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# Understanding and treatment of heart failure

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## Abstract

Despite ever-improving management options, paediatric heart failure continues to be a significant global health problem. The young age of presentation increases the number of causes of heart failure, which include congenital defects, primary or secondary heart muscle disease and high output systemic failure. Therapy is aimed towards correcting the underlying cause, or at least halting symptoms and progression. Recent drug trials have highlighted the importance of paediatric randomised control trials to determine the effectiveness of established adult heart failure medications in children, in whom the underlying pathology is different. This review aims to describe the main causes and treatments of heart failure in children.

**Keywords** cardiomyopathy; heart muscle; inotrope medication; left ventricle dysfunction

## Definition

Heart failure is defined as inability of the heart to supply sufficient oxygenated blood to meet the metabolic demands of the body. It is a clinical syndrome characterised by an alteration in cardiac output and an increase in venous pressure, which may be associated with progressive chronic deterioration in structure and function of the heart muscle.<sup>1</sup>

## Aetiology

Heart failure can be broadly divided into systemic diseases and diseases that arise from within the heart itself. Systemic causes include states of high output failure such as thiamine deficiency<sup>2</sup> or anaemia, where the cardiac output is maintained but cannot compensate for an increased circulatory demand.<sup>3</sup> A reduction or an increase in the circulatory volume can also provoke cardiac failure.

Problems arising from within the heart include those that cause reduced filling, and those that cause reduced ejection (although

the two are frequently linked). Decreased filling is due to reduced capacity, caused by hypertrophic cardiomyopathy (where relaxation is impaired during diastole<sup>4</sup>) or structural problems such as pericardial tamponade or constrictive pericarditis. A decrease in ejection fraction is due to obstruction (for example due to coarctation of the aorta on the left, or pulmonary hypertension on the right side) or problems with myocyte contraction (due to ischaemic damage or to intrinsic heart muscle disease<sup>5</sup>).

## Physiological response

Neurohormonal responses to reduced cardiac output result in systemic vasoconstriction and fluid retention. Peripheral vasoconstriction reduces cardiac output and can result in a compensatory ventricular hypertrophy. Stroke volume initially improves with fluid retention, but falls as the heart passes a certain point on the Starling curve and becomes overloaded.

Inside the heart, beta-adrenergic receptors ( $\beta_1$ ) are stimulated acutely and cause increased inotropy and chronotropy, which may compensate acutely, but with time this process becomes maladaptive as the receptors become downregulated and desensitised.

Myocytes are terminally differentiated cells, electrically linked to contract simultaneously in response to pacemaker generated currents. Cell depolarisation opens membrane calcium channels and the resulting calcium influx activates ryanodine receptors in the membrane of the sarcoplasmic reticulum (an intracellular calcium store). This causes calcium-induced calcium release into the cell cytoplasm, which acts on the sarcomeres to generate the force needed for cellular contraction. In order for relaxation to occur, calcium must be ejected from the cell membrane in exchange for sodium or re-sequestered into the sarcoplasmic reticulum via an adenosine triphosphate (ATP)-driven pump.

In heart failure there is an increase in cardiac workload. This results in myocyte hypertrophy and remodelling. Structural changes can also arise due to a direct cause for the failure such as a cardiomyopathy, or in response to valvular regurgitation or a restricted outflow tract. The changes are very diverse depending on the underlying pathology and include dilatation and an alteration in the thickness of the chamber walls. There is also fibrosis of the heart muscle where cell death occurs. These structural changes predispose the individual to develop arrhythmias.<sup>1</sup>

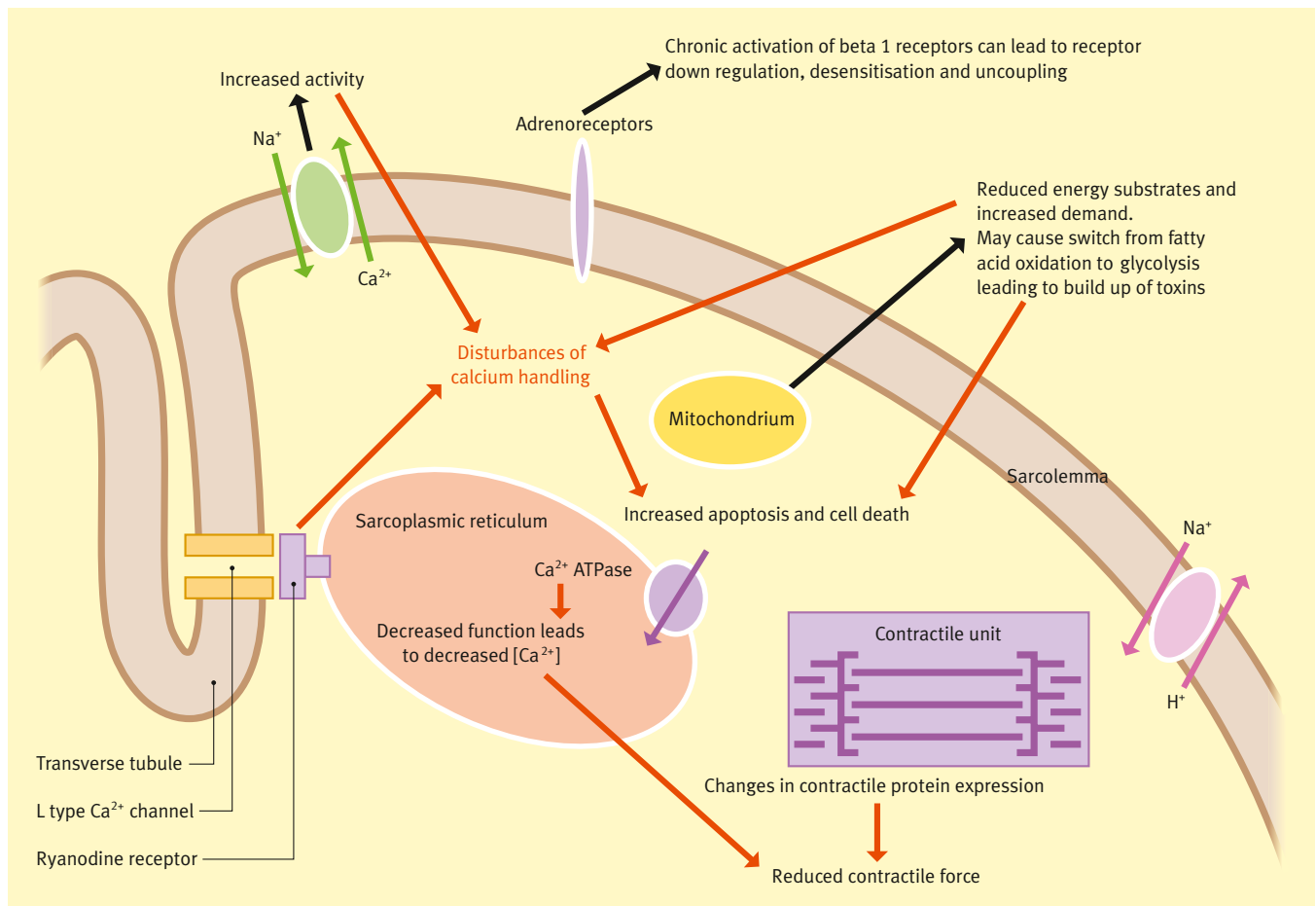
The available oxygen supply becomes limited, leading to a change from fatty acid oxidation to glycolysis.<sup>6</sup> This change coupled to the increased workload of each cell results in and increase in the rate of necrosis and apoptosis of the myocytes.<sup>7</sup> Since they cannot be regenerated, a vicious circle of cell death and increased workload on the remaining cells forms.

The acidosis that occurs as a result of glycolysis interferes with excitation-contraction coupling and with cellular relaxation. There are also complex changes within the cell proteins, including enzymes and membrane proteins that alter intracellular calcium handling (see Figure 1).<sup>8</sup> It has recently been postulated that there are changes in the cell contractile machinery, where rat models show a reversion of myosin back to a foetal phenotype.<sup>9</sup> The microbiological changes in heart failure appear to be extremely complex and varied depending on the aetiology of the failure. In addition, most studies are limited to autopsies or to animal models for obvious reasons.

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**Figure 1** Effects of heart failure on myocardial cells.

### Antenatal heart failure

Heart failure occurring *in utero* will result in ascites and restricted growth or in intrauterine death (see Table 1 for likely causes of heart failure for the different age groups). The most likely causes for antenatal heart failure are:

- **anaemia** – caused by rhesus sensitisation or foetal–maternal transfusion
- **arrhythmias** – usually supraventricular tachycardias that are an important reversible cause of heart failure, which can be managed medically
- **intrinsic heart muscle disease** – such as myocarditis or cardiomyopathies
- **structural problems** – in particular valvular regurgitation.

### Age of presentation and likely causes of heart failure

Age of presentation	Differential diagnoses for cause of heart failure
Antenatal	Arrhythmias and anaemia
<1 week	Duct-dependent structural defects
2 months to 1 year	Left to right shunts
0 years to 18 years	Cardiomyopathies

**Table 1**

### Congenital heart disease

The incidence of congenital heart disease, such as ventricular septal defects and atrioventricular septal defects, is approximately eight per 1000 live births. Routine foetal ultrasonography is performed at 18–20 weeks and will show most structural problems. Screening is also carried out if there is a positive family history or a chromosomal abnormality associated with an increased incidence of congenital heart disease. Management is largely surgical after delivery, and mortality rates have improved to 4%<sup>10</sup> in the UK. As a result, an increasing number of children with heart defects previously considered lethal are now surviving into adult life.

Simple heart defects may mask more complex structural problems, and these should always be ruled out in children presenting with heart failure where the clinical picture is more severe than can be explained by the diagnosed defect – for example, a simple atrial septal defect alone should not cause heart failure.<sup>11</sup>

### Heart failure in the first week

- Usually an acute presentation of an obstructed heart associated with the closure of the arterial duct
- Arrhythmias
- Cardiomyopathies (consider metabolic problems)

### Duct closure

In the foetus, the arterial duct channels blood between the pulmonary artery and the aorta. If there is a congenital heart defect

obstructing the left ventricle outflow tract, the systemic circulation is initially maintained by the patent duct, which typically closes 48 hours after birth. With duct closure, acute heart failure occurs and these infants need immediate emergency care and prostaglandins to re-open the duct. They will eventually require intervention with operation or cardiac catheterisation.

### Structural problems resulting in duct-dependent circulation

- Hypoplastic left heart syndrome
- Critical stenosis of the aortic valve
- Coarctation of the aorta
- Interruption of the aortic arch

### Heart failure in the first 3 months

- Left-to-right shunts produce a gradually worsening clinical picture
- Arrhythmias
- Cardiomyopathies (consider metabolic problems)

At birth, the pulmonary vascular resistance is very high, gradually falling in the first few months of life. As it falls, blood bypasses the higher resistance systemic circulation and as a result structural defects cause blood to mix between the systemic and the pulmonary circulation – a left to right shunt. These infants present with chronic, worsening heart failure usually characterised by non-specific features, such as faltering growth, difficulty in feeding and failure to meet expected developmental milestones. Without treatment, pulmonary vascular disease (Eisenmenger's syndrome) will develop. Hence, surgical or interventional catheterisation at a few months of age will occlude the defect, reduce or abolish the left-to-right shunt and avoid the need for a heart and lung transplant.

### Shunts causing heart failure

- Ventricular septal defect
- Atrioventricular septal defect
- Persistent arterial duct
- Aorto-pulmonary window
- Arterio-venous malformations

### Heart failure from 0–18 years

- Cardiomyopathies
- Arrhythmias
- Other

The most common cause of heart failure in this population is cardiomyopathy. If presenting in infancy, faltering growth is again seen, but if presenting at a later age such signs will not be as immediately apparent, but poor exercise tolerance is the predominant symptom.

