in Saudi Arabia: A study protocol. Medicine (Baltimore). 2021;100(30):e26704.
6. Haikel KAB, Tulaihi BA. Awareness of Systemic Lupus Erythematosus among Primary Health Care Patients in Riyadh, Saudi Arabia. Open Access Maced J Med Sci. 2018;6(12):2386-92. doi:10.3889/oamjms.2018.370
7. Smith EMD, Lythgoe H, Midgley A, Beresford MW, Hedrich CM. Juvenile-onset systemic lupus erythematosus: Update on clinical presentation, pathophysiology and treatment options. Clin Immunol. 2019;209:108274. doi:10.1016/j.clim.2019.108274
8. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71(9):1400-12.
9. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021;80(1):14-25.
10. Oglesby A, Korves C, Laliberté F, Dennis G, Rao S, Suthoff ED, et al. Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. Appl Health Econ Health Policy. 2014;12(2):179-90.
11. Aringer M, Petri M. New classification criteria for systemic lupus erythematosus. Curr Opin Rheumatol. 2020;32(6):590-6. doi:10.1097/BOR.0000000000000740
12. Feng X, Zou Y, Pan W, Wang X, Wu M, Zhang M, et al. Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. Lupus. 2014;23(3):327-34.
13. Ma M, Hui-Yuen JS, Cerise JE, Iqbal S, Eberhard BA. Validation of the 2019 European League Against Rheumatism/American College of Rheumatology Criteria Compared to the 1997 American College of Rheumatology Criteria and the 2012 Systemic Lupus International Collaborating Clinics Criteria in Pediatric Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2020;72(11):1597-601.
14. Kuhn A, Bonsmann G, Anders HJ, Herzer P, Tenbrock K, Schneider M. The Diagnosis and Treatment of Systemic Lupus Erythematosus. Dtsch Arztebl Int. 2015;112(25):423-32. doi:10.3238/arztebl.2015.0423
15. Trindade VC, Carneiro-Sampaio M, Bonfa E, Silva CA. An Update on the Management of Childhood-Onset Systemic Lupus Erythematosus. Paediatr Drugs. 2021;23(4):331-47. doi:10.1007/s40272-021-00457-z
16. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017;377(8):713-22. doi:10.1056/NEJMoa1603693
17. Abdul-Mohsen MF, Lardhi AA. A dramatic decline in university hospital admissions of acute rheumatic fever in the eastern region of Saudi Arabia. J Saudi Heart Assoc. 2011;23(2):87-91.
18. Alqanatish J, Alfadhel A, Albelali A, Alqahtani D. Acute rheumatic fever diagnosis and management: Review of the global implications of the new revised diagnostic criteria with a focus on Saudi Arabia. J Saudi Heart Assoc. 2019;31(4):273-81. doi:10.1016/j.jsha.2019.07.002
19. Palafox B, Mocumbi AO, Kumar RK, Ali SKM, Kennedy E, Haileamlak A, et al. The WHF Roadmap for Reducing CV Morbidity and Mortality Through Prevention and Control of RHD. Glob Heart. 2017;12(1):47-62.
20. Dougherty S, Khorsandi M, Herbst P. Rheumatic heart disease screening: Current concepts and challenges. Ann Pediatr Cardiol. 2017;10(1):39-49.
21. Dougherty S, Okello E, Mwangi J, Kumar RK. Rheumatic Heart Disease: JACC Focus Seminar 2/4. J Am Coll Cardiol. 2023;81(1):81-94. doi:10.1016/j.jacc.2022.09.050
22. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016;2:15084.
23. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015;131(20):1806-18.
24. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, et al. Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries: Two-Year Follow-Up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). Circulation. 2016;134(19):1456-66.
25. Ralph AP, Noonan S, Wade V, Currie BJ. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Med J Aust. 2021;214(5):220-7. doi:10.5694/mja2.50851
26. Liu M, Lu L, Sun R, Zheng Y, Zhang P. Rheumatic Heart Disease: Causes, Symptoms, and Treatments. Cell Biochem Biophys. 2015;72(3):861-3. doi:10.1007/s12013-015-0552-5
27. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet. 2012;379(9819):953-64. doi:10.1016/S0140-6736(11)61171-9
28. Nakamura Y. Kawasaki disease: epidemiology and the lessons from it. Int J Rheum Dis. 2018;21(1):16-19. doi:10.1111/1756-185X.13211
29. Busaleh F, AlKadhem SM, Albarrak A, Almubarak AA, Aldandan MM, Almajed JM, et al. Kawasaki Disease Shock Syndrome in the Eastern Region of Saudi Arabia: Case Series. Cureus. 2021;13(5):e14961. doi:10.7759/cureus.14961
30. Al-Harbi KM. Kawasaki disease in Western Saudi Arabia. Saudi Med J. 2010;31(11):1217-20.
31. Rife E, Gedalia A. Kawasaki Disease: an Update. Curr Rheumatol Rep. 2020;22(10):75. doi:10.1007/s11926-020-00941-4
32. Seki M, Minami T. Kawasaki Disease: Pathology, Risks, and Management. Vasc Health Risk Manag. 2022;18:407-16. doi:10.2147/VHRM.S291762
33. Saguil A, Fargo M, Grogan S. Diagnosis and management of kawasaki disease. Am Fam Physician. 2015;91(6):365-71.
34. Fukazawa R, Kobayashi J, Ayusawa M, Hamada H, Miura M, Mitani Y, et al. JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease. Circ J. 2020;84(8):1348-407. doi:10.1253/circj.CJ-19-1094
35. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. Expert Rev Clin Immunol. 2017;13(3):247-58. doi:10.1080/1744666X.2017.1232165
36. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Muñoz-Ramírez M, Garrido-García M, et al. Kawasaki disease shock syndrome: Unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60(9):781-90. doi:10.1111/ped.13614
37. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, Treatment, and Long-Term Management

of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017;135(17):e927-99. doi:10.1161/CIR.0000000000000484

38. Lo MS, Newburger JW. Role of intravenous immunoglobulin in the treatment of Kawasaki disease. Int J Rheum Dis. 2018;21(1):64-9. doi:10.1111/1756-185X.13220
39. Chang LS, Kuo HC. The role of corticosteroids in the treatment of Kawasaki disease. Expert Rev Anti Infect Ther. 2020;18(2):155-64. doi:10.1080/14787210.2020.1713752
40. Marchesi A, Tarissi de Jacobis I, Rigante D, Rimini A, Malorni W, et al. Kawasaki disease: guidelines of the Italian Society of Pediatrics, part I - definition, epidemiology, etiopathogenesis, clinical expression and management of the acute phase. Ital J Pediatr. 2018;44(1):102. doi:10.1186/s13052-018-0536-3
41. Rashid AK, Kamal SM, Ashrafuzzaman M, Mustafa KG. Kawasaki disease and its treatment - an update. Curr Rheumatol Rev. 2014;10(2):109-16. doi:10.2174/1573397111666150120144457