Rheumatologic Emergencies in Newborns, Children, and Adolescents

Jonathan D. Akikusa, MBBS[a,b,*]

KEYWORDS

- Neonatal heart block • Macrophage activation syndrome
- Pulmonary renal syndrome
- Catastrophic antiphospholipid syndrome • Cardiac tamponade

Pediatric rheumatic diseases can present with a wide spectrum of clinical illness, affecting virtually any organ in the body. Although they have the potential to cause significant morbidity and even mortality if not recognized and managed appropriately, in most situations the institution of treatment is not time critical. There are a few situations, however, in which prompt recognition and treatment is essential to preserve organ function and even life. This article provides a problem-oriented review of five such rheumatologic emergencies. Although each may occur in the context of known preexisting rheumatic disease, they may also be the initial presentation of the diseases concerned and may, therefore, be encountered by general pediatricians, intensivists, or emergency room physicians. This article does not deal with the extensive list of disease- and treatment-related complications that may occur in patients with known rheumatic illness, because although they require timely recognition and management, the patient's prior history is likely to prompt consideration of rheumatologic differentials and involvement of a pediatric rheumatologist. It also does not deal with other conditions, such as septic arthritis and osteomyelitis, which although occasionally a diagnostic challenge – particularly in the neonate – and important to recognize and treat promptly, are rarely life threatening. The reader is referred to another article in this issue for more information on these conditions.

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[a] Rheumatology Service, Department of General Medicine, Royal Children's Hospital, 3 West Clinical Offices, 50 Flemington Road, Parkville, 3052, Victoria, Australia; [b] Murdoch Childrens Research Institute, Royal Children's Hospital, 50 Flemington Road, Parkville, 3052, Victoria, Australia

* Corresponding author. Rheumatology Service, Department of General Medicine, Royal Children's Hospital, 3 West Clinical Offices, 50 Flemington Road, Parkville, 3052, Victoria, Australia.

E-mail address: Jonathan.akikusa@rch.org.au

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The objective of this article is to assist pediatricians, intensivists, and emergency room physicians in the recognition of clinical scenarios involving critically unwell children in which rheumatic diseases are an important, and in some cases the main, differential. Included is a guide to the key clinical and laboratory features that may be used to identify the relevant illness and an overview of initial treatment approaches. It is not the intention of this review to present detailed diagnostic criteria for the conditions considered, many of which are dealt with elsewhere in this issue. Similarly, although broad treatment principles are presented, the assumption is that after a diagnosis is confirmed the assistance of a physician experienced in the management of pediatric rheumatologic disease will be sought or the reader will consult a more detailed text.

THE FETUS OR NEONATE WITH COMPLETE HEART BLOCK

Rheumatologic Differential
Neonatal lupus erythematosus with complete heart block

The diagnosis of complete atrioventricular heart block (CAVB) in the perinatal period is uncommon, with an estimated incidence of approximately 1 in 15,000 live births. As an isolated finding it is associated with the presence of transplacentally acquired maternal antibodies to Ro/SSA or La/SSB in more than 85% of cases, in a condition termed "neonatal lupus erythematosus" (NLE).[1,2] Without treatment the prognosis of affected infants is guarded, with reported rates of in utero and 1-year mortality of 23% and 54%, respectively.[3] It is important that pediatricians recognize the implications of this finding and the need for urgent assessment to confirm its cause and institution of appropriate monitoring and referrals for ongoing management.

Clinical Presentation

The development of CAVB in utero in fetuses with NLE may be preceded by second-degree heart block or may occur rapidly in the apparent absence of preceding lesser degrees of block.[4] Onset may be at any time after 16 weeks gestation. Although most cases occur before the 30th week, fetuses remain at risk to term.[5] Affected fetuses with lesser degrees of heart block at the time of delivery remain at risk of developing CAVB in the neonatal period and beyond.[6]

The clinical presentation of CAVB in the fetus and neonate is with bradycardia.[5] Complications of significant bradycardia, such as hydrops and pericardial effusion in the fetus and congestive cardiac failure in the neonate, may also be seen.[5] Second-degree heart block also presents with bradycardia (heart rate <120 beats per minute), although of a lesser degree than CAVB. The detection of bradycardia in the fetus or neonate mandates immediate referral for assessment as to cause. The confirmation of heart block is by estimation of the PR interval using specialized echocardiographic techniques antenatally or by electrocardiogram after birth. Neonates with heart block in the setting of NLE may manifest other findings typical of the condition, which might serve as a clue to the underlying diagnosis. These include an annular skin rash, typically of the face and scalp; elevation of hepatic enzymes; and thrombocytopenia.

