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SYMPOSIUM ON PEDIATRIC RHEUMATOLOGY-II

Approach to a Patient with Connective Tissue Disease

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Abstract Connective tissue disease (CTDs), though rare in childhood, are an important cause of morbidity. Most of them involve multiple organ systems and are associated with presence of autoantibodies. Systemic lupus eryethematosus (SLE) is the most common CTD, the others being Juvenile dermatomyositis, systemic sclerosis, mixed connective disease and Sjogren syndrome. The clinical presentation of CTD in childhood can range from an acute severe illness mimicking a serious infection, to an insidious onset of disease with gradual accumulation of symptoms and signs over wks to months. The presence of multi-system involvement, evidence of inflammation and lack of any obvious cause should alert a clinician to the possibility of CTD. Diagnosis is usually clinical and features like malar rash, Raynaud's phenomenon, Gottron's rash, photosensitivity, oral ulcers suggest a possibility of CTD. Presence of autoantibodies like anti-nuclear antibodies, anti-dsDNA etc. provide supportive evidence to a diagnosis of CTD. Most CTDs are treated with immunosuppressive drugs with good success. Early recognition and prompt treatment results in excellent outcome

Keywords Autoantibodies · Autoimmune diseases · Connective tissue disease · Systemic lupus erythematosus

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Introduction

Connective tissue disorders (CTDs) are defined as a group of acquired diseases resulting from persistent immune mediated inflammation. In most CTDs there is immune dysregulation resulting in generation of autoreactive T cells or autoantibodies. Autoantibodies/autoreactive T cells can attack any organ of the body, resulting in a wide array of signs and symptoms. Early diagnosis and treatment is paramount in reducing morbidity and mortality. As CTDs can be life-threatening though rarely, it is imperative that pediatricians should have a high index of suspicion in a child presenting with multisystem diseases [1].

The classic autoimmune CTDs include systemic lupus erythematosus (SLE), juvenile dermatomyositis/polymyositis (JDM/PM), systemic sclerosis (SSc), Sjögren's syndrome (SS), undifferentiated CTD (UTCD) and overlap syndromes e.g. mixed CTD (MCTD). Most clinicians do not include systemic necrotising vasculitides e.g. polyarteritis nodosa (PAN), Churg-Strauss syndrome (CSS) and Wegener's granulomatosis (WG) in the category CTD.

The clinical presentation of CTD in childhood can range from an acute severe illness mimicking a serious infection, to an insidious onset of disease with gradual accumulation of symptoms and signs over wks to months. Many of the early symptoms can be non-specific such as unexplained fever, fatigue or loss of appetite. One should suspect CTD when a child has a multi system disease with no apparent cause. Other clinical features that suggest CTD include prolonged fever, oral ulcers, Raynaud's phenomenon, skin rash (malar rash, Heliotrope rash, nodules), photosensitivity, alopecia, pleuropericarditis, glomerulonephritis, arthritis, unexplained abdominal pain, muscle weakness, sicca symptoms (dry eyes and dry mouth). Constitutional symptoms

such as fever, anorexia, muscle ache, fatigue and weight loss are present in the majority of patients with CTDs.

Systemic Lupus Erythematosus (SLE)

The classic presentation is that of a female, usually in the second decade who is unwell, with fever, arthralgia or arthritis and may have an erythematosus butterfly rash extending over the cheeks and bridge of the nose (Fig. 1). However, classic features occur in only 1/3rd at presentation and the rest may present with central nervous system (CNS), renal dysfunction, serositis and hematological features as well as systemic symptoms.

The diagnosis of SLE rests on a combination of clinical and laboratory features. The revised American College of Rheumatology (ACR) [2] classification criteria (Table 1) are commonly used by rheumatologists to classify SLE, but are also helpful in diagnosis. If a patient has at least 4 of the 11 criteria at one time or over period of observation, then the patient is likely to have SLE. These criteria have a sensitivity of 96% and specificity of 100%.