Children with congenital heart disease may also present with heart failure, either following surgery or due to structural abnormalities, such as anomalous coronary artery from the pulmonary artery, which causes poor left ventricular function.<sup>10,12</sup>

### Cardiomyopathies

Cardiomyopathies are diseases of heart muscle. The most common type of cardiomyopathy is dilated cardiomyopathy, which is usually idiopathic (70% of cases), although an increasing number

of genetic causes are being identified. In this condition there is ventricular dilatation and impaired systolic and diastolic function, leading to cardiac failure, conduction defects and arrhythmias. It is important to remember structural causes of dilated cardiomyopathy, such as anomalous origin of the left coronary artery from the pulmonary artery. In this condition, the falling pulmonary vascular resistance gradually leads to infarction of the left ventricle. The infant will present with heart failure, poor growth and screaming episodes on feeding (due to angina).<sup>13</sup> The importance of this and similar conditions is that it can be surgically treated once recognised. Similarly, valvular regurgitation may lead to heart failure and dilated cardiomyopathy, which may benefit from surgical intervention.<sup>14</sup>

The other main forms of cardiomyopathy – as classified by the World Health Organisation – are restrictive cardiomyopathy and hypertrophic cardiomyopathy. There is often considerable overlap between the three, and the severity of the clinical presentation can be very varied.

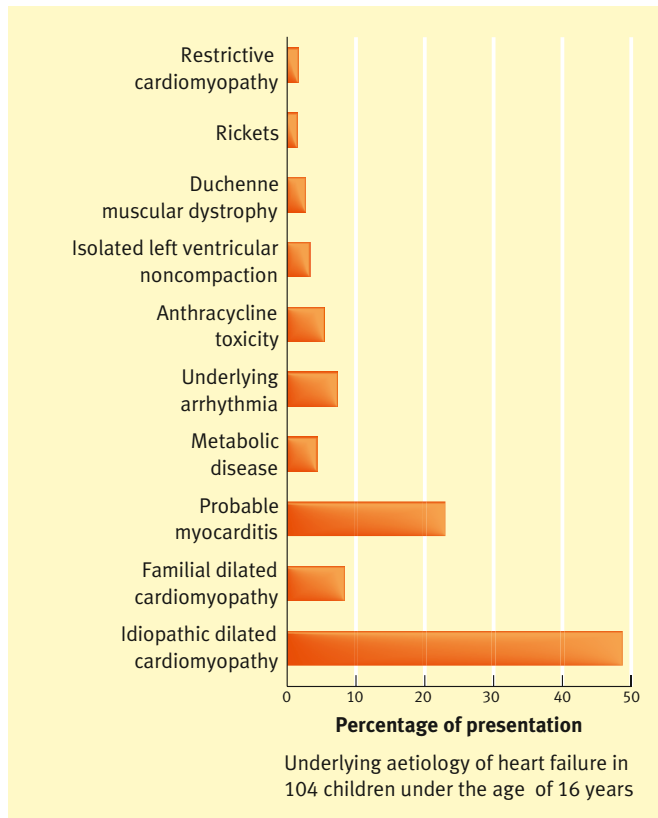
A recent prospective study of heart muscle disease in UK and Ireland has shown the incidence of new onset heart failure due to cardiomyopathy in children under 16 years to be 0.87/100 000 (see Figure 2).<sup>15</sup>

### Other causes of heart muscle disease

- Myocarditis – spontaneous inflammation of the myocardium either due to an infective cause (such as Coxsackie or rubella) or because of an autoimmune or idiopathic process. The outcome is variable, and can lead to cardiac failure, which may be fatal or require heart transplantation. The most common cause of myocarditis worldwide is Chagas' disease (caused by trypanosome cruzi), which is endemic in South America. The underlying causes of myocarditis are often not discovered, and myocardial biopsy (which is the gold standard investigation) is not routinely performed
- Infection and inflammation
  - Rheumatic fever
  - Infective endocarditis leading to acute valvular regurgitation and long-term mixed valve disease
- Drugs and toxins (e.g. anthracyclines)
- Degenerative – primary myopathies or neurodegenerative disease, such as Friedreich's ataxia
- Metabolic (see Table 2)

### Signs and symptoms

- Tachycardia
- Venous congestion
  - Ascites
  - Hepatosplenomegaly
  - Tachypnoea
  - Difficult breathing – grunting, chest wall retraction and nasal flare in young children
- Fatigue
- Failure to thrive
- Cool peripheries
- Exercise intolerance
- Pallor
- Altered consciousness



**Figure 2** New onset heart failure due to heart muscle disease in the UK (2003). Data taken from Andrews et al. 2008.<sup>15</sup>

### Presentation of heart failure in different age groups

The initial signs and symptoms of heart failure reflect normal adaptive mechanisms undertaken to achieve normal cardiac output, such as tachycardia. Later, features of venous congestion become apparent. Finally the symptoms are related to low cardiac output.

The clinical picture is very closely related to age (see Table 3). In young children, where the growth rate is normally rapid, the predominant feature is failure to thrive. As their lungs fill up with fluid, features of respiratory distress become obvious too.

Neonates with left-sided heart failure, caused either by poor pump function, or by outflow obstruction usually develop the signs and symptoms quickly – over a few days early in life. Conversely those with a left-to-right shunt, who become volume overloaded, show a slower, more insidious progression of disease.

In older children, failure to thrive is much less apparent. Indeed they may even gain weight due to fluid retention. The most obvious symptom, which is perhaps the best way to gauge the progression of heart failure, is decreased exercise tolerance.

### Management

This section will look at the management of acute decompensated heart failure. Then the actions of the main drug groups used to treat failure will be explained.

### Metabolic causes of heart muscle disease

Metabolic condition	Description	Pathology	Prognosis
Infantile Pompe's disease (Glycogen storage disease type II)	Lysosomal storage disease (alpha-1,4-glucosidase deficiency)	Glycogen deposits in heart, liver and skeletal muscle - congestive cardiac failure CCF, cardiomegaly, hepatomegaly and generalised muscle weakness	Poor. Death occurs in infancy (prognosis of mitochondrial disorders). Very variable.
<ul style="list-style-type: none"> <li>Myoclonic epilepsy with ragged red fibres</li> <li>Chronic progressive external ophthalmoplegia</li> <li>MELAS</li> <li>Leigh's disease</li> <li>Kearns-Sayre syndrome</li> </ul>	Mitochondrial disorders	Most common cardiac manifestations include dilated/ hypertrophic cardiomyopathies and conduction defects. Suspect in children with multi-system pathologies (often respiratory, neurological and renal abnormalities)	Variable
Mucopolysaccharidosis, mucopolipidosis, Fabry disease	Storage diseases	Lipid deposits cause cardiac enlargement	Variable
Primary carnitine deficiency, carnitine palmitoyltransferase abnormalities and defects in long chain fatty acid oxidation	Problems with lipid metabolism	Cardiomyopathies can occur	Variable

Congestive cardiac failure CCF; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.

**Table 2**



### Presentation of heart failure in different age groups

Age	Symptom
Infant	Faltering growth Respiratory distress - use of accessory muscles, nasal flare, grunting Altered consciousness
Older children	Decreased exercise tolerance Poor appetite

**Table 3**

### Acute heart failure

The aim of treatment of acute decompensation is to ensure adequate perfusion and oxygenation of end organs, looking to normalise cardiac output and treat any reversible causes. Acute severe heart failure is best treated on the paediatric intensive care unit. Wherever possible, the underlying primary cause should be treated early. For an obstructive problem, surgery may be indicated; high output failure demands diuretics; and poor pump function requires positive inotropes and a reduction in the afterload.

Heart failure may be complicated by respiratory failure – which may necessitate mechanical ventilation via an endotracheal tube. [Table 4](#) lists possible management options. Some investigations should be undertaken promptly: in young children it is important to rule out sepsis and structural heart lesions first, by blood cultures and echocardiography respectively. Broad spectrum antibiotics are given. If a duct-dependent lesion is found or if it cannot be ruled out quickly, it is important to commence a prostaglandin E<sub>1</sub> infusion immediately. This intervention may exacerbate other causes of failure but it is lifesaving in duct-dependent causes of heart failure.

An intravenous infusion of dopamine is given. This is a positive inotrope, whose action is explained in more detail later. If this does not work other inotropes may be given, such as dobutamine. Anaemia, if present, must be corrected for obvious reasons. Other investigations are guided by clinical history, for example tracheal aspiration and blood serology for viral causes of myocarditis such as Coxsackie, rubella and other endemic infections depending on geography. Muscle biopsy may be indicated if mitochondrial disease is suspected and immunological

tests can be performed if systemic lupus erythematosus or other rheumatological disease is queried.

Volume status must be closely monitored, usually by insertion of a central venous catheter. Septic children whose heart failure is due to cardiogenic shock will benefit from fluid resuscitation. Others who have had chronic heart failure for some time and acutely decompensate may require furosemide, which can be given by intravenous infusion. An important complication to be aware of is over-diuresis, particularly in patients who have been treated with diuretics for chronic failure.

Sodium nitroprusside is also used in the emergency setting to markedly reduce both preload and afterload. It is also used for hypertensive crises and causes a profound fall in blood pressure, so close monitoring is essential, as is attention to the blood cyanide concentration, which may rise to dangerously high levels due to the metabolism of the drug. Glyceryl trinitrate is very occasionally used.

Once the child has been stabilised, outpatient treatment will consist of diuretics, with other agents being added as appropriate. The place for positive inotropes and nitrates outside of the acute management of decompensation is limited. Whilst the aim of treatment of acute failure is restoration of cardiac output sufficient to perfuse end organs adequately, the goals of chronic heart failure must also take into consideration the harmful maladaptive processes, which result if underlying cause are not reversed – necrosis, apoptosis, beta-adrenergic receptor downregulation and remodelling process that takes place within the myocytes.

### Ongoing management

Medical treatment may focus on the preload, afterload or the contractility of the heart itself. Diuretics and venodilators reduce the preload, especially important in fluid overload. Cardiac contractility may be enhanced by catecholamines, sympathomimetics and drugs that work further downstream, which are useful in combating poor pump function but may increase myocardial oxygen demand. The afterload may be reduced by vasodilation using angiotensin-converting enzyme (ACE) inhibitors or some nitrates. Other drugs focus on preventing maladaptive change in the heart, such as beta-blockers. See [Table 5](#) for some management principles of the common causes of paediatric heart failure.

### Diuretics

Diuretics reduce preload by increasing the excretion of sodium and water. This provides symptomatic relief of congestion and consequently diuretics are the mainstay of treatment in chronic heart failure. There are no randomised controlled trials (RCTs) comparing diuretics with placebo in the treatment of heart failure in children, indeed diuretics are part of the background standard care in trials evaluating newer treatments. Loop diuretics, such as furosemide or bumetanide are usually the first line. They inhibit the sodium/chloride/potassium (Na<sup>+</sup>ClK) co-transporter in the loop of Henle and block a large proportion of sodium re-absorption – some 20% of the filtered sodium load. The main complication of loop diuretics is hypokalaemia caused by kaliuresis due to their action on the Na<sup>+</sup>ClK co-transporter and stimulation of the renin-aldosterone-angiotensin (RAA) system. This may be prevented by either the addition of potassium supplements, or a potassium sparing diuretic. Eventually tolerance to the diuretics

### Acute heart failure – possible management options

	Management
Airway	Intubation may be required
Breathing	Oxygen
Circulation	Positive inotropes - dopamine first line Central line to monitor fluid volume
Investigations	ECG, ECHO, bloods Specific investigations guided by age at presentation

ECG, electrocardiogram; ECHO, echocardiogram.

**Table 4**

### Management principles of the common causes of paediatric heart failure

Underlying cause	Management
Duct-dependent structural defect	Prostaglandin E1 to maintain patent duct Stent or shunt insertion
Left-to-right shunt	If premature neonate, give i.v. indomethacin to close PDA Diuretics to prevent overload and development of pulmonary hypertension Surgical repair of defect
Cardiomyopathy	Beta-blockers ICD for arrhythmia Heart transplant

PDA, patent ductus arteriosus; ICD, implantable cardioverter defibrillator.

**Table 5**

may develop due to activation of the RAA system, sympathetic innervation and distal tubule hypertrophy counteracting the natriuresis. This problem is generally dealt with by the addition of another diuretic that acts elsewhere in the tubules. It is usual to add a thiazide diuretic or metolazone. They block a NaCl co-transporter in the distal convoluted tubule. Other diuretics that may be added to a loop diuretic are acetazolamide, dopamine and theophylline.

Sometimes apparent tolerance may be due to other reasons, such as inadequate perfusion of the kidneys. This may be remedied by increasing the cardiac output by the addition of a beta agonist. Low albumin, metabolic alkalosis and low chloride have also been noted to cause diuretic resistance.