Approach to Investigation

The detection of isolated CAVB or lesser degrees of heart block in the fetus or neonate should prompt testing for the presence of antinuclear antibodies, specifically those against Ro/SSA and La/SSB, in maternal and neonatal serum. Found in approximately

0.5% of asymptomatic pregnant women, these antibodies are associated with a 1% to 2% risk of CAVB in the fetus in the absence of a prior affected pregnancy. This risk is increased to 15% to 20% if there is a history of a prior pregnancy complicated by fetal CAVB.[4] In association with fetal heart block, these antibodies confirm the presence of neonatal lupus syndrome and appropriate monitoring and treatment should be instigated.

Treatment Overview

The management of fetuses with heart block has not been the subject of randomized trials and some aspects remain controversial. Fetal conduction block in NLE is thought to be the result of immune-mediated damage to the atrioventricular (AV) node.[7] This damage results in scarring with CAVB as the end result. The suspected role of the immune system in this process raises the possibility that immunosuppression administered to the at-risk fetus might reduce AV node damage and prevent CAVB.

Based on data from observational studies it is generally accepted that treatment of the fetus using fluoridated corticosteroids, such as dexamethasone, administered to the mother has a role in the treatment of second-degree heart block. Such treatment may prevent progression to CAVB and in some cases may result in regression of the degree of block.[4,8] More controversial is their use, with their potential side effects on the mother and fetus, in the management of first-degree heart block and established CAVB. This controversy has arisen because it is unclear if the former is a risk factor for the development of CAVB or if the latter is reversible.[4,8]

Irrespective of whether corticosteroids are used, an essential component of the management of fetal heart block is frequent monitoring for complications of bradycardia, or for other cardiac abnormalities associated with neonatal lupus syndrome, such as endocardial fibroelastosis. Fetal heart rates greater than 55 to 60 beats per minute are usually tolerated and early delivery of the fetus is not required in the absence of other complications. Early delivery should be considered if the fetal heart rate is less than 55 to 60 beats per minute. β-Sympathomimetic agents may be used as a temporizing measure. A significant proportion of babies with CAVB require cardiac pacing after birth and delivery should be effected at a center with ready access to this capability.[5]

Neonates who present with CAVB should be managed according to their degree of circulatory decompensation. The rate of pacemaker placement in the neonatal period is lower in this group than in those diagnosed in utero, although over the longer term the rate of both groups is similar.[5] Neonates followed in utero with first- and second-degree heart block require ongoing follow-up because they remain at risk for the development of higher degrees of heart block over time.

THE FEBRILE CHILD WITH PANCYTOPENIA

Rheumatologic Differential
Macrophage activation syndrome secondary to:
Systemic lupus erythematosus
Systemic juvenile idiopathic arthritis
Kawasaki disease

The differential diagnosis of fever in association with pancytopenia includes such entities as sepsis, myelodysplastic syndromes, and malignancy, all of which pediatricians

are familiar with and routinely work-up, treat, and refer when appropriate. Less commonly appreciated is the rheumatologic differential of macrophage activation syndrome (MAS). This potentially fatal disorder, a secondary form of hemophagoctyic lymphohistiocytosis (HLH), may complicate the initial presentation and subsequent course of a number of pediatric rheumatic diseases.[9–12] Although it may also be seen in the context of infection, malignancy, and immunodeficiency, this discussion is limited to rheumatic disease–triggered MAS. Without appropriate treatment MAS has the potential to cause rapid clinical deterioration and death. Because many of the routine laboratory findings associated with this condition are protean and overlap with those of other disorders, particularly sepsis, misdiagnosis through lack of awareness is a significant risk.[13] The reader is referred elsewhere in this issue for more comprehensive information. This section provides an overview of the key features helpful in the recognition of MAS triggered by rheumatic disease and provides a guide to making the diagnosis and its initial management.

