Kawasaki syndrome (KS) is the leading cause of acquired heart disease in children in several parts of the world. It is estimated that up to 3500 children in the US develop KS each year. In the absence of therapy, 15–25% will develop coronary artery abnormalities as a result of intense vasculitis [1, 2]. These include aneurysms and ectasia, responsible for the 2% mortality reported in Japanese children with KS before the introduction of intravenous immunoglobulin (IVIG). Smaller aneurysms tend to resolve over a period of 1–2 yr, but giant aneurysms predispose to risk for myocardial ischaemia and infarction requiring anticoagulation therapy and close follow-up. The timely administration of IVIG has been shown to reduce the incidence of coronary artery disease to about 3–8% [3] and mortality to less than 0.2% [4]. Rarely, children who subsequently develop coronary artery stenosis will require more aggressive intervention, including percutaneous transluminal angioplasty, coronary artery stenting, bypass grafting and even cardiac transplantation [5, 6]. The long-term impact of Kawasaki disease in the adult population is not clearly known, but clinically silent coronary artery aneurysms may be recognized only years later at the time of a sudden cardiac event, even death [7, 8]. Moreover, impaired vasodilatatory capacities of coronary and peripheral arteries coupled with other findings such as decreased global left ventricular function and abnormal electrocardiograms persist for several years after KS [9, 10].

The aetiology and pathogenesis of KS remain unknown. Based on the clinical, laboratory and epidemiological features it appears that the extensive immune activation seen in children with KS is the end result of interaction between a predisposed host and an infectious agent [11].

Formal clinical criteria for the diagnosis of KS, as suggested by the US Center for Disease Control (CDC) are primarily for epidemiological purposes and are not designed for helping with diagnosis in individual patients [12]. Since early treatment will help to reduce major complications, there is a clinical urgency to diagnose this disease. However, several clinical features seen in KS overlap with other diseases, especially viral infections. There is no specific test which will help make this diagnosis with certainty. Therefore there is a need for a new set of criteria which will help the general practitioner with early diagnosis.

Diagnosis is particularly challenging in patients less than 1 yr of age, who are more likely to have an atypical presentation as well as coronary artery involvement [13]. Atypical presentation (45%) and coronary artery complications (64%) are significantly more common in infants than in children older than 1 yr (12 and 9%, respectively) [14]. Laboratory markers are non-specific and no definitive test is currently available to aid in the early diagnosis of KS. Acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are frequently elevated in KS. Their usefulness is limited, however, by their lack of specificity [15]. Serum levels of various cytokines, including TNF-α and IL-1, IL-2, IL-6, IL-8 and IFN-γ [16–21], have been shown to be elevated in children with KS, but none of them have been proven useful in the clinical setting.

# Diagnosis of atypical/incomplete KS: the clinician’s dilemma

There is increasing evidence that a number of patients with KS do not fulfil classical clinical criteria, but still develop coronary artery disease [22]. The term atypical/incomplete KS has been proposed to refer to this subgroup of patients. To the best of our knowledge, no clear distinction is made between atypical and/or incomplete KS in the literature and these words are used interchangeably.

As recently stated [23], we define atypical KS as one in which atypical symptoms/signs, not belonging to the classical criteria, herald the onset of the disease. Acute surgical symptoms, meningeal irritation, renal impairment, pneumonia and retropharyngeal abscess are some examples of atypical features at the onset of KS.

The term incomplete is used to refer to children who exhibit less than the required number of criteria at onset and for several days thereafter. They may or may not demonstrate atypical clinical features. Some of these patients may eventually develop typical features of KS, thus becoming a complete KS; but will do so over a period of days to weeks leading to delay in diagnosis and treatment [24].

In any individual child, criteria need not all be present at the same time. They may appear sequentially. Some features such as conjunctivitis may disappear while others appear. Therefore, the clinician may have to rely on history and not insist on seeing all the classical features of KD personally. Furthermore, not all children with KS develop the complete picture before coronary involvement is recognized. Also, patients with atypical onset KS may not develop the typical features for a long time thus risking delay in diagnosis.

The timing of clinical presentation is critical for an early therapeutic approach, but without clinical criteria and specific laboratory tests, prompt identification of these patients is a major challenge for clinicians. Moreover the impact of undiagnosed atypical and incomplete cases of KS in the pool of coronary artery disease in adults is unknown.

Management of atypical and incomplete cases of KS remains controversial and standardized guidelines are urgently needed [25]. As already pointed out, it is not uncommon for children who do not fulfil the classical clinical criteria to develop coronary artery aneurysms [22]. Approximately 30% of patients with suspected KS receive IVIG treatment in the absence of classical clinical criteria required for a definitive diagnosis, suggesting that practising physicians are already prescribing treatment without waiting for the fulfilment of the CDC criteria [26]. One consequence is that patients with high persistent fever and skin manifestations, who subsequently turn out to have a viral infection or systemic JIA are diagnosed as having atypical KS and receive unnecessary treatment with IVIG with attendant risks and cost.