#### ACE inhibitors

ACE inhibitors are used to good effect in the reduction of afterload – this makes them particularly effective in the treatment of heart failure caused by left-to-right shunt, regurgitant aortic flow and left ventricular dysfunction.

In heart failure, the RAA system is activated. Renin is produced in the juxtaglomerular apparatus of the kidney, in response to a fall in blood pressure or blood volume. It cleaves a plasma globulin called angiotensinogen to form angiotensin I. Angiotensin I, itself reasonably inert, is converted by angiotensin-converting enzymes to angiotensin II, which acts primarily via the AT1 receptor to cause generalised vasoconstriction, secretion of aldosterone and the re-absorption of sodium in the proximal convoluted tubule. ACE inhibitors prevent the conversion of angiotensin I to active angiotensin II, thus ACE inhibitors reduce cardiac afterload by vasodilatation, improve tissue perfusion and reduce congestion by natriuresis. Not only are ACE inhibitors very useful symptomatically, they also reduce cardiac myocyte remodelling by preventing fibrosis. The long-term use of ACE inhibitors may be limited by a phenomenon known as ‘aldosterone escape’ – aldosterone secretion is stimulated independent of angiotensin II production and thus the positive effects of ACE

inhibition are reversed. The effectiveness of ACE inhibitors has been shown by large multicentre trials in adults. One systematic review that compared mortality in populations with severe heart failure between 3 and 42 months showed a reduction in mortality of 23% in those treated with ACE inhibitors compared with placebo.<sup>16</sup> In children, studies have been more limited – one showed improved mortality<sup>17</sup> and another showed reduced end-diastolic volume.<sup>18</sup> A variety of ACE inhibitors are used in the treatment of heart failure in children: captopril, lisinopril and enalapril are routinely used. They are all available as oral preparations. As in adults, ACE inhibitors are contraindicated in children with bilateral renal artery stenosis or severe stenosis of a single functioning kidney. Particular care must be taken when a child is also taking diuretics – the first dose of an ACE inhibitor may cause very severe hypotension. Therefore, the first dose must be very low and, where possible, the diuretic dose should be reduced, or the child must be put under close observation. In neonates, particularly those who are premature, ACE inhibitors are generally avoided – the response is very unpredictable, which may be a result of a different composition of AT1 and AT2 receptors.

#### Angiotensin II receptor antagonists

Angiotensin receptor antagonists act in a similar way to ACE inhibitors. There are no problems of aldosterone escape with these drugs, nor do they cause the cough due to bradykinin accumulation. Some difference in their effect compared with ACE inhibitors may be postulated since the sartans are specific AT1 blockers, and young children have a relatively higher concentration of AT2 receptors. These drugs are not widely used in clinical practice, and are reserved for children who cannot tolerate ACE inhibitors as there is much less evidence for them, although the limited number of adult studies suggest they are just as effective.<sup>19</sup> Losartan is the most commonly used angiotensin receptor antagonist in clinical practice.

#### Inotropic medications

A variety of drugs act primarily to increase the force of cardiac contraction. They may act directly on the beta-adrenergic receptors, downstream in the cyclic adenosine monophosphate (AMP) cascade, on the sodium ion channels or on the sodium-calcium exchanger – all of which act to increase the amount of intracellular calcium available for myocyte contraction, or to sensitise the contractile machinery to the calcium already present.

- Dobutamine and adrenaline stimulate  $\beta_1$  receptors directly acting in the same way as endogenous catecholamines, and have the same limitations – the eventual receptor downregulation, necrosis and apoptosis of the myocytes and an increase in oxygen demand.
- Phosphodiesterase inhibitors – such as amrinone, enoximone and milrinone – work downstream. They prevent the breakdown of cAMP by phosphodiesterase III to reduce the afterload. Despite the initial symptomatic benefit of these drugs, a Cochrane review of phosphodiesterases in adults showed that they are associated with increased mortality due to a pro-arrhythmic effect.<sup>20</sup> Nonetheless, oral enoximone is commonly used in paediatric specialist centres for its combination of inotropic and vasodilatory effects.
- Levosimendan is a positive inotrope that acts independently of the adenylyl cyclase pathway. Levosimendan binds troponin



C to sensitise the cardiac myocytes to calcium. It also activates  $K_{ATP}$  channels in vascular smooth muscle – opening them to cause relaxation – and thus reducing preload and afterload. The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial – an RCT comparing dobutamine with levosimendan in 1327 adults requiring inotropic support – showed levosimendan was equally as effective with no significant difference in mortality at 6 months.<sup>21</sup> Retrospective studies in small numbers of children have shown the drug to be safe and to allow a reduction in the use of conventional inotropes – which are associated with increased long-term mortality.<sup>22,23</sup>

### Cardiac glycosides

It is thought that cardiac glycosides, such as digoxin, inhibit the sodium-potassium pump – the consequent increase in intracellular sodium reduces the inward sodium current, which is also what drives the sodium-calcium exchanger – so there is also an increase in intracellular calcium. Digoxin thus has positive inotropic effects. Digoxin also causes an increase in vagal outflow, which slows the rate and allows the heart to fill up adequately; however, this increase may further drive the maladaptive sympathetic nervous system response. Digoxin has a narrow therapeutic window and its levels in the bloodstream must be monitored to avoid toxicity. It is not routinely used in children.

### Nitrates

Drugs which are metabolised to nitric oxide – such as glyceryl trinitrate, isosorbide mononitrate and nitroprusside – cause a fall in peripheral vascular resistance, which may translate to a fall in preload or afterload or both depending on the type of nitrate used. Nitric oxide activates guanylate cyclase to increase the formation of cGMP, activating protein kinase G leading to the relaxation of vascular smooth muscle. These drugs have been limited so far to the acute setting, but an increased use for them may be found in chronic heart failure. The VHeFT trial showed that nitrates and hydralazine improved survival in adult patients with symptomatic heart failure.<sup>24</sup> Nitrates are particularly useful in patients who cannot tolerate ACE inhibitors.

### Beta-blockers

It seems somewhat counterintuitive to use negative inotropes in the treatment of heart failure. Nonetheless beta-blockers are invaluable in treating some of the counter-regulatory features of the syndrome, namely the activation of the sympathetic nervous system and RAA system. Reduction in RAA system activation reduces the preload and consequently reduces ventricular wall stress and cardiomyocyte remodelling. Initially beta-blockers may exacerbate the symptoms of heart failure, so it is important to start on a very low dose and titrate carefully. The initial relapse is less severe with drugs like carvedilol, compared with propranolol, as it causes a degree of peripheral vasodilation. It is known that beta-blockers improve symptoms and survival in adults – one systematic review showed a mortality reduction of 8% compared with placebo in heart failure of any severity<sup>25</sup>; this was increased to 25% when the heart failure was more severe.<sup>26</sup> When different beta-blockers were compared with each other, it was found that carvedilol extends survival compared with metoprolol.<sup>27</sup> This is probably due to the peripheral

vasodilatation caused by carvedilol – the drug also reduces preload. A recent RCT failed to show a statistically different outcome for carvedilol compared with placebo in 161 children and adolescents with symptomatic heart failure.<sup>28</sup> This trial illustrates the potential danger of extrapolating results from adult RCTs to paediatrics where the pathophysiology is not equivalent, yet also highlights the challenges of developing evidence-based therapeutics in children – it is not simple to design well-powered and ethical trials.

### Anticoagulation

Chronic heart failure puts children at an increased risk of ventricular mural thrombus. Aspirin prophylaxis may be indicated after cardiac surgery and in patients with diastolic heart failure, who are at particular risk of emboli. However, there have been some reports of aspirin exacerbating heart failure, by reducing the effects of ACE inhibitors and diuretics.<sup>29</sup> Warfarin may also be used prophylactically, although this requires frequent monitoring of international normalised ratio.

### Surgery

Congenital cardiac problems can generally be treated definitively with surgery or catheterisation in developed countries. Cardiomyopathies and myocarditis are treated supportively with drugs and most patients recover or are stabilised with medication. If this does not control symptoms, cardiac transplantation is the only effective treatment. Whilst waiting for a donor heart, bridging devices may be used. The most common is a left ventricular assist device, a pump which replaces the left ventricle. Blood is pulled from the left ventricle into a pump that sits in the upper abdomen. From there the blood is forcibly ejected into the aorta. Occasionally, the left ventricular assist device prevents the need for future transplantation and the function of the failing heart returns.

The Fontan operation may be performed for children with only one functioning ventricle. Although this procedure is life-saving in infants, it is associated with development of dilated cardiomyopathy and subsequent heart failure later in life.

### Conclusion

Heart failure, although rare, is still a cause of considerable morbidity and mortality in children. It may present at any stage from foetus onwards. Heart failure is a clinically defined syndrome, just as in adults. Its causes, however, could not be more different, including: a wide variety of congenital structural defects, metabolic disease, infection, and autoimmune disease. As ever, knowledge of aetiology is imperative for successful management. Medical and surgical advances have increased survival substantially, but present complications of their own, making the management of paediatric heart failure a complex but rewarding field. The challenge in the future will be to find evidence-based therapies for children. ♦

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### Practice points

- Paediatric heart failure is a clinical diagnosis.
- Age of onset helps determine aetiology.
- The main aim of acute management is to optimise cardiac output.
- Surgical management is the only definitive treatment for structural congenital heart lesions.
- Long term medical management aims to reduce maladaptive processes, manage symptoms and where possible reverse the underlying cause.
- Existing medical management is largely based on data from adult trials and well designed, high powered trials need to be carried out in children.

# Physiology and treatment of hypertension

Deepa Athavale

Malcolm A Lewis

## Abstract

Secondary hypertension in children is a rare but important cause of morbidity and mortality. Whilst severe hypertension can be symptomatic more often it is not and blood pressure measurement is mandatory in all children at risk. The vast majority of childhood secondary hypertension is related to renal disease and treatment is with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Primary or essential hypertension in children is being increasingly recognised. Lifestyle factors and obesity play a significant role. If long-term morbidity is to be avoided early detection assessment and intervention is required.

**Keywords** causes; children; hypertension; investigation; management

## Introduction

Hypertension in children was recognised as a rare problem, usually secondary to a renal or endocrine pathology. As in adults, this secondary hypertension of childhood is recognised as carrying significant morbidity and mortality, both from the underlying disease processes and the effects of the hypertension itself.<sup>1</sup> More recently, however, the focus has changed from secondary to primary hypertension in childhood. The origins of primary or essential hypertension in childhood have been well documented.<sup>2</sup> Moreover, with the rise in obesity prevalent in the western world, the incidence of hypertension in paediatrics is also on the increase.<sup>3</sup> Unfortunately, whilst hypertension can clearly be defined as the blood pressure (BP) above which cardiovascular morbidity develops in adults, such a clear cut off is not available for children, where BP varies with both age and size.<sup>4</sup> This has led to the definition of paediatric hypertension as being a BP above the 95th centile for age and height. This definition itself is questionable as it inevitably labels 5% of the population as being hypertensive without consideration of other factors.

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This review seeks to define the complexities and challenges of the diagnosis, assessment and management of hypertension in children.

## Pathophysiology

The pathophysiology of hypertension is best understood with knowledge of the mechanisms behind normal BP control. Mean arterial blood pressure (MAP) is related to cardiac output, vascular tone and intravascular volume as shown in the formula below:

$$\text{MAP} = (\text{CO} \times \text{SVR}) + \text{CVP}$$

where CO = cardiac output, SVR = systemic vascular resistance and CVP = central venous pressure.

As MAP is represented by the mean of the area under the curve in the normal pulse wave, it is clear that alterations in diastolic pressure secondary to changes in vascular tone and filling pressure have a more marked effect on MAP than changes in systolic pressure. Factors influencing vascular tone include the autonomic nervous system and the renin-angiotensin system (RAS). These systems are also involved in the control of cardiac output by affecting contractility. The RAS system is also involved in volume control as are other hormonal systems including atrial natriuretic peptide and anti-diuretic hormone. Rapid changes in BP tend to be mediated through the autonomic nervous response whilst more medium- and long-term responses are mediated through the hormonal systems. Diseases or conditions that lead to inappropriate responses by these systems can lead to hypertension.

One clear example of such an inappropriate response is in patients with renal artery stenosis. Here, secondary to reduced BP beyond the area of the stenosis, the kidney senses a reduction in perfusion pressure. As a result, similar to the normal renal response to blood loss and hypotension, renin is secreted to stimulate a rise in BP. This continues until an appropriate perfusion pressure is achieved beyond the stenosis. The cost of this is sustained systemic hypertension.