Clinical Presentation

Cytopenias in association with fever and splenomegaly are important clues to the possibility of MAS. In the absence of formal diagnostic criteria, those used for the diagnosis of familial HLH have become the default in this condition (See article by Gowdie and Tse elsewhere in this issue for further exploration of this topic). Caution needs to be exercised, however, in the rigid application of these criteria to rheumatic disease-triggered MAS, where significant cell count changes associated with the underlying disease may mask the presence of evolving cytopenias (eg, in Kawasaki disease [KD] and systemic juvenile idiopathic arthritis [sJIA]) or result in misattribution with respect to cause (eg, in systemic lupus erythematosus [SLE]). Under these circumstances falling cell counts, particularly platelets and/or neutrophils, even if still within the normal range, may be an important clue to the presence of MAS. Other suggestive abnormalities of common laboratory parameters are extreme hyperferritinemia, fasting hypertriglyceridemia, or hypofibrinogenemia with coagulopathy and elevation of hepatic enzymes. In rheumatic disease–triggered MAS, clinical or laboratory findings of the underlying rheumatic disorder are also present. These must be carefully sought in all cases of suspected MAS. The most common rheumatologic disorders associated with MAS are SLE, sJIA, and KD. The important clinical and laboratory features that must be looked for when evaluating a patient for the presence of these disorders are outlined in **Table 1**. Formal diagnostic criteria for these conditions are dealt with elsewhere in this issue. It should be noted that SLE itself may cause fever and cytopenias; however, the profound neutropenia typically seen in MAS is uncommon and its presence should alert the clinician to the possibility of the latter.

Approach to Investigation

The investigations that should be ordered when MAS is suspected and the values that suggest its presence, based on the current criteria for HLH,[14] are outlined in **Box 1**. The current criteria also include testing natural killer cell activity and levels of soluble CD25; however, these may not be available in all laboratories. Although demonstrating excessive hemophagocytosis in bone marrow or lymph node biopsies provides good evidence of the presence of MAS, its absence does not exclude MAS. Even in fatal cases of HLH the sensitivity of autopsy samples from these tissues for the detection of hemophagocytosis has been reported to be just 39% and 74%, respectively.[15]

Investigations that may be useful in the diagnosis of an underlying rheumatologic disorder are outlined in **Table 1**. Because MAS may be triggered by conditions

Table 1
Important clinical and laboratory features of rheumatic diseases that may present with macrophage activation syndrome

	Kawasaki Disease	Systemic Juvenile Idiopathic Arthritis	Systemic Lupus Erythematosus
M:F	M = F	M = F	M<F
Typical age	Less than 5 yr	No age peak, may occur at any age, uncommon <1 yr	Older children, adolescents
Rash	*Polymorphous*	*Evanescent, salmon pink, macules*	*Photosensitive, esp. malar distribution. Discoid*
Oromucosal changes	*Strawberry tongue* *Cracked lips*	—	*Oral ulceration, esp hard palate*
Conjunctivitis	*Nonpurulent*	—	—
Lymphadenopathy	*Cervical >1.5 cm*	*Generalized, may be associated hepatosplenomegaly*	Generalized, may be associated hepatosplenomegaly
Arthritis	Present in ~25% Mostly large joint	*Required for diagnosis, may not be present initially*	*Present in ~60%* *Both large and small joint*
Peripheral changes	*Palmar erythema, edema, peeling subacutely*	—	*Edema if nephrotic, vasculitic skin changes*
Serositis	Pericarditis	*Pericarditis, pleural effusions*	*Pericarditis, pleural effusions*
Neurologic	Irritability, aseptic meningitis	—	*Chorea, psychosis, headache, seizures*
Urinalysis	Sterile pyuria	—	*Active sediment, Hematuria and/or proteinuria*
Changes in common laboratory parameters without MAS	Elevation of ESR, CRP, WCC, Thrombocytosis subacutely	Elevation of ESR, CRP, WCC, PLT Ferritin markedly raised Anemia common	Elevation of ESR. CRP usually normal. *Hemolytic Anemia, low PLT and WCC may occur*
Autoantibodies	—	—	*Positive ANA, aPL, anti-dsDNA, anti-Sm antibodies*

Italicized features are diagnostic criteria for the indicated condition. The reader is referred to the relevant article in this issue for more detailed information on each of these conditions.