SLE is a disease that has a varied presentation with possible involvement of every organ system. The three early features are fatigue, fever and arthralgias. Malar rash (Fig. 1), characteristic of SLE, is seen only in 30% of children at presentation, and in 70% during the course of the illness. It is unexplained multisystem involvement that alerts an astute clinician to a diagnosis of SLE. Other organ system involvement include:

> **Hematological system:** Thrombocytopenia, Auto immune hemolytic anemia, Leucopenia, lymphopenia; **Renal disease:** Nephrotic syndrome, Acute nephritis, Hypertension; **Central nervous system involvement:** Seizures, Psychosis, Stroke, Organic brain syndrome, Chorea

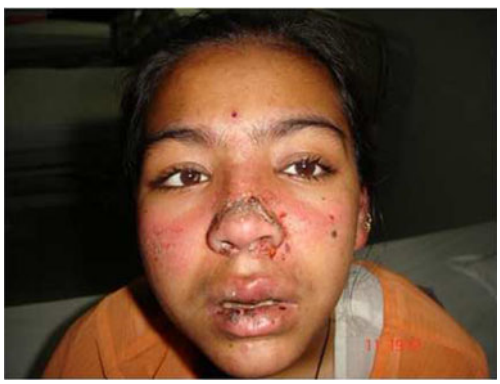

Fig. 1 Malar rash and ulcers on the lips in a child with SLE

Table 1 ACR criteria for classification of systemic lupus erythematosus

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Mouth ulcers.
5. Arthritis
6. Serositis (pleuritis or pericarditis)
7. Renal disorder (proteinuria or urine sediment abnormalities)
8. Neurological disorder (seizures or psychosis)
9. Hematologic disorder (anemia, leukopenia or lymphopenia on two or more occasions, thrombocytopenia)
10. Abnormal ANA titer
11. Immunologic disorder (Positive finding of antiphospholipid based on: IgG or IgM anti-cardiolipin antibodies or Lupus anti-coagulant, abnormal anti-dsDNA or anti-Sm values)

> **Lung disease:** Pleural effusion or acute/chronic pneumonitis; **Cardiovascular system:** Pericarditis, myocarditis, Libman Sacks endocarditis; **Mucocutaneous disease:** Photosensitivity, malar rash, alopecia, oral and nasal ulcers; **Gastro-intestinal involvement:** GI vasculitis, sterile peritonitis; **Musculoskeletal**: Arthritis, arthralgia, myalgia, inflammatory myositis.

The important differential diagnosis to be considered are infections (bacterial and viral), malignancy, vasculitis and chronic granulomatous diseases like sarcoid and auto-inflammatory syndrome.

The facial rash of parvovirus B19 infection can appear similar to the malar rash of SLE, and arthritis can also be seen in these patients [3]. Epstein–Barr virus can present with a broad range of findings including fevers, rash, arthritis, elevated liver enzymes and hematologic abnormalities. Patients with fever, low blood counts and lymphadenopathy need exclusion of malignancy as cause. Differentiation of pediatric SLE from other pediatric rheumatic diseases, such as systemic onset juvenile idiopathic arthritis (SoJIA) or vasculitis is helped by presence of leucocytosis and thrombocytosis in the later two conditions. The differential diagnosis of a child or adolescent presenting with acute nephritis, and/or renal insufficiency, should include post-streptococcal glomerulonephritis, antineutrophil cytoplasmic antibody (ANCA)-positive vasculitides, pauci-immune glomerulonephritis as well as SLE. Medications most commonly implicated in drug-induced SLE in children include several of the anti-convulsants (e.g. phenytoin and cabamazepine), isoniazid and minocycline [4].

Juvenile Dermatomyositis

Juvenile dermatomyositis as the name suggests primarily affects the skin and muscles. The age of onset has two peaks, between 5 and 9 yrs and between 11 and 14 yrs, with a predominance of females [5].Heliotrope rash on the eyelids, Gottrons papules on the knuckles (Fig. 2) and proximal muscle weakness are the classical features of JDM. The muscle weakness mainly affects the shoulder and pelvic girdle muscles but can involve neck, respiratory and pharyngeal muscles. Children with JDM can have vasculitic ulcers on extensor surfaces and gastrointestinal vasculitis. Rarely, children can present with inflammatory myositis without skin involvement the so called polymyositis.