## Measurement of BP

The first true measurement of BP was made by the Rev Stephen Hales in the mid-18th century. This was achieved by cannulating a major artery in a horse then watching the tidal rises and falls in blood level in an 8ft high manometer tube. More conventional BP measurement using cuff compression of an artery to determine systolic pressure was devised by Riva-Rocci in 1896. This system was modified by Korotkoff in 1905 who noted the sounds generated by arterial opening and closure between the systolic and diastolic pressures.<sup>5</sup> This system remains the gold standard for non-invasive BP monitoring today. Whilst with today's technology it is possible to have continuous intra-arterial monitoring of BP, it needs to be appreciated that the values generated are not going to be exactly the same as with non-invasive monitoring and that all studies of long-term outcome are based upon non-invasive monitoring, usually using a mercury sphygmomanometer. The conditions used for casual BP measurement need to be standardised if results are to be reproducible. BP ought to be measured with the child sitting or lying in a relaxed environment.

Whilst standards have been derived in this way, all too often BP is not assessed in this way leading to the erroneous diagnosis of hypertension.

### The BP cuff

The selection of an appropriate cuff is a critical element in the correct measurement of BP. The smaller the area of arterial compression the higher the pressure needed to achieve occlusion. Whilst it is described that the circumference of the arm midway between the acromion and the olecranon should be used for the cuff width, this is only appropriate for those of average proportions and will lead to too small a cuff being used in those with very thin arms and the converse for the obese. The width of the cuff ought to be two-thirds of the distance from the acromion to the olecranon. In practice, because of the distance from the axilla to the acromion, this is the largest cuff that will fit the arm and allow access to the antecubital fossa with a stethoscope. The bladder of the cuff itself ought to cover at least two-thirds of the circumference of the arm. If in doubt it is always worthwhile removing the bladder from the cuff to see its true size.

### Manual BP measurement

All manual devices depend upon the use of auscultation to define the systolic and diastolic BP. The systolic BP is defined as the point at which the tapping sounds are first heard on cuff deflation (Korotkoff 1), the diastolic BP is taken as the point at which the sounds disappear (Korotkoff 5), unless the sounds persist at all pressures in which case the point of muffling (Korotkoff 4) is taken. Common errors in BP measurement are to over inflate the cuff, causing distress, deflate the cuff too rapidly allowing poor definition of the true systolic and diastolic BP or deflate the cuff too slowly causing distress. It is the authors' practise to first inflate the cuff whilst palpating the brachial pulse until it disappears to define the level of the systolic pressure and then re-inflate the cuff to 10 or 15 mmHg above this level and auscultate on slow deflation. It is only by using this technique that one can use the minimal inflation pressure whilst being certain that an auscultatory gap has not been missed (with consequent failure to diagnose hypertension). Whilst the systolic BP as judged by palpation is often a few mmHg below that assessed by auscultation, the systolic BP defined using a Doppler device over the artery will be a few mmHg above the systolic by auscultation. Care, therefore, needs to be taken in the assessment of systolic BP in infants where this technique is used.

A variety of devices are available for manual BP measurement. Whilst the mercury sphygmomanometer remains the gold standard, an increasing number of establishments are banning the use of these devices because of the dangers of mercury spillage. Anaeroid sphygmomanometers measure BP by using a bellows and lever system. They are subject to considerable drift and require regular recalibration if they are to be relied upon. More recently a number of manometers using an electronic pressure transducer have become available, of which the Accoson Greenlight 300 is fully validated accurate and practical device used by the authors.<sup>6</sup>

### Automated casual BP measurement

Automated devices are commonly used in practice for ease and convenience. They work either by detecting Korotkoff sounds by

a microphone or arterial blood flow by ultrasound or through oscillometry. Oscillometry depends upon the detection of small changes in cuff bladder pressure secondary to arterial pressure changes in the arm. It is susceptible to movement artefact (which is important when dealing with children) but oscillometric devices are now generally accepted in clinical practice. A plethora of these are on the market, the most common belonging to the Dinamap<sup>®</sup> family, this being an acronym for 'Device for indirect, non-invasive mean arterial blood pressure'. This acronym is important. The MAP on an oscillometric machine is defined as the lowest pressure at which maximal oscillation in the cuff is detected. Each machine takes the point of commencement and disappearance of oscillations (which are not the systolic and diastolic pressures as measured by auscultation) and the MAP as defined above and uses an algorithm to calculate systolic and diastolic pressure. The algorithms are different for each machine. Thus, systolic and diastolic pressures as measured using an oscillometric device do not necessarily relate to those measured by auscultation and it is widely clinically accepted that they are generally higher than mercury sphygmomanometer measurements.<sup>7</sup> Moreover, the only values that will be the same on different machines are those for MAP. This raises the question as to whether MAP rather than systolic and diastolic BP ought to be used for the assessment of BP when oscillometric machines are used.

### Automated ambulatory BP monitoring

First devised in 1962 with modification a few years later, ambulatory BP monitoring (ABPM) has developed over the years to become a valuable asset in BP measurement. There is good accumulating evidence in adults showing it to be accurate as well as a good predictor of clinical outcome.<sup>8</sup> It is advantageous in children as it allows measurements over a prolonged period, away from a clinical setting, devoid of human error and taking into account the natural circadian rhythm of BP.

As with oscillometric machines for casual BP measurement, ABPM monitors ought to be validated by either the British Hypertensive Society or American Association for the Advancement of Medical Instrumentation.

Devices come with different sizes of cuffs and can be programmed to different frequencies of cuff inflation over the day and night time periods. Data is collected for systolic, diastolic and mean BP plus heart rate on each inflation. A 24-hour mean, daytime mean and nocturnal mean BP plus BP load (percentage of measurements over a predetermined threshold, usually the 95th percentile for age or height in children) are calculated upon data download. In normal circumstances, a nocturnal dip is seen with a fall of BP of up to 20% at night. Normal reference ABPM data required for comparison are available.<sup>9</sup>

ABPM is questionably the most important advance in BP measurement since the utilisation of the Korotkoff sounds. The frequency of measurements throughout the day allow a true picture to be seen of the mean BP and its variability. It allows patients with 'white coat' hypertension to be quickly diagnosed. It permits reproducible data for monitoring treatment and interventions.

### Definition of hypertension

The definition of paediatric hypertension is arbitrary and based on epidemiological data provided by American 4th Task Force

data.<sup>3</sup> It is derived from compilation of normal distributive data for BP in children. Almost all the values were obtained using mercury sphygmomanometer BP measurements. The study included a few oscillometric BP measurements in infants.

Hypertension is defined as the systolic or diastolic BP being equal to or greater than the 95th centile for age, height and gender, measured on at least three different occasions. Pre-hypertension is a state defined as BP values falling between the 90th and 95th centiles. The Task Force defines two stages of hypertension. Stage 1 hypertension is a BP between the 95th centile and 5 mmHg over the 99th centile. Stage 2 hypertension is a BP above the 99th centile + 5 mmHg. Whilst the 99th centiles do not appear in the Task Force tables these are 7–10 mmHg above the 95th centiles. Thus Stage 1 or mild hypertension represents a BP between the 95th centile and 15 mmHg above this. Stage 2 or moderate hypertension is a BP more than 15 mmHg above the 95th centile. Severe hypertension can then be classified as patients whose BP is over 25 mmHg above the 95th centile or patients with a BP below this who are symptomatic.

It needs to be remembered that these commonly used centiles were derived using the mercury sphygmomanometer. As it is well recognised that values from oscillometric machines are different the use of these centile for oscillometric readings is inappropriate. UK centile charts using one oscillometric machine have been derived.<sup>10</sup> A study is required to look at the positive and negative predictive value of using an oscillometric machine and these centiles to diagnose hypertension compared with a mercury sphygmomanometer (or equivalent) and the Task Force centiles.

## Causes of hypertension in children

The most common and important causes of hypertension are listed in Table 1. In many cases the hypertension is not the presenting problem and the cause is obvious. This applies to patients presenting with acute renal problems such as Henoch Schoenlein nephritis or nephritic syndrome and patients with chronic renal diseases such as polycystic kidney disease or renal dysplasia / scarring. At least 80% of children with secondary hypertension have an underlying renal pathology and this is therefore the starting point when approaching investigation and treatment.

Renovascular disease is important and needs recognition as inappropriate use of ACE inhibitors or angiotensin receptor blockers can lead to loss of renal function in renal artery stenosis. This needs to be particularly considered in patients with neurofibromatosis or William's syndrome.

The most common renal tumour is a Wilms' tumour and this is usually obvious as the cause of hypertension at presentation. Haemangiopericytoma's are exceptionally rare minute tumours of the juxtaglomerular apparatus. Angiomyolipomata are more common and frequently seen in patients with Tuberous Sclerosis but rarely cause problems. Recently it has been shown that Siro-limus can cause regression of growing angiomyolipomata.<sup>11</sup>

Obstructive uropathy is important because here the underlying cause needs treatment to allow resolution of the hypertension. Inappropriate use of antihypertensive drugs to lower the BP in a patient with acute hypertension from obstructive uropathy from a neuropathic bladder can lead to problems of severe hypotension when treatment with catheterisation is then instituted.

## Causes of hypertension in children

Origin of hypertension	Examples of causes
Renal parenchymal disease	Renal scarring Renal dysplasia Polycystic kidney disease Chronic glomerulonephritis Chronic renal failure Acute renal failure Acute glomerulonephritis Nephrotic syndrome Acute vasculitis
Vascular and renovascular disease	Renal artery stenosis Coarctation of the aorta Renal arterial or venous thrombosis Micro-embolic disease e.g. after umbilical catheterisation or bacterial endocarditis Hypertensive damage to intra-renal vessels Trauma Arterio-venous fistulae Renal trauma and compression
Renal tumours	Wilm's tumour Haemangiopericytoma Angiomyolipomata
Obstructive uropathy	Pelvi-ureteric junction obstruction Bladder outlet obstruction Neuropathic bladder
Catecholamine excess	Phaeochromocytoma Neuroblastoma
Corticosteroid excess	Iatrogenic Cushing's syndrome Conn's syndrome Glucocorticoid remediable hypertension Apparent mineralocorticoid excess Liddle's syndrome Gordon's syndrome
Neurological causes	Raised intracranial pressure Seizures Guillain-Barre syndrome Poliomyelitis Spinal cord injury
Drugs/dietary causes	Caffeine Alcohol Oral contraceptives Cocaine Sympathomimetic drugs
Essential hypertension 'White coat' hypertension	

Table 1

Other symptoms and signs, a family history and the presence of a low plasma renin usually give the clues that an endocrine cause for hypertension may be present. The presence of a causative neurological disease is usually plainly evident though it can



sometimes be difficult to discern whether seizures are a cause or a result of hypertension.