Abbreviations: ANA, antinuclear antibody; aPL, antiphospholipid; CRP, C-reactive protein; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; PLT, platelets; Sm, Smith; WCC, white cell count.

Box 1
Useful investigations in suspected MAS

Full blood examination (≥2 of three cell lines affected)

- Hemoglobin <90 g/L
- Neutrophils <1 × 10^9/L
- Platelets <100 × 10^9/L

Fasting triglycerides

- ≥3 mmol/L

Fibrinogen

- ≤1.5 g/L

Ferritin

- ≥500 μg/L

Bone marrow or lymph node biopsy:

- Excessive hemophagocytosis

other than rheumatic diseases, in particular infection and malignancy, appropriate investigations to exclude these possibilities should also be undertaken. In the absence of an identifiable trigger, genetic testing for primary HLH should be performed irrespective of the age of the child. Although primary HLH typically manifests in infancy, presentations in older children and adults are being increasingly recognized.[16,17]

Treatment Overview

After the diagnosis of MAS is confirmed or, in a critically ill child in whom a complete evaluation is not possible, considered highly likely, treatment should be commenced without delay. In situations where infection cannot be excluded, concurrent treatment with appropriate antimicrobial therapy should be given. In general, the initial treatment of MAS is the same irrespective of the underlying trigger. High-dose intravenous steroid pulsed methylprednisolone (30 mg/kg/dose over 30–60 minutes, maximum 1 g) administered daily is considered first-line therapy. This is typically continued for 3 days or until clinical and laboratory parameters begin to improve. Therapy is usually then switched to daily divided-dose steroids, starting at 2 mg/kg/d. Other treatments that may be used in the acute management of MAS complicating rheumatic diseases include cyclosporin, intravenous immunoglobulin, and anakinra.[18–20] These agents are most often considered in critically unwell children or those who fail to respond to corticosteroids. On rare occasions, in children whose disease is resistant to the previously mentioned measures, the chemotherapy protocol designed for the treatment of primary HLH involving the administration of dexamethasone and etoposide is required. In general, the therapy needed to control rheumatic disease-triggered MAS will also treat the underlying rheumatic disorder. Additional disease-specific therapy is required only in patients with KD for whom intravenous immunoglobulin remains the only therapy proved to reduce the risk of coronary artery aneurysms. After the episode of MAS is controlled, the long-term management of these patients is determined by their underlying rheumatic disorder.

THE CHILD WITH RESPIRATORY DISTRESS AND RENAL FAILURE

Rheumatologic Differentials
Pulmonary renal syndrome secondary to:
Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis
Systemic lupus erythematosus
Goodpasture syndrome

An important differential diagnosis for the child presenting with respiratory distress and renal failure is pulmonary renal syndrome (PRS), a term describing the clinical presentation of diffuse alveolar hemorrhage in combination with rapidly progressive glomerulonephritis. It has been reported as a manifestation of several multisystem illnesses; however, three main causes predominate: (1) antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (primarily granulomatosis with polyangiitis and microscopic polyangiitis); (2) SLE; and (3) less commonly in children, Goodpasture syndrome.[21–24] It may be the presenting feature of each of these conditions and, if unrecognized, can be rapidly fatal as a result of devastating pulmonary hemorrhage.[24]

Clinical Presentation

Patients typically present with dyspnea and cough in association with hypoxemia in air.[25] Hemoptysis in this context is a strong clue to the presence of pulmonary hemorrhage but may not be present in all cases. Chest radiography demonstrates a diffuse alveolar filling process (**Fig. 1**) and a full blood count reveals anemia or falling hemoglobin. Renal involvement is evident as elevation of serum creatinine and urea, the finding of which should prompt analysis of urinary sediment for evidence of glomerulonephritis. In