According to the Bohan and Peter criteria [5] (Table 2), a diagnosis is considered definite if a patient has at least three criteria plus the typical rash for dermatomyositis and four criteria for polymyositis. The diagnosis is considered probable if the patient has two criteria plus the typical rash for dermatomyositis and three for polymyositis. The diagnosis is considered possible if fewer criteria are present. These criteria are likely to be replaced since the use of MRI where available has made diagnosis possible without the use of muscle biopsy or EMG studies.

Scleroderma

The most characteristic feature of scleroderma is thickening of the skin due to increased collagen deposition. Scleroderma can be divided into two main categories: localized scleroderma (morphea) in which there is skin sclerosis but usually no vascular or internal organ involvement, and juvenile systemic sclerosis, in which there is diffuse skin sclerosis along with internal organ involvement.

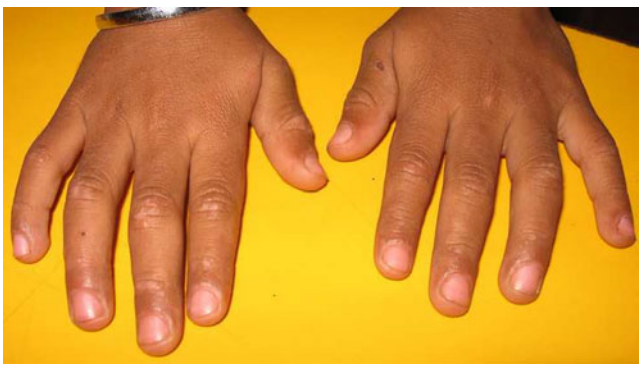

Fig. 2 Gottron's papules in a child with JDM

Juvenile Localized Scleroderma

Juvenile localized scleroderma mainly involves localised areas of skin with few autoantibodies. It has been shown to be associated with extra-cutaneous manifestations in up to 20% of patients. Juvenile localized scleroderma can be divided into five general types: plaque morphea, generalized morphea, bullous morphea, linear scleroderma, and deep morphea. Linear scleroderma is a form commonly seen in children where there is a longitudinal band of skin thickness leading to contractures. It progresses slowly and may involve one or two limbs [6].

Juvenile Systemic Sclerosis (JSSc)

Juvenile systemic sclerosis is extremely rare in children. It typically starts with Raynaud's phenomenon. It is more common in females. Skin involvement presents as skin thickening, hidebound skin, hyperpigmentation, contractures due to skin thickening. Later, the skin shows thinning of the skin and hypopigmentation. The other symptoms include, heartburn, malabsorption, pulmonary fibrosis, pulmonary arterial hypertension and arthritis.

A set of provisional criteria has been developed recently out of a consensus meeting of the Classification Committee for Systemic Sclerosis, a collaborative committee of the American College of Rheumatology and the Pediatric Rheumatology European Society [7]. (Table 3).The classification criteria showed sensitivity of 90% and specificity of 96%. It was considered that specificity should be given priority over sensitivity to limit over-diagnosis of the condition in children.

Sjogren's Syndrome

Sjogren's syndrome is probably the rarest CTDs in childhood. The usual symptoms include dry mouth (difficulty in eating dry food and speech) and dry eyes besides systemic features. It is usually primary, but can also be secondary to other CTDs. The diagnosis is based on objective evidence of dry eyes, dry mouth, presence of autoantibodies (ANA, anti-SSA or anti-SSB antibodies) or evidence of lymphocytic sialedinitis on minor salivary gland biopsy.

Mixed Connective Tissue Disease (MCTD)

MCTD is a syndrome where clinical features of multiple CTDs are present along with presence of high titre anti-RNP antibodies. Raynaud's phenomenon is present in nearly 95% of patients. Kusukawa' criteria can be used for diagnosis [8] (Table 4).

Table 2 Bohan and Peter criteria for diagnosis of inflammatory myositis

Criteria	Description
Muscle involvement	Symmetrical and progressive proximal muscle weakness (± dysphagia and respiratory involvement)
Muscle biopsy	Necrosis of type I and II fibers
	Phagocytosis
	Regeneration with basophilia
	Large vesicular sarcolemmal nuclei
	Prominent nucleoli
	Atrophy in a perifascicular distribution
	Variation in fiber size
	Inflammatory exudates, often perivascular
Elevation of muscle enzymes	Particularly creatine phosphokinase, Often aldolase, AST, lactate dehydrogenase
Electromyogram	Short, small, polyphasic motor units, fibrillations, positive sharp waves
	Insertional irritability
	Bizarre, high-frequency repetitive discharges
Dermatologic features	Lilac discoloration of the eyelids (heliotrope) with periorbital edema
	Scaly and erythematous dermatitis over the dorsum of the hands (Gottron's sign)
	Involvement of the knees, elbows and medial malleoli, face, neck and upper torso