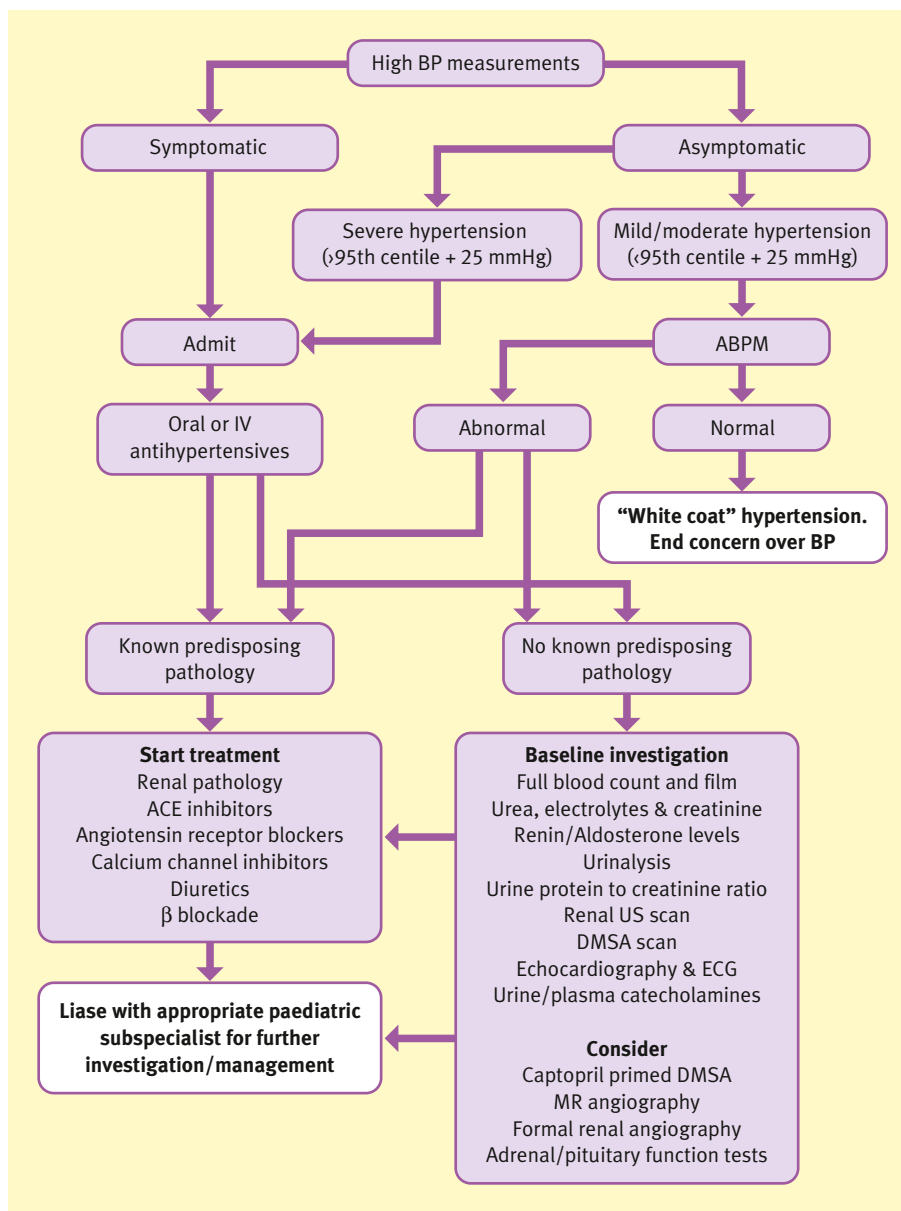
Dietary causes and drugs, both prescribed and unprescribed, are important factors that need consideration as hypertension can be resolved without recourse to antihypertensive medication in many cases. Essential hypertension is becoming increasingly commonly recognised in paediatric patients. This relates both to the more frequent routine measurement of BP in the population and lifestyle changes with an epidemic of obesity in the young. It remains important in these cases to rule out anxiety and 'white coat' hypertension.

### Investigation and management of hypertension in children

The investigation and management of a child with high BP measurements is dependent upon the clinical state of the child. A plan of action is shown in Figure 1.

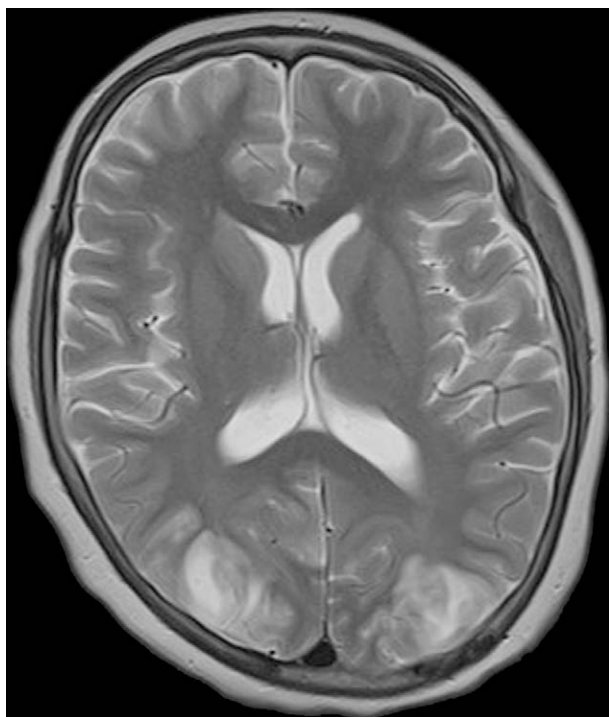
### Symptomatic hypertension

Only a minority of children with a high BP will have symptoms from this. Whilst children may have mild symptomatology such as headaches and nosebleeds, the majority of symptomatic patients have a severe presentation with convulsions. On magnetic resonance imaging these patients often have dramatic changes of leucoencephalopathy, usually posterior in distribution (Figure 2). Other patients can present with a picture identical to either haemolytic uraemic syndrome (without diarrhoea) or thrombotic thrombocytopenic purpura. Symptomatic patients need simultaneous investigation and treatment, preferably in a tertiary nephrology centre. Whilst those with mild symptoms can initially be managed with oral antihypertensives, those with severe symptoms usually need intravenous treatment with labetalol (1–3 mg/kg/hour) or sodium nitroprusside. The latter should only be used with continuous invasive BP monitoring. BP needs to be slowly reduced to prevent neurological sequelae in those whose hypertension may



**Figure 1** Algorithm for the management of children with high casual blood pressure readings.





**Figure 2** Magnetic resonance scan in a child with symptomatic hypertension showing changes of leukoencephalopathy. The child had convulsions and on recovery poor vision. All resolved with time and normalisation of blood pressure.

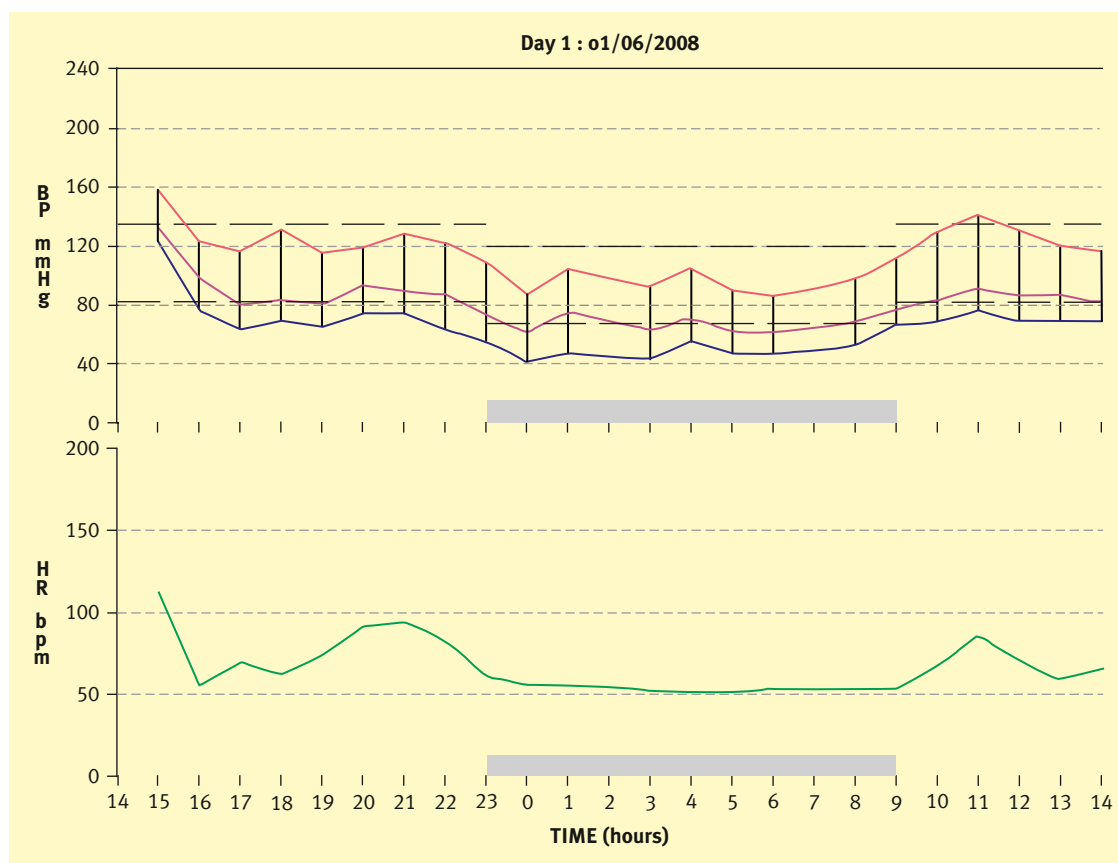
have been longstanding. Control of intravascular volume is essential to prevent heart failure and may require diuretics or dialysis.

### Asymptomatic hypertension

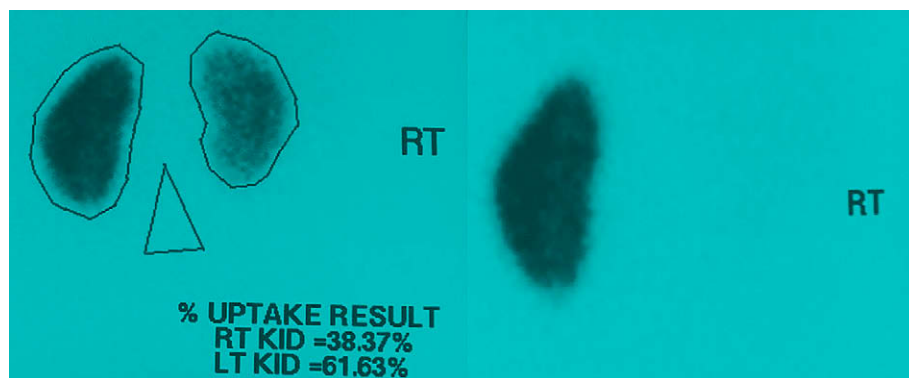
Asymptomatic hypertension can be divided into two groups. Those whose hypertension is clearly severe despite their lack of symptoms are patients whose BP is 25 mmHg or more above the 95th centile. They deserve admission and immediate investigation and treatment in the way symptomatic patients do lest they develop symptoms.

For those who have mild or moderate hypertension, the first step is to obtain home ambulatory monitoring. It is surprising how often this shows the patient to be normotensive. The ambulatory monitoring trace in Figure 3 is from a teenage girl who presented with headaches and repeatedly had BP measurements between 150 and 160 mmHg systolic. The first reading was whilst she was still at hospital. The rest were at home and normal. Her headaches resolved when her examinations finished. Children too young for home ambulatory monitoring should be admitted to a day unit and have frequent casual measurements made in an atmosphere of quiet play.

Patients with hypertension on ambulatory monitoring can be divided into two groups. Those with a known predisposing cause for hypertension, such as renal parenchymal scarring, simply need to start treatment. For renal parenchymal disease, where hyperreninaemic hypertension is the cause, primary treatment with an angiotensin-converting enzyme inhibitor (ACEI) (such



**Figure 3** Extract from the ambulatory tracing of a 14-year-old girl with headaches and high casual blood pressure (BP) measurements. After the first hospital reading her BP is normal with good nocturnal dipping.



**Figure 4** Dimercaptosuccinic acid (DMSA) scan (left) showing a smooth kidney but reduced right-sided function. Repeat scan 48 hours later (right) after captopril shows disappearance of the right kidney indicating rennin-dependent perfusion. The patient had a right renal artery stenosis.

as enalapril or ramipril) or angiotensin receptor blocker (ARB) (such as valsartan or candesartan) is appropriate. Patients in this category developing hypertension and starting treatment ought to then have repeat renal functional assessment, echocardiography, an ECG. Repeat renal imaging needs to be considered. Patients with no known predisposing pathology require investigation into the cause of their hypertension. This is outlined in [Figure 1](#). It needs to be remembered that a small or irregular kidney on DMSA can be secondary to renal artery stenosis as well as parenchymal scarring. Treatment with ACEIs or ARBs should not commence until it has at least been shown that there is not renin-dependent renal perfusion. This can be done by repeating a DMSA scan with the administration of 0.7 mg/kg (maximum 50 mg) of captopril at the time of the DMSA injection. As can be seen from [Figure 4](#), where there is hypertension secondary to a main renal artery stenosis there is a temporary disappearance of that kidney. Where the renin-dependent perfusion involves a segment of a kidney just that segment would disappear. When this happens, angiography is indicated and treatment with an ACEI or ARB is contraindicated lest ischaemic damage to the kidney ensues.