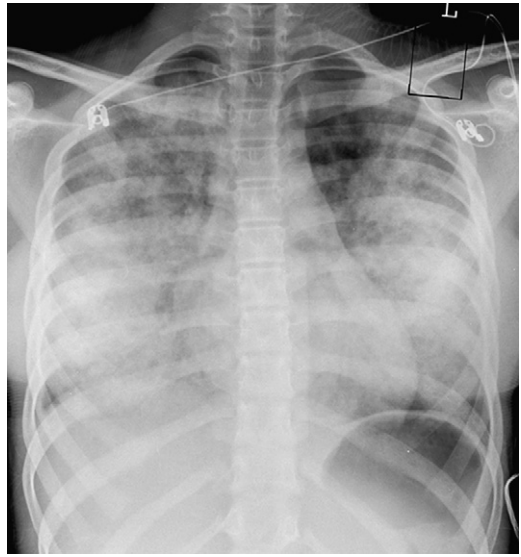

Fig. 1. Diffuse alveolar filling associated with respiratory distress, hemoptysis, and anemia in a 13-year-old girl subsequently diagnosed with an ANCA-associated vasculitis.

addition to these generic features of PRS, patients may have clinical findings related to the specific underlying disorder. Clinical features suggestive of ANCA-associated vasculitis include prominent constitutional symptoms, such as fever and arthralgias; concurrent upper airway disease including oral or nasal ulceration, sinusitis, saddle nose, and subglottic stenosis; the presence of conjunctivitis, scleritis, or episcleritis; and the presence of peripheral palpable purpura or petechiae-like skin lesions suggestive of leukocytoclastic vasculitis.[21,26] The specific type of ANCA-vasculitis diagnosed is determined by the particular combination of clinical and serologic features found. Clinical features suggestive of SLE are outlined in **Table 1**. The clinical features of Goodpasture syndrome are typically those arising from its effect on the kidneys and lungs.[24]

Approach to Investigation

Respiratory distress in combination with renal failure may be the result of PRS or may occur as the result of coincidental pathologies in the respiratory and renal systems.[23] Because clinical deterioration in the former can be very rapid, the priority in the investigation of patients with this combination of clinical features is to determine whether pulmonary hemorrhage and glomerulonephritis are present. If they are then the presence of

Box 2
Investigation of suspected PRS

A. Tests to confirm the presence of PRS
   - First-line testing
     - Chest radiograph: diffuse alveolar filling
     - Full blood count: anemia, falling hemoglobin
     - Creatinine and urea: abnormal elevation
     - Urinalysis: proteinuria, hematuria, cellular casts
   - Second-line testing (if first-line testing inconclusive for pulmonary hemorrhage)
     - D_{LCO}: increased in the presence of intra-alveolar bleeding
     - Bronchoalveolar lavage: presence of red cells, hemosiderin-laden macrophages

B. Tests to confirm the cause of PRS
   - Autoantibody screening for
     - ANCA-associated vasculitis: ANCA, if positive then test for anti-PR3 or anti-MPO specificity
     - SLE: ANA, anti-ENA, anti-dsDNA, anti-Sm, anticardiolipn, lupus anticoagulant
     - Goodpasture syndrome: anti-GBM antibodies
   - Tissue diagnostics
     - Renal biopsy: ANCA vasculitides: pauci-immune, necrotizing, crescentic glomerulonephritis
     - SLE: glomerular immune deposits with histologic changes of lupus nephritis
     - Goodpasture syndrome: typical pattern of IgG deposition in glomeruli with crescentic changes

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ANA, antinuclear antibodies; D_{LCO}, diffusing capacity of lung for carbon monoxide; ENA, extractible nuclear antigens; GBM, glomerular basement membrane; MPO, myeloperoxidase; PR3, proteinase 3.

PRS is confirmed and subsequent investigations should be directed toward determining the underlying cause. **Box 2** outlines investigations and expected findings useful in establishing the presence and cause of PRS. In most cases the patient's history, examination, and simple first-line investigations are sufficient to confirm the presence of PRS and allow commencement of presumptive treatment.