Undifferentiated Connective Tissue Disorders

Undifferentiated connective tissue disorders are symptom complex that does not fit any well defined CTD but has features of CTDs. UCTD may eventually develop into classic CTDs or it may remain undifferentiated.

Fever is the hallmark of almost all CTD. Often children with CTD present with pyrexia of unknown origin. Along

Table 3 Provisional criteria for the classification of juvenile systemic sclerosis (JSSc)

Major criterion (required):	Proximal sclerosis/induration of the skin
Minor criteria (2 required):	
Cutaneous	Sclerodactyly
Peripheral Vascular	Raynaud's
	Nailfold capillary abnormalities
	Digital tip ulcers
Gastrointestinal	Dysphagia
	Gastroesophageal reflux
Cardiac	Arrhythmias
	Heart failure
Renal	Renal crisis
	New onset arterial hypertension
Respiratory	Pulmonary fibrosis (HRCT/radiography)
	Decreased DLCO
	Pulmonary arterial hypertension
Neurologic	Neuropathy
	Carpal tunnel syndrome
Musculoskeletal	Tendon friction rubs
	Arthritis
	Myositis
Serologic	Antinuclear antibodies
	SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM-Scl, antifibrillin or anti-RNA polymerase I or III)

Table 4 Kasukawa criteria for mixed connective tissue disease

Patients must meet all three of the following criteria to be diagnosed with MCTD:

1. Raynaud's or swollen fingers or hands or both
2. Anti-RNP antibody positivity
3. At-least one abnormal finding from two or more of the following categories:
   - Signs or symptoms of SLE (polyarthritis, facial rash, serositis, lymphadenopathy, leukopenia, thrombocytopenia)
   - Signs or symptoms of scleroderma (sclerodactyly, pulmonary fibrosis, vital capacity <80% of normal, carbon monoxide diffusion <70% of normal, decreased esophageal motility)
   - Signs or symptoms of dermatomyositis (muscle weakness, elevated creatine kinase, EMG abnormalities).

with fever, the child usually has some other symptoms and signs or has laboratory abnormality like leucopenia or proteinuria that alerts the clinician to a diagnosis of CTDs. With detailed history and meticulous examination, often the diagnosis of CTD is evident. Fever is usually high grade in SLE though present in only 50–60% and low grade in dermatomyositis and systemic sclerosis.

Investigations

Investigations in the young child with suspected CTD depends on the clinical features and the organ involved. Complete blood counts help in identifying leucopenia, lymphopenia, thrombocytopenia or reticulocytosis with anemia in a child with SLE, whereas presence of leucocytosis and thrombocytosis suggests a possibility of SoJIA, vasculitis or bacterial infection. Coombs test should be done if there is a suspicion of auto-immune haemolytic anemia. Normal C-reactive protein (CRP) with high ESR suggests a diagnosis of SLE. Levels raised beyond that expected by the clinical findings (for example, a dramatically raised ESR in the face of a mild oligoarthritis affecting two or three joints) or dissociation of markers of inflammation (such as a high ESR with normal or low platelet count) should arouse suspicion of malignancy.

Muscle enzymes—including creatine kinase and lactate dehydrogenase are usually raised in myositis, but marked elevation of LDH alone may be a marker of malignancy.

Antinuclear antibodies (Fig. 3) are present in nearly 98% of patients with SLE but are also present in majority of patients with systemic sclerosis, Sjogren Syndrome. Low titres of ANA occur in significant numbers of normal "healthy" children. In lupus the titres are more likely to be high. About half the patients with JDM are ANA positive. Raised titres of antibodies to double-stranded DNA are often present in SLE especially in presence of lupus nephritis. Low C3 (often in conjunction with low C4) is a marker of disease activity in SLE.