If primary investigation yields a cause for the hypertension then treatment can be started. Where a cause is not found, and there are no biochemical or family history clues to suggest a diagnosis such as Liddle's syndrome or glucocorticoid remediable hypertension (treatable with amiloride and spironolactone respectively), then a presumptive diagnosis of essential hypertension can be made. Whilst it is reasonable to make this presumed diagnosis, particularly in the presence of other risk factors such as obesity, all children with sustained hypertension ought to be at least discussed with a paediatric nephrologist. ♦

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# Cardiomyopathy in childhood

Philip Roberts

Michael Burch

## Abstract

Cardiomyopathies are a heterogeneous group of disorders of both genetic and non-genetic aetiology. Their importance lies in the fact that although the mortality for structural congenital heart disease has been reduced from around 40% to 5% in the past 40 years there has been little change in the prognosis for paediatric patients with cardiomyopathies. Around one-third of children with a cardiomyopathy will die or require transplantation. Advances in genetics over the past decade have resulted in the recognition that a large proportion of cardiomyopathies are genetic in origin. Management of these patients is best in centres offering cardiology, genetic and metabolic input. This article aims to briefly review the broad categories of cardiomyopathies encountered in childhood.

**Keywords** cardiomyopathy; childhood

## Introduction

The true incidence of cardiomyopathy in childhood remains unclear for several reasons: there is no universally accepted definition or classification of cardiomyopathies and epidemiological studies performed to date have variable inclusion criteria. Furthermore, there is likely to be significant geographical variation reflecting both environmental and genetic factors.

Although rare, the importance of cardiomyopathies lies in the fact that around one-third of cardiomyopathies will progress to death or require cardiac transplantation. Cardiomyopathies are the most common reason for cardiac transplant in childhood.<sup>1</sup> Although major advances have been made in the management of childhood heart disease, there has been only minimal change in outcome over the past 30 years for those with cardiomyopathies. Cardiomyopathy may be the first manifestation of both an inborn error of metabolism or neuromuscular disorder with attendant genetic implications.

Initial attempts at definition and classification were made in 1980 and 1995 by the World Health Organization and International

Society and Federation of Cardiology task force. Originally cardiomyopathies were defined as primary myocardial disorders of unknown cause. Where the aetiology of the heart muscle disease was known they were classified as secondary or specific cardiomyopathies.<sup>2</sup> Genetic advances of the past decade have resulted in more recent attempts by the American Heart Association (AHA) 2006 and European Society of Cardiology 2007 to offer revised classifications with the principle difference between the two being the inclusion of the 'channelopathies' by the AHA as cardiomyopathies.<sup>3,4</sup>

When faced with a symptomatic patient with evidence of cardiac muscle disease on electrocardiography (ECG), chest x-ray and echocardiogram, the question of how best to proceed on the patient journey from diagnosis to therapeutic intervention is in our opinion more pragmatically addressed by aligning with the European Society of Cardiology position statement, remembering that this has been principally drawn up by an adult working group.

Several important differentials for ventricular myocardial dysfunction are traditionally not classified as cardiomyopathies. However, these will also be included as, in some cases, such rate related cardiomyopathy and endocrine disorders, treatment can result in complete recovery and, therefore, it is particularly important to identify these cases.

## Definition

A cardiomyopathy is a myocardial disorder in which the heart muscle is structurally and functionally abnormal. Traditionally, the absence of haemodynamically significant structural heart disease is included and adult definitions would also include the absence of coronary heart disease, systemic and pulmonary hypertension and valvular heart disease significant enough to cause the observed myocardial dysfunction. Clearly it is possible for combinations of the above to coexist.

The type of cardiomyopathy is grouped according to ventricular morphology and function into:

- dilated cardiomyopathy (DCM)
- hypertrophic cardiomyopathy (HCM)
- restrictive cardiomyopathy (RCM)
- arrhythmogenic right ventricular cardiomyopathy (ARVC)
- unclassified.

Each morphological phenotype is then sub-classified into familial/genetic and non-familial/non-genetic. The genetic group can then be further grouped into known genetic types and unidentified defects. The non-genetic group is classified into idiopathic or specific disease subtypes.

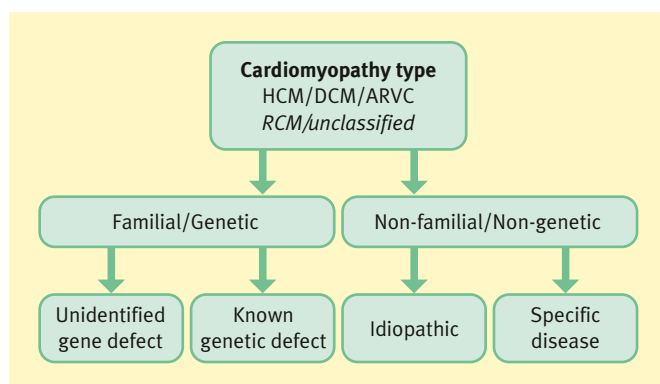
As with many conditions, there can be overlap between the morphological groups and indeed during the evolution and natural history of any cardiomyopathic process progression from one morphology to another. The ventricular morphological classification and consequent pathophysiology, however, determine both mode of presentation and what medical management strategies are likely to be required (Figure 1).

## Incidence

The true incidence of childhood cardiomyopathy is unknown. Studies from Australia, Finland and two regions in North America

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**Figure 1** Classification of cardiomyopathies. (Adapted from Perry, et al. position statement of European Society of Cardiology, European Heart Journal (2008) 29, 270-276).

suggest an incidence of between 0.74 and 1.24/100,000 children. More recently, a prospective study in the UK gave an incidence of 0.87/100,000 for new onset heart failure (a marker for symptomatic cardiomyopathies) and 0.76/100 000 for DCMs.<sup>5</sup> None of the studies include an estimate for asymptomatic cardiomyopathies.

Except for RCM when the median age of presentation is 36 months, the incidence of cardiomyopathies is significantly higher in infancy than subsequent childhood, although there is a second peak in adolescence reflecting neuromuscular disorders and onset of autosomal dominant HCM.<sup>6,7</sup>

DCM is the most common morphological phenotype (50%) followed by HCM (40%) with the remainder being made up of RCM, ARVC and unclassified cardiomyopathies.<sup>6,7</sup>

## Aetiology

The possible aetiologies of cardiomyopathies are vast (see Table 1). They should be divided into genetic and non-genetic causes. Currently genetic causes are identified in around 20% of childhood cardiomyopathies and this is likely to increase. Further division of the non-genetic causes using a pathological approach into inflammatory, infective, infiltrative, iatrogenic and nutritional is helpful clinically.

It is essential to identify causes for which treatment may be curative and, therefore, chronic arrhythmia and endocrine causes resulting in myocardial dysfunction are also included in Table 1.

## Sex

After infancy, there is a preponderance of males that reflects the X-linked muscular dystrophies.<sup>6,7</sup>

## Geographical

Some studies have demonstrated a difference in areas that may not only reflect the racial group but also environmental factors. Studies in the United States have shown black and Hispanic groups to be more affected and an Australian study showed aboriginal children to be more commonly affected.<sup>6,7</sup>

## Pathology

Pathological findings will depend on the aetiology. Usually tissue is not available and currently it is not routine practice in the UK to undertake endomyocardial biopsies. The exception in our institution being when a patient is being placed on extracorporeal membrane oxygenation.

## DCM

Macroscopically, the heart is large and globular with biventricular and bi-atrial dilatation. The weight of the heart is increased, mural thrombi may be present, coronaries are normal and the endocardium thin. Microscopically, there is myocyte hypertrophy and degeneration with varying degrees of interstitial fibrosis. A lymphocytic infiltrate may be present.

## HCM

Macroscopically, the ventricles are non-dilated with symmetric or asymmetric ventricular hypertrophy. The atria are often enlarged. There may be fibrous plaque formation on the left ventricular aspect of the interventricular septum secondary to systolic anterior motion of the mitral valve. There are variable amounts of myocardial fibrosis and atrioventricular valve thickening. Microscopically, there is myocyte disarray, myocyte hypertrophy and variable amounts of fibrosis.

Other findings depend on the aetiology but may include fibro-fatty replacement of the myocardium in the case of ARVC, abnormal mitochondria in mitochondrial disease and glycogen deposits in glycogen storage diseases.

## Clinical

As with all clinical medicine the assessment should be based on a detailed history, examination and tailored investigations.

Important points in the history include both features suggestive of a generalised systemic process (neuromuscular, metabolic) as well as features specific to the cardiovascular system. Family history is important in identifying modes of inheritance and unexplained early death should always be asked about. Consanguinity is a risk factor. The mode of presentation reflects the age of the patient and underlying ventricular morphology and resultant pathophysiology accepting that there can be clinical overlap between the groups. Increasingly, diagnoses are made antenatally.

Symptoms usually reflect effort intolerance (feeding difficulty in infants, exercise intolerance in children) and more occasionally chest pain and palpitations. Growth may be poor.

Possible signs include dyspnoea, sweating (cold and clammy), poor perfusion, tachypnoea, tachycardia, hepatomegaly, murmurs, a 3rd heart sound and hepatomegaly. General examination with attention to dysmorphic features and evidence of a systemic process is important.

## HCM

In this subgroup we consider all forms of cardiomyopathy that result in hypertrophy of the ventricular myocardium either symmetrically or asymmetrically. Haemodynamic causes for ventricular hypertrophy such as arterial valve and great artery stenosis are

**Possible aetiologies of cardiomyopathies**

	<b>HCM</b>	<b>DCM</b>	<b>RCM</b>	<b>Unclassified</b>	<b>ARVC</b>
<b>Familial</b>	Familial unknown gene  Sarcomeric protein mutations β myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin T Troponin C α tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin A-myosin heavy chain Titin Muscle LIM protein Glycogen storage disorders Pompe, Danon, Forbes, PRKAG2 Lysosomal storage disorders Hurler's, Anderson-Fabry Disorders of fatty acid metabolism MCAD, LCAD, VLCAD Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies  Syndromic HCM Noonan syndrome LEOPARD syndrome Friedreich's ataxia Beckwith-Weideman syndrome Swyer's syndrome Phospholamban promoter Familial amyloid	Familial unknown gene  Sarcomeric protein mutations – see HCM Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated cardiomyopathy Intercalated disc protein mutations (See ARVC)	Familial unknown gene  Sarcomeric protein mutations Troponin I (RCM and HCM) Essential light chain of myosin Familial amyloidosis Transthyretin(RCM + neuropathy) Apolipoprotein(RCM + neuropathy) Desminopathy Pseudoxanthoma elasticum Haemochromatosis Anderson – Fabry disease Glycogen storage disease Mulibryanism	LVNC Barth syndrome Lamin A/C ZASP A-dystrobrevin	Familial unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3
<b>Non-familial</b>	Obesity  Infant of diabetic mothers  Twin-twin transfusion syndrome Athletic training Amyloid (AL/prealbumin)	Myocarditis  Infective – viral, bacterial, parasitic Immune – SLE  Toxic - alcohol Kawasaki disease Eosinophilic (Churg Stauss syndrome)	Amyloid (AL/prealbumin)  Scleroderma  Endomyocardial fibrosis  Hypereosinophilic syndrome Idiopathic Drugs (serotonin, methysergide)	Tako Tsubo CMO	

*(Continued)*



**Possible aetiologies of cardiomyopathies (continued)**

HCM	DCM	RCM	Unclassified	ARVC
	Drugs - anthracyclines	Carcinoid heart disease		
	Pregnancy	Metastatic cancers		
	Endocrine – vitamin D deficiency	Radiation		
	Nutritional – thiamine, carnitine, selenium,	Drugs - anthracyclines		
	Rate-related cardiomyopathy			

Adapted with permission from Perry et al. Eur Heart J 2008; 29: 270-276. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; LIM, TCAP, CRYAB, MCAD, medium chain acyl-CoA; LCAD, long chain acyl-CoA; VLCAD, very long chain acyl-CoA; SLE, systemic lupus erythematosus; LVNC, left ventricular non-compaction; ZASP, CMO, cardiomyopathy.