Treatment Overview

Patients with PRS are frequently critically ill at presentation or have a high risk of becoming so if treatment is delayed. Once the presence of PRS is confirmed, presumptive treatment should be commenced. Investigations to determine the underlying cause are rarely available acutely and do not significantly alter immediate therapy requirements. If the presence of concurrent infection cannot be excluded, appropriate antimicrobial cover should be administered. Patients should be managed in a setting in which renal and respiratory support can be provided if needed because they continue to be at risk of significant deterioration until treatment measures are well underway.

Initial therapy for PRS consists of high-dose intravenous pulsed methylprednisolone (30 mg/kg/dose over 30–60 minutes, maximum 1 g) daily for at least 3 days followed by high-dose prednisolone (1–2 mg/kg/d). Plasmapheresis is standard therapy in Goodpasture syndrome and has been shown to be of benefit for renal survival in patients with severe ANCA-associated vasculitis.[27] Although not proved to increase survival, in the context of significant alveolar hemorrhage, particularly in patients requiring respiratory support, it has become standard adjunctive therapy in PRS irrespective of the underlying cause. The third component of therapy for PRS is cyclophosphamide, administered either orally or intravenously.

THE CHILD WITH MULTIPLE ORGAN DYSFUNCTION WITH OR WITHOUT OBVIOUS THROMBOSIS

Rheumatologic Differential
Catastrophic antiphospholipid syndrome

One of the most difficult differentials in pediatric rheumatology is catastrophic antiphospholipid syndrome (CAPS), which as its name implies may be rapidly fatal if not recognized promptly. The difficulty in recognizing this syndrome arises as a result of its rarity and the nonspecific manner in which it may present. Patients with CAPS have an underlying predisposition to thrombosis as a result of persistent antiphospholipid antibodies (lupus anticoagulant and anticardiolipin). These may occur as a primary phenomenon or in the context of an underlying connective tissue disease, the commonest of which is SLE. Whether primary or secondary, their presence may not be suspected until an index event, of which CAPS may be one.[28,29] In approximately two-thirds of patients with CAPS an underlying triggering event can be identified.[28,30] The commonest trigger is infection. Others include surgery; trauma; malignancy; and in cases associated with SLE, flares of the underlying disease. The primary pathology in CAPS is multisystem microvascular thrombosis with a secondary systemic inflammatory response as a result of tissue damage.[29] Patients present with progressive multiorgan dysfunction in the context of an apparently primary inflammatory disease. They may not have obvious features to suggest a thrombotic process, in which case more subtle features must be carefully sought. There are other rheumatologic differentials for multiorgan dysfunction in the context of acute inflammatory disease including

SLE and the primary systemic vasculitides, particularly those affecting medium and small vessels. The reader is referred to the relevant articles of this issue to familiarize themselves with the key features of those conditions.

Clinical Presentation

No one symptom or clinical finding is diagnostic of CAPS. Diagnostic criteria for the syndrome have been proposed and subsequently validated (**Box 3**).[31,32] They provide a conceptual framework for the evaluation of patients presenting with complex multisystem disease in whom the diagnosis of CAPS is being considered.

Data regarding the common clinical features of CAPS are derived from a registry of predominantly adult patients.[28–30] Manifestations resulting from thrombosis are a key feature, although because of the size of the vessels involved may not initially be appreciated as such. Large-vessel thrombosis, as seen in antiphospholipid syndrome, does occur in CAPS; however, small-vessel and microvascular thrombosis is more common. Cardiopulmonary manifestations are the most frequent at presentation. These typically include acute dyspnea and respiratory failure in the context of acute respiratory distress syndrome. Pulmonary embolus and alveolar hemorrhage may also occur. The next commonest organ involvement is the central nervous system, typically as cerebral infarction, seizures, and encephalopathy. Cerebral venous sinus thrombosis may also be seen and be a more obvious clue to an underlying thrombotic tendency. Renal and abdominal involvement are the third and fourth most frequently involved systems at presentation, with renal failure, proteinuria, and significant abdominal pain common presenting features. Over the course of an episode of CAPS more than 80% of patients experience an intra-abdominal thrombotic event; therefore, any new abdominal symptom should be carefully evaluated. Less common organ involvement includes the skin, with livedo reticularis, purpura, and ulcers all being described.