It is clear that clinicians use several additional clues which are not specific for the disease but which do occur in a large number of patients with KS, so that they can initiate early treatment [27].
Table 1. Principal additional clues, helpful for diagnosis of Kawasaki syndrome

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Laboratory findings</th>
<th>Instrumental findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability/aseptic meningitis</td>
<td>Elevated AST, ALT, γ-glutamyl transpeptidase</td>
<td>Hydrops of the gallbladder</td>
</tr>
<tr>
<td>Polyarthriis</td>
<td>Sterile pyuria</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Perineal rash or peeling</td>
<td>Increased ESR and CRP</td>
<td>Myocarditis/pericarditis/myocardial infarction</td>
</tr>
<tr>
<td>Erythema induration at site of BCG administration</td>
<td>Mild anaemia</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular diseases: pulse deficits, limb ischemia, gangrene</td>
<td>Leucocytosis with a left shift</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Thrombocytosis</td>
<td>Brightness of coronary arteries</td>
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<td></td>
<td>Low Na levels</td>
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<td></td>
<td>Low albumin levels</td>
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<td></td>
<td>Abnormal plasma lipids</td>
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<tr>
<td></td>
<td>Hypereosinophilia/elevated serum IgE levels</td>
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</tbody>
</table>

These clues commonly associated with KS include cardiovascular, gastrointestinal, articular, urinary and neurological signs and symptoms [23, 28] (Table 1). Unfortunately studies evaluating the diagnostic value of these additional clinical features are lacking. In addition, the CDC criteria currently used to diagnosed KS do not include laboratory findings such as elevated aspartate aminotransferase (AST) and amino alanine transferase (ALT), sterile pyuria, increased ESR and CRP, and leucocytosis with a left shift which are commonly present during the acute onset of disease. Thrombocytosis is not very helpful for a prompt diagnosis and treatment, since it rarely occurs before day 10 or 11.

Participants at the Seventh International Kawasaki Symposium recognized the need for revision of guidelines for KD since approximately 30% of children in the 16th Japanese nationwide surveillance were treated on or before the 4th day of illness and because of the increasing recognition of coronary artery lesions in patients with atypical or incomplete KD. Some of the participants believed that incorporation of laboratory measures and important non-principal symptoms would likely improve sensitivity without undue reduction in specificity [26].

In a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young of the American Heart Association, Newburger et al. [23] have provided a new algorithm and a diagnostic table to aid clinicians in deciding which children with fever for ≥5 days and fewer than four classic criteria and children with fewer than 4 days of fever may be considered to have KD and thus be eligible for treatment. These ideas are based on available evidence but have not been formally tested in a prospective fashion.

In our view, a set of criteria organized in the format of Duckett Jones criteria for acute rheumatic fever may be of help in diagnosing atypical and incomplete KD. This should include some of the less prominent classical features and laboratory abnormalities as minor criteria and also should allow for the diagnosis of definite and probable KS. In order to test this idea, we conducted a retrospective study to evaluate the prevalence of classical clinical criteria in patients with KD and coronary artery abnormalities (CAA) [29]. We reviewed the clinical records of all children with the discharge diagnosis of KS at the A. I. Dupont Hospital-Wilmington, DE, USA and at the A. Meyer’s Children Hospital-Firenze, Italy between January 1999 and April 2004. Among 406 children (310 from Wilmington, 96 from Firenze) diagnosed with KS, 23 had CAA. Of these 23 (17 and 6) patients, 15 (65.2%) did not fulfill the classical criteria at the time of presentation. However, when additional features commonly associated with KS such as perineal rash, sterile pyuria, myocarditis, arthritis, retropharyngeal abscess (phlegmon), hydrops of gallbladder, increased ALT and AST, low serum albumin and thrombocytosis were combined with the classical features, an early diagnosis was possible in all but one of these patients.

One of the most common clinical challenges for general paediatricians and subspecialties is to identify children with atypical or incomplete features of KS. General paediatricians are usually the first to evaluate children with persistent fever. Increasingly, they make the diagnosis of KD even in the absence of classic features because of concerns about coronary heart disease as shown by a recent report from San Diego county [30]. In that study, half of general paediatricians surveyed had diagnosed KD in febrile patients who did not fulfill four of the five principal clinical criteria.

Developing more comprehensive criteria that include some of the less common and less classical features could enhance diagnostic sensitivity without losing the specificity of current epidemiological criteria. This should help clinicians, general paediatricians especially, with earlier diagnosis and intervention. Such a study is currently in progress in our institutions.

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