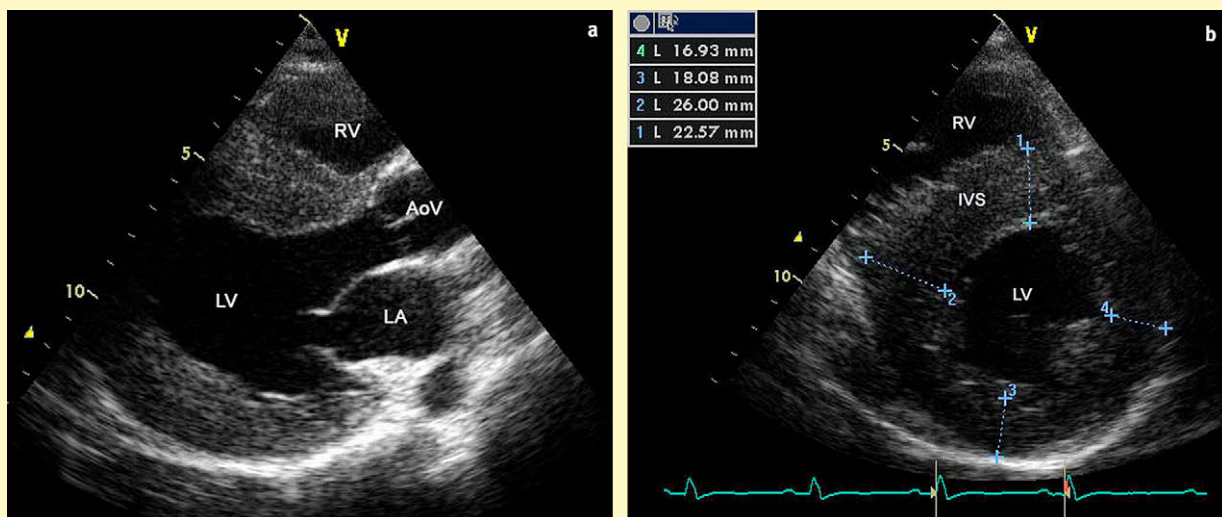
**Table 1**

excluded. In infancy, HCM is most commonly associated with a syndromal diagnosis or inborn error of metabolism as opposed to later when it is most commonly inherited as an autosomal dominant condition with variable expression. HCM is the most common cause of sudden cardiac death in young adults (see Figure 2).

The ventricular hypertrophy usually results in supernormal ventricular contraction although this can be variable and depends on the stage of the disease process. Dynamic obstruction of ventricular outflow tracts (both muscular and systolic anterior motion of the mitral valve) and diastolic dysfunction with poor myocardial relaxation can develop. Understanding how a hypertrophied ventricle may behave helps to predict both what symptoms and signs may be anticipated and also what treatment strategies may help. The following are examples of the more common causes of HCM in childhood.

**Noonan syndrome**

This is relatively common (1:1000–2500 live births) and the most common cause of HCM in children <4 years of age.<sup>8</sup> Features include: hypertelorism; down-slanted palpable fissures; low set posteriorly rotated ears with thickened helices; ptosis; deeply grooved philtrum; micrognathia; low posterior hairline; excess neck skin; cryptorchidism in males; superior pectus carinatum and inferior excavatum; cubitus valgus; clinodactyly; pigmented naevi; lymphatic dysplasia; and intestinal and pulmonary lymphangiectasia. Antenatal diagnosis is suspected if there is a HCM and pleural effusions. Two-thirds of patients have a cardiac defect most commonly pulmonary valvar stenosis or HCM. The HCM is often severe in the neonatal period but once through this most children do well although the HCM remains significant. Most cases are sporadic, 30% are inherited as an autosomal dominant



Echocardiograms showing a hypertrophic cardiomyopathy in the long axis **a** and short axis **b** of the heart, respectively. The measurements indicate gross thickening of the left ventricular myocardium.

**Figure 2**



condition. LEOPARD syndrome is very similar but with marked pigmented naevi.

### Beckwith-Wiedemann syndrome

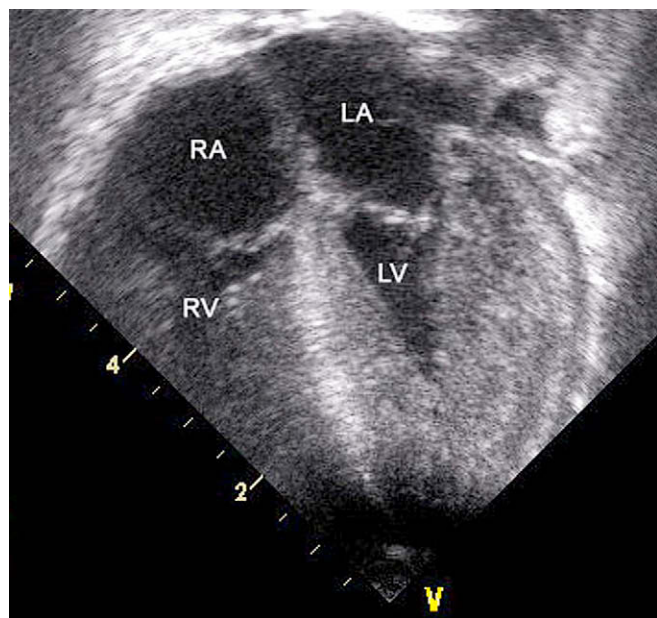
This is typified by the combination of macrosomia, exomphalos and visceromegaly. Other features include neonatal hypoglycaemia secondary to pancreatic cell hyperplasia, transverse linear ear lobule creases, hemihypertrophy and malignancy (Wilms, adrenal, hepatic and rhabdomyosarcomas). The condition is rare (1:14,000 births) and usually sporadic, although autosomal dominant inheritance is described with variable penetrance.<sup>9</sup> A variety of structural abnormalities involving chromosome 11 have been demonstrated.

### Pompe disease

Pompe disease is secondary to acid maltase deficiency. It is a lysosomal glycogen storage disease. Children present in infancy with poor muscle tone, reduced deep tendon reflexes, hepatosplenomegaly and a progressive hypertrophic cardiomyopathy. The ECG shows marked increased ventricular voltages (see Figure 3). Inheritance is autosomal recessive with mutations on chromosome 17 affecting the acid maltase enzyme. The diagnosis is suspected by demonstrating vacuolated lymphocytes and then confirming reduced or absent  $\alpha$ 1,4 glucosidase in skin fibroblasts. The prognosis is poor with death usually in the first year. Enzyme replacement is being used on a trial basis.

### Fatty oxidation defects

Myocardial energy is predominantly derived from long chain fatty acid (LCFA) oxidation in the mitochondria. Several proteins are required for LCFA and carnitine transport in the cardiomyocyte and the subsequent beta oxidation process. These proteins are nuclear encoded and autosomal recessive in inheritance.



**Figure 3** Echocardiogram showing a four-chamber view of the heart. There is marked thickening of all the ventricular myocardium and with time the function will deteriorate.

### Carnitine

Carnitine is important in transport of LCFAs, peroxisomal fatty acid oxidation products and ketoacids derived from branched chain amino acids into the mitochondrial matrix for terminal oxidation. Carnitine deficiency can either be primary (defective transport of carnitine from the serum into the cells) or secondary, which results from heterogeneous causes including inborn errors of metabolism, various acquired forms of disease and iatrogenic causes secondary to medication. The primary form is characterised by more profound reductions in carnitine. The clinical picture from carnitine deficiency depends on the degree of deficiency and the tissues affected. In the myopathic form, carnitine levels are only reduced in muscle. The systemic form results in multisystem disease and presents in infancy or early childhood with episodic hypoglycaemia, ammoniaemia, acidosis, hepatomegaly and cardiomyopathy. Treatment includes oral carnitine, bicarbonate, intravenous glucose and anti-failure measures. As with many inborn errors of metabolism, undercurrent illness may precipitate decompensation. Occasionally oral carnitine therapy reverses the cardiomyopathy.

### Carnitine palmitoyltransferase (CPT)

CPT has two forms: CPT I and CPT II. Abnormalities of CPT I – which is found on the inner mitochondrial membrane – do not cause cardiomyopathy but can cause a metabolic crisis. Mutations of the gene encoding CPT II – also located on the inner mitochondrial membrane – result in a spectrum of disease from severe neonatal metabolic decompensation (hypoketotic hypoglycaemia, acidosis, cardiomyopathy and death) to a later presentation with heart block and ventricular tachycardia and finally to the least severe disorder with recurrent paroxysmal myoglobinuria and not usually associated with cardiac disease.<sup>10</sup>

### Beta oxidation defects

These can result from medium chain, long chain and very long chain acyl-CoA (MCAD, LCAD, VLCAD) deficiency. Fatty acyl-CoA oxidation involves four enzymatic steps the first of which involves the above enzymes.

*MCAD deficiency* is the most common fatty acid oxidation defect estimated to occur in 1:6000–10,000 births.<sup>10</sup> Decompensation is provoked by intercurrent illness and fasting resulting in vomiting, lethargy, hypoglycaemia, coma and possible sudden death. Occasionally DCM may be seen instead of HCM.

*VLCAD deficiency* presents similarly with both HCM and DCM being described and is often fatal.<sup>11</sup>

*LCAD deficiency* – results in an infantile cardiomyopathy with a similar presentation to MCAD and VLCAD deficiencies. Mortality is high at around 50%.<sup>12</sup> The fatty acid oxidation defects result in secondary carnitine deficiency and abnormal urinary organic acids with low ketones and increased dicarboxylic acids. Aggressive treatment with glucose and haemodynamic cardiac support may reverse the cardiomyopathy.

### Mitochondrial HCM

Mitochondria are the power houses of cells responsible for ATP production. Typically, mitochondrial abnormalities affect the most metabolically active organs, which include the heart, skeletal muscles, eye, brain and liver. Mitochondrial DNA is maternally

inherited and encodes the vital respiratory chain enzymes. However, nuclear encoded proteins are also imported into the mitochondria so mitochondrial dysfunction can arise from either route. Each cell contains several mitochondria and each mitochondrion contains several copies of the circular mitochondrial molecule, which in turn has multiple copies encoding ribosomal and transfer RNA. It is this combination that results in a mix of normal and mutant mitochondrial protein and enzyme systems the proportions of which determine the degree to which an organ is affected and the clinical phenotype.<sup>13</sup> Cardiac disease is most commonly present with respiratory chain defects.<sup>14</sup> Resulting cardiac disease includes HCM, DCM and a mixed hypertrophic-dilated phenotype. The latter should always raise the suspicion of a mitochondrial abnormality when present in an infant.<sup>15</sup>

In addition to standard treatment strategies, coenzyme Q, carnitine and vitamins have been tried but typically do not alter the clinical course.<sup>15</sup>

The diagnosis of a mitochondrial problem should be based on the clinical picture in conjunction with a muscle biopsy showing red ragged muscle fibres and mitochondrial respiratory chain analysis of the biopsy tissue.

### **Autosomal dominant familial HCM**

This is secondary to mutations encoding the sarcomeric proteins. Typically the HCM does not develop until the onset of the pubertal growth spurt and, even then, when an individual has a known mutation, the HCM may only become evident in adult life.

### **Maternal diabetes**

Maternal diabetes is a cause of a self-limiting HCM reflecting foetal hyperinsulinism secondary to poor maternal glucose control. The myocardial hypertrophy will resolve with time.

### **Twin-to-twin transfusion syndrome (TTTS)**

This occurs in approximately 15% of monochorionic twin pregnancies and results in ventricular hypertrophy of the recipient's myocardium with the right ventricle being more affected than the left. Significant right ventricular outflow tract obstruction may develop in association with the ventricular hypertrophy. Treatment of TTTS remains controversial but in severe cases where laser therapy has been used to treat the placental arteriovenous anastomoses, regression of the hypertrophy has been documented.<sup>16</sup>

## **DCM**

In this condition the left ventricle is dilated with the right ventricle variably involved (see [Figure 3](#)). Typically, ventricular systolic function is reduced and from this the symptoms and signs resulting from pulmonary venous congestion, systemic venous congestion and a low cardiac output state can be predicted. Investigations required are similar to those for HCM but with the addition of viral studies (culture, serology, immune fluorescence, polymerase chain reaction).

The following represent some of the more common causes of DCM.

### **Myocarditis or inflammatory cardiomyopathy**

Myocarditis or inflammatory cardiomyopathy may be responsible for up to 40% of DCMs. The most common aetiological agents

include adenoviruses and enteroviruses (Coxsackie group). Rarer causes include other infections including bacteria, parasitic such as Chagas disease and connective tissue disorders such as systemic lupus erythematosus.

### **Familial DCM**

This occurs in up to 30% of cases. This is usually autosomal dominant but autosomal recessive, X-linked and mitochondrial inheritance are all possible.

### **Barth syndrome**

This is an X-linked cardiac and skeletal myopathy arising from a mutation affecting the tafazzin protein family. Classically, there is a neutropenia and DCM, although left ventricular non-compaction is noted in some series.<sup>7,15</sup> Myocyte hypertrophy and fibrosis is present and mitochondrial abnormalities are noted on electron microscopy of the heart and skeletal muscle. Other findings include hypercholesterolaemia, lactic acidosis, hypoglycaemia and respiratory chain abnormalities. A cardiomyopathy and neutropenia in a male are diagnostic. Urine analysis shows 3-methylglutaconic aciduria. The gene has been mapped to Xp28. Interestingly mutations result in a spectrum of clinical disorders ranging from classic Barth syndrome to DCM to left ventricular non-compaction.<sup>15</sup>

### **X-linked DCM**

X-linked DCM includes those cardiomyopathies that are found in association with the muscular dystrophies, such as Duchenne and Becker. There is also an X-linked DCM that presents in male teenagers, which follows a rapidly progressive course and has been mapped to Xp21.

### **Vitamin D deficiency**

Vitamin D deficiency resulting in hyperparathyroidism and hypocalcaemia is a cause of a severe DCM associated with significant mortality that occurs in breastfed infants of dark-skinned populations where there is a combination of inadequate exposure to sunlight (usually a combination of clothing and northern climate) and inadequate dietary intake. The condition is curable with vitamin D supplementation but recovery of ventricular function on average takes 1 year.<sup>17</sup>

### **Rate-related DCM**

These arise from any prolonged tachycardia whether supra-ventricular (more commonly) or ventricular in origin. Typically, tachyarrhythmias are well tolerated in childhood in the absence of ischaemic coronary vascular disease. However, eventually the myocardium tires and the ventricles progressively dilate.

Treating and controlling the arrhythmia results in cure. An ECG and 24-hour tape should be performed in all patients with a newly diagnosed DCM.

### **Chemotherapy induced DCM**

Chemotherapy induced DCM is a relatively frequent cause of cardiomyopathy in this patient group and usually related to the use of anthracyclines. Echocardiography is now a standard part of chemotherapy protocols using cardiotoxic agents. New

onset effort intolerance should always raise the possibility of an anthracycline-induced cardiomyopathy as part of the differential diagnosis in this patient group (Figure 4).

### RCM

This is the rarest form of cardiomyopathy in childhood representing in around 3% of cases. RCM typically presents after the first year of life and later in childhood. Usually no cause is identifiable although a familial variety is recognised.

As implied in the name, the pathophysiology arises from an inability of the ventricular myocardium to relax giving the classic two-dimensional echocardiographic picture of small ventricles associated with large dilated atria known as the 'ice-cream cone' appearance (see Figure 5). Symptoms result from systemic and pulmonary venous congestion and a low cardiac output. The differential diagnosis includes a constrictive pericarditis. This form of cardiomyopathy requires careful ongoing monitoring for the development of pulmonary hypertension. Once this develops cardiac transplantation is recommended to avoid irreversible pulmonary vascular damage.

### ARVC

ARVC is defined by the presence of right ventricular dysfunction (regional or global) in the presence of histological evidence of fibro-fatty replacement of the right ventricular myocardium and/or ECG abnormalities in accordance with published criteria.<sup>4</sup> The estimated prevalence is 1:5000. In parts of Europe, ARVC is a well-recognised cause of sudden death in young people.

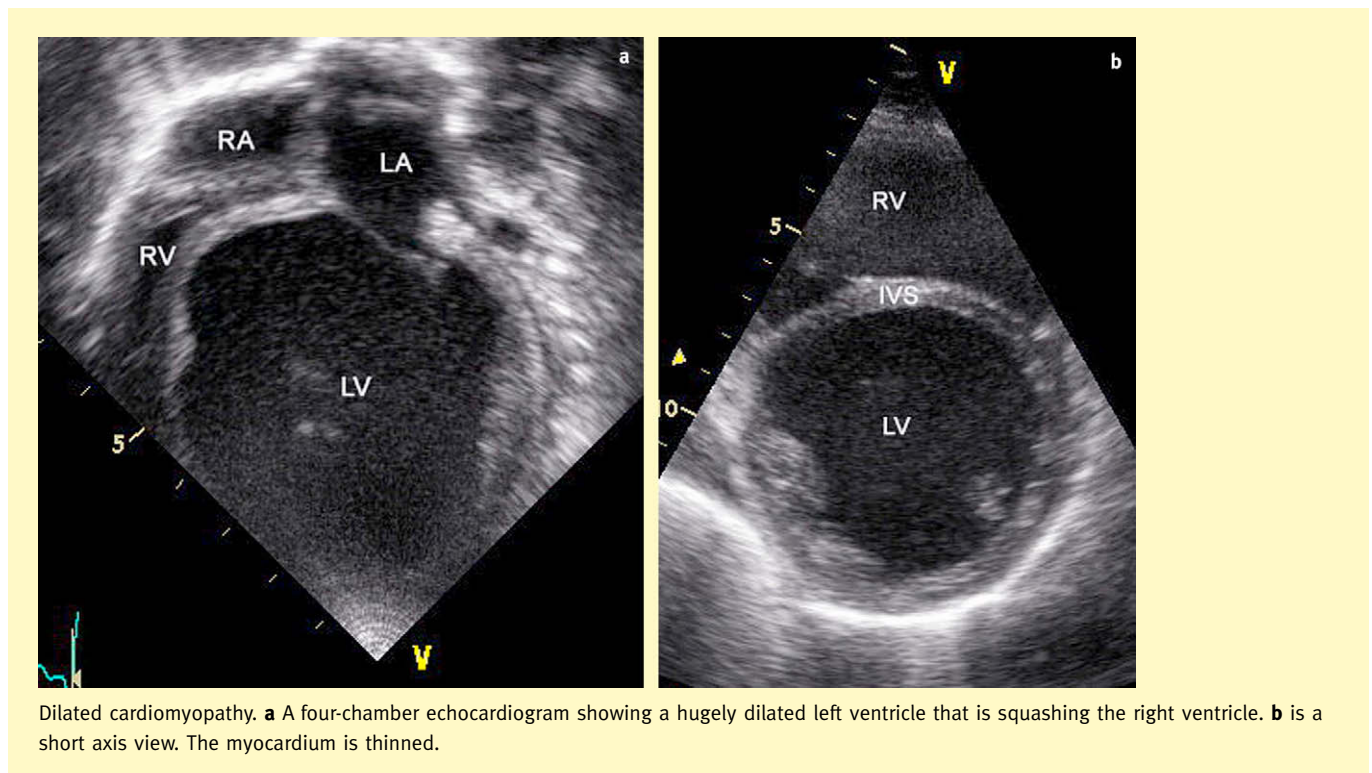
Magnetic resonance imaging (MRI) is now commonly used to demonstrate fibro-fatty change in the myocardium and is excellent for assessing ventricular function. Autosomal recessive and dominant mutations in genes encoding cell adhesion have been shown to be responsible.

### Unclassified cardiomyopathies

The entity of ventricular non-compaction is included in this group. The normal left ventricular endocardium is usually smooth with minimal trabeculation in contrast to the right ventricle, which is heavily trabeculated. Ventricular non-compaction is the term given to the echocardiographic finding of abnormal trabeculation of the ventricles with deep sinusoids and recesses typically within the left ventricle (Figure 6). It is felt to represent an embryological arrest and can occur in isolation or with structural congenital heart disease. The resultant pathophysiology is variable but usually results from a combination of dilated and hypertrophic physiology. Echocardiographic diagnosis is made when the endocardial layer is twice the thickness of the outer epicardium. Barth syndrome can result in this appearance.

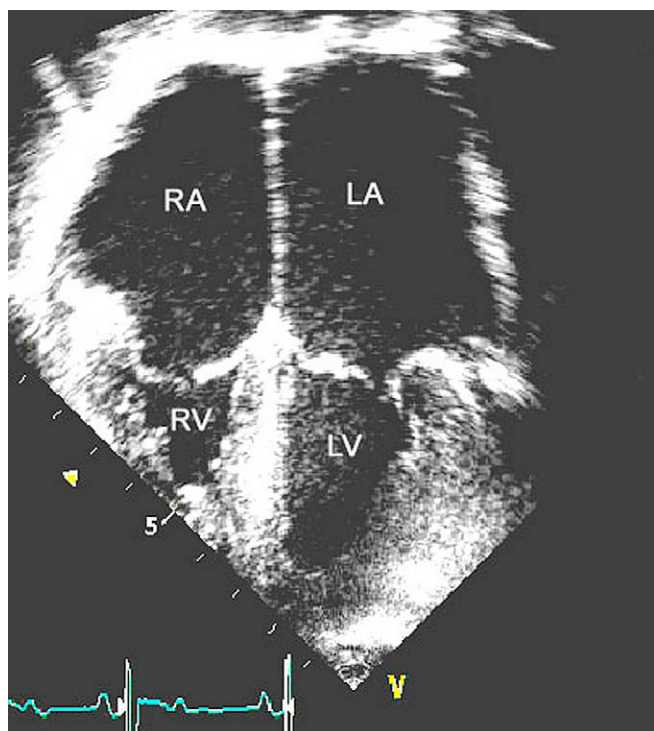
### Investigations

These should be divided into those that confirm a diagnosis of a cardiomyopathy and those that help identify the underlying aetiology. Given the huge number of possible causes a large number of investigations will often need to be taken and commonly a specific aetiological diagnosis is not made.



**Figure 4**

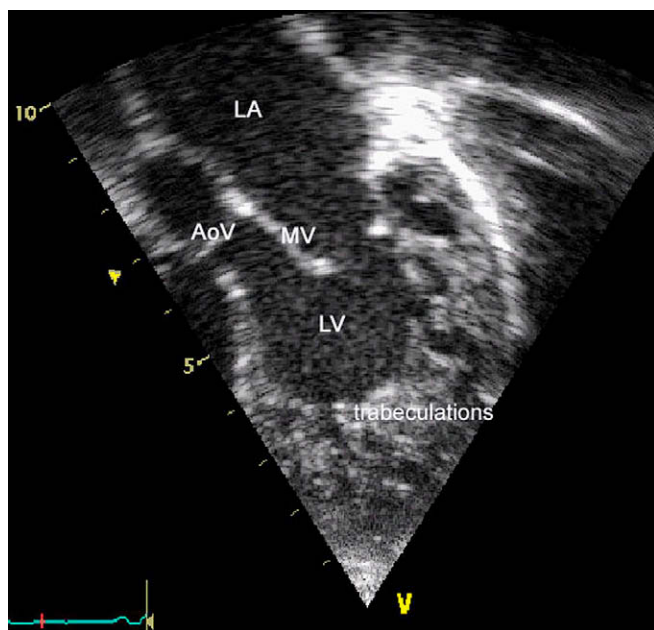




**Figure 5** Four-chamber echocardiogram showing bi-atrial enlargement also known as the 'ice-cream cone' appearance.

#### Establishing a diagnosis

- Chest x-ray
- ECG
- Echocardiography.



**Figure 6** Echocardiogram showing the left heart structures and left ventricular non-compaction. The apex of the left ventricle is normally smooth but in this case heavily trabeculated.

MRI will probably play a larger role in the future. Endomyocardial biopsy may be useful but is not commonly performed in the UK.

#### Establishing aetiology

Suggested investigations are listed in Table 2. This list is not comprehensive but serves as a starting point.

All patients should be seen by a paediatric cardiologist but it is helpful and saves time for the initial investigations to be made as several have a significant delay in turnaround time.

#### Management

##### Dilated cardiomyopathy

Diuretics, angiotensin-converting enzyme inhibitors and beta blockade with a non-selective action are the mainstay of therapy. Digoxin has a role with its positive inotropic and negatively chronotropic effect.

##### Hypertrophic cardiomyopathy

Selective beta blockade is the mainstay of therapy in young children. Infants often may need diuretics in the early stages when there may be a difficult balance between the need for an adequate preload to fill stiff hypertrophied ventricles and pulmonary and systemic venous congestion. Anti-arrhythmics and anti-angina therapy may be required.

In older patients, especially where ventricular arrhythmias have been documented and there is a risk of sudden death, automatic implantable defibrillators are used.

Surgical myomectomy