In addition to clinical manifestations related to thrombosis, patients may also exhibit systemic inflammation and have laboratory features suggestive of disseminated intravascular coagulation or thrombotic microangiopathy, including thrombocytopenia,

Box 3
Criteria for the diagnosis of CAPS

Definite CAPS requires all of the following

1. Evidence of vessel occlusion, or effect of vessel occlusion, in $\geq$3 organs, systems, or tissues
2. Occurrence of diagnostic features simultaneously or in <1 week
3. Histopathology demonstrating small-vessel occlusion in at least one affected organ or tissue
4. Presence of antiphospholipid antibodies (LAC/aCL) persistent over at least 6 weeks

Probable CAPS if

- Only two organ systems affected, or
- Occurrence of two diagnostic features in <1 week and the third within 4 weeks, or
- Histopathologic demonstration of small-vessel occlusion not possible, or
- Persistence of APL unable to be demonstrated because of death of patient

Abbreviations: aCL, anticardiolipin antibodies; APL, antiphospholipid antibodies; LAC, lupus anticoagulant.

anemia, and features of hemolysis on blood film.[29,33] For patients with CAPS in the context of associated diseases, such as SLE or malignancy, clinical features of the associated condition may be apparent. The reader is referred to **Table 1** and elsewhere in this issue for a description of the key features of SLE. Patients may have features of underlying infection, the single most common trigger for CAPS. If the possibility of CAPS is not considered, the clinical and laboratory picture may be mistaken for overwhelming sepsis.

Approach to Investigation

Bearing in mind the specific requirements of the criteria reviewed previously, the investigation of a patient with suspected CAPS has three main objectives: (1) to confirm the presence of a thrombotic disorder; (2) to confirm the presence of antiphospholipid antibodies (ie, lupus anticoagulant and anticardiolipin antibodies); and (3) to detect underlying triggers for the episode.

Identifying the presence of a thrombotic disorder is relatively straightforward when large vessels are involved. However, in CAPS thrombosis more commonly affects smaller vessels, which may be more difficult to detect.[28,30] Clues to such involvement include evidence of organ infarction (eg, kidney, spleen, or bowel) on imaging, or organ failure (eg, cardiac or renal) in association with markers of abnormal activation of coagulation and peripheral destruction of blood elements, such as elevated fibrin degradation products, thrombocytopenia, hemolytic anemia (with or without features of microangiopathy, such as schistocytes), or fully manifested disseminated intravascular coagulation. Tissue samples (eg, skin or kidney) may provide further evidence of small-vessel thrombosis and occlusion.

Assays for antiphospholipid antibodies should be performed as soon as the diagnosis of CAPS is suspected. In patients with no prior history of antiphospholipid antibodies, their persistence must be demonstrated to meet criteria for CAPS.

Approximately two-thirds of patients have an identifiable trigger for the episode of CAPS.[28] The commonest is infection, particularly of the respiratory system, skin, and urinary tract, for which patients should be carefully screened. Other common triggers that should be excluded in the absence of another obvious cause are malignancy and flare of an underlying connective tissue disease, most commonly SLE.

Therapy Overview

Patients with CAPS are often critically ill. The need for management in an intensive care setting should be anticipated; general supportive measures including ventilation and dialysis are frequently required acutely. It is often not possible to exclude infection as an underlying trigger for CAPS acutely and empiric antimicrobial therapy should be strongly considered. Specific therapy for CAPS is directed toward the two underlying pathologic processes in this disorder: thrombosis and the secondary systemic inflammatory response. Although there have been no randomized trials of therapy, early institution of currently suggested treatments has reduced mortality in CAPS from 50% to 30%.[29] Thrombosis is managed using parenteral and subsequently oral anticoagulation. Systemic corticosteroids, typically in high dose, are administered to mitigate systemic inflammation. Plasmapheresis is also frequently used, particularly in those with evidence of microangiopathy, and intravenous immunoglobulin may be of benefit. Other measures including vasodilators, fibrinolyics, and embolectomy may have a role in individual patients.