Antibodies against extractable nuclear antigens can sometimes be disease specific (Table 5). Anticentromere antibodies in patients with CREST syndrome and anti-Sm antibodies in SLE are disease-specific.

Imaging techniques like MRI of the proximal muscles (fat-suppressed T2 or short tau inversion recovery sequences), EMG and muscle biopsy (needed when other tests are inconclusive) are needed to confirm myositis. Muscle biopsy should ideally be done after MRI has defined the site of involved muscle, to avoid sampling errors. Nail Fold capillaroscopy can help analyse microvascular abnormalities like architectural disorganization, giant capillaries, hemorrhages, loss of capillaries, angiogenesis and avascular areas in dermatomyositis, systemic sclerosis, lupus and MCTD [9].

Depending on the organ involved other modalities like MRI brain, MR venography for venous thrombosis, CSF studies, EEG and renal biopsy may be needed to fully assess the organ involved.

Serological studies to exclude infections like viral, streptococcal and mycoplasma may be useful in early diseases. Rising titres are often helpful but require paired testing, particularly in the convalescent phase of illness.

General Principles of Treatment

Mild activity in CTDs can be managed with non-steroidal anti- inflammatory and/or anti-malarials. Low-dose corticosteroids are needed to suppress mild to moderate symptoms. In severe systemic disease or if there is internal organ involvement, more immunosuppression is required. This

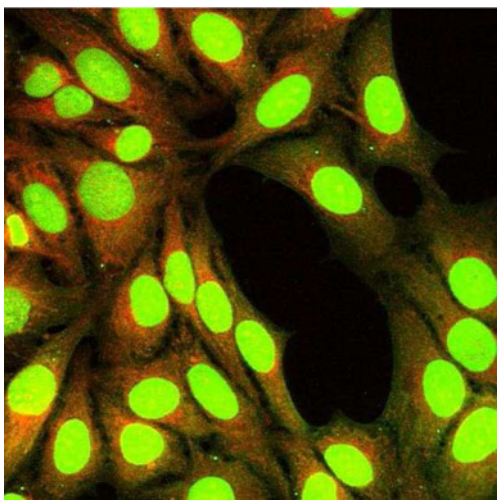

Fig. 3 Antinuclear antibodies as detected using Hep2 cells and Indirect immunofluorescence assay

Table 5 Antibodies to extractable nuclear antigens in different connective tissue diseases (CTDs)

Autoantibody	Associated CTD
Anti-Sm	High specificity of SLE, but low sensitivity
Anti-Ro (SSA)	Occurs in SLE, especially with cutaneous involvement, and is common in Sjögren's syndrome. Seen in mothers with neonatal SLE
Anti-La (SSB)	Sjögren's syndrome, SLE
Anti-RNP	Non-specific, but is part of the criteria for MCTD; also occurs in SLE
Anti-Jo-1	Highly specific for a severe form of PM-DM, but not sensitive
Antihistone	Seen in SLE and drug-induced SLE
Anticentromere	Often found in limited scleroderma (CREST)
Antitopoisomerase (Scl-70)	Sometimes found in diffuse scleroderma; can correlate with intersitial lung disease in scleroderma

Anti -Sm anti -Smith; *SLE* systemic lupus erythematosus; *SSA* Sjögren's syndrome A; *SSB* Sjögren's syndrome B; *Anti-RNP* anti-ribonucleoprotein; *MCTD* mixed connective tissue disease; *PM-DM* polymyositis and dermatomyositis; *CREST* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias

could involve the use of high-dose oral corticosteroids or pulse methylprednisolone or cyclophosphamide in order to induce a remission, which is subsequently maintained using an optimum dosage of prednisolone and azathioprine. A balance has to be struck between disease control and the side-effects of maintenance therapy.

The effects of disease on internal end organs require specific treatment, such as medication for hypertension due to kidney disease or for heart failure due to cardiomyopathy. The response to treatment should be judged primarily by clinical outcomes, as laboratory parameters may not necessarily be a true reflection of disease activity. Most children need to be followed up regularly.

SLE All children with SLE should be treated with sun avoidance, sunscreen, and protective clothing because UV exposure can exacerbate skin and systemic disease. Mild disease can be managed with NSAIDs such as naproxen and ibuprofen. For severe arthralgias, arthritis, skin lesions and constitutional symptoms, anti-malarial agents such as hydroxychloroquine (up to 6 mg per kilogram per day) are helpful. In children with major organ disease, those in crisis, or those with active nephritis, high-dose prednisolone (1–2 mg per kilogram per day) usually is indicated. Steroid-sparing agents, include azathioprine, methotrexate, mycophenolate mofetil (MMF), and cyclosporine should be started early to decrease the dose of corticosteroid and thus avoid toxicity. Major organs like CNS and kidney involvement needs more intense immunosuppression with cyclophosphamide [10], Azathioprine [11] or MMF [12] or rituximab [13]. The choice and timing of immunosuppressants in juvenile SLE is still empiric and no uniform agreement is found among different clinicians [14].

JDM Corticosteroids have been the traditional mainstay of therapy for the JDM; onset is rapid, and clinical efficacy is seen within days to wks. Current recommendations for mild to moderate disease include prednisolone at 2 mg per kilogram per day, with a rapid taper to 1 mg per kilogram per day as soon as a partial response is achieved [15]. Methotrexate has been shown to work well in JDM, especially in maintaining remission. In the case of severe disease with respiratory and pharyngeal muscle disease, incomplete or poor response to oral steroids (steroid resistance), intravenous methylprednisolone pulse (IVMP) (30 mg/kg per treatment, maximum 1000 mg) may be given for a rapid control of the systemic inflammation [16]. Use of MTX started within 4 wks after the beginning of corticosteroids in the absence of improvement in muscle enzymes may decrease the incidence of long-term complications such as calcinosis [17]. IVIG is indicated for relapse, incomplete response, or as a steroid-sparing agent. The dose, the number of courses, and the time interval varies among the different studies published [18]. Cyclophosphamide has been used in severe and refractory JDM [19]. Other medications that have been used in treating JDM include cyclosporin A [20] and hydroxychloroquine [21]. Topical tacrolimus can be used as an attractive adjunct for refractory skin disease in JDM [22].

Localised Scleroderma Morphea generally is of cosmetic concern only, and therefore treatments with potential toxicity are not justified. In general, these lesions remit spontaneously with residual pigmentation as the only abnormality. Therefore, topical therapies such as moisturizing agents, topical glucocorticoids, or calcipotriene may be used. Methotrexate has shown encouraging results in linear scleroderma [23]. JSSc treatment is basically symptomatic and depends on the organ involved. Recent studies

have shown encouraging results with the use of mycophenolate mofitil [24].

Sjogren Syndrome Treatment of SS is usually symptomatic with use of artificial tears, protection of eye from injury, oral saliva substitutes, good dental hygiene and NSAIDs for joint pains.

Outcome

SLE

Although the clinical course of SLE is variable, children with mild disease and without major organ involvement represent less than 5% of pediatric cases. Majority of patients experience a chronic course with periods of flare. Flares must be treated aggressively to avoid organ damage. 40% of children at onset and usually 60–70% during the course have lupus nephritis, the single most predictor of poor outcome. However, effective use of corticosteroids and other immunosuppressive drugs has improved the survival from 30% in 1970s to more than 90% at 10 yrs [25, 26].

JDM

One-third of children with JDM have a monocyclic course (disease that goes into permanent remission after about 2 yrs of activity); the remaining two-third have a chronic continuous or polycyclic course [27]. Children with chronic relapsing course are at high risk for developing calcinosis, progressive muscular debilitation and respiratory failure. Aggressive, early intervention with high-dose corticosteroids currently appears to be the most efficacious treatment that can be offered in an effort to halt or slow disease progression

JSSc

Generally, the prognosis of JSSc is better than for adult onset SSc with survival rates for 5, 10 and 15 yrs being 89%, 80–87.4% and 74–87.4%, respectively. Skin tightness and joint contractures inevitably lead to severe disability. Paradoxically, the skin may eventually soften years after onset of the disease. The most common causes of death in children are related to cardiac, renal, and pulmonary systems. Arrhythmias may develop during the course of the disease secondary to myocardial fibrosis. Cardiomyopathy, although rare, can be one of the causes of early death. Interstitial lung disease and renal failure or acute hypertensive encephalopathy lead to potentially fatal outcomes in a few children and seem more likely to occur early in the course of the disease [28].

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