THE CHILD WITH PERICARDIAL TAMPONADE

Rheumatologic Differentials
Serositis secondary to:
Systemic lupus erythematosus
Systemic juvenile idiopathic arthritis

Pericardial tamponade is an uncommon life-threatening complication of pericarditis with effusion. Autoimmune disorders account for between 5% and 12% of pericardial effusions in adults and 13% and 30% in children.[34–36] The most common rheumatic diseases associated with pericardial effusions in children are SLE and sJIA, which are the most commonly reported in association with pericardial tamponade.[34,35,37–41] In both conditions pericardial tamponade may occur in the course of established disease or as an initial manifestation.[37–40,42] Although the immediate management of pericardial tamponade is similar irrespective of cause, it is important to identify the presence of an associated rheumatic condition because disease involvement of other organ systems may require management distinct from that of the pericardial issues and tamponade may recur if the underlying disease is not treated.[38,39] It is also important to be aware of, and investigate appropriately for, other causes of pericardial effusion including infection and malignancy.[34,35] In up to 48% of children no cause is identified.[34]

Clinical Presentation

Pericardial tamponade typically presents with dyspnea, tachypnea, and chest pain. Clinical signs include distended neck veins, facial suffusion, tachycardia, pulsus paradoxus, muffled heart sounds, and in advanced stages hypotension. Fever is common.[34] In addition to signs of tamponade, there may be clinical features of the underlying rheumatic disease. **Table 1** provides an overview of clinical features suggestive of SLE and sJIA. These entities are discussed in more detail elsewhere in this issue.

Approach to Investigation

Urgent echocardiography is required in all cases of suspected pericardial tamponade. This confirms the presence of pericardial fluid, provides an assessment of its effect on cardiac mechanics, and allows planning of therapeutic intervention. In patients with subacute presentations, common in those with rheumatic disease–associated pericardial tamponade, the clinical features of tamponade may be more subtle than those described previously and a chest radiograph demonstrating gross enlargement of the cardiac silhouette may be the first clue to the diagnosis (**Fig. 2**). After the diagnosis has been established and treatment instituted, identification of an underlying cause is the next priority. This should begin with sending pericardial fluid obtained during therapeutic pericardiocentesis for appropriate microbial studies and other serologic investigations relevant for identifying possible infective causes of pericardial effusion. Investigations relevant in the work-up for SLE and sJIA are outlined in **Table 1**.

Therapy Overview

The first priority in management of pericardial tamponade is to restore adequate cardiac output by removal of the pericardial fluid. Temporizing measures to maintain cardiac output, such as giving intravenous volume and sympathomimetics, may be

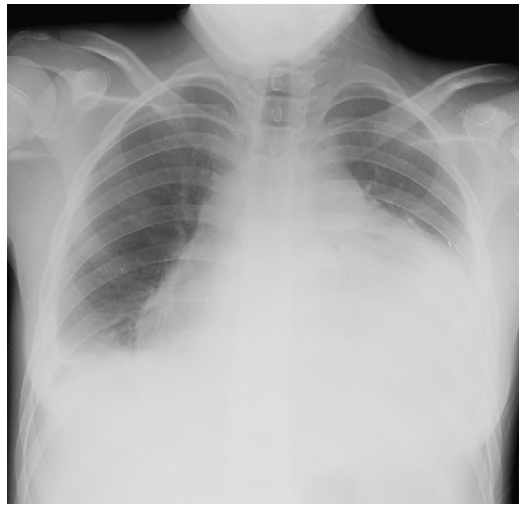

Fig. 2. Bilateral pleural effusions and gross enlargement of the cardiac silhouette in a 13-year-old girl presenting with a 1-week history of increasing chest pain and dyspnea. Echocardiogram confirmed pericardial effusion with tamponade, relieved by drainage of 1000 mL of fluid from the pericardial sac. Subsequent testing revealed the presence of antinuclear antibody, anti–double stranded DNA, and anticardiolipin antibodies and nephritis, confirming a diagnosis of SLE.

considered until this is achieved based on clinical circumstances. Once the adequate cardiac output has been restored and the cause identified, specific treatments can begin. For SLE and sJIA this involves a period of immunosuppression with corticosteroids with or without other agents based on clinical response and other organ involvement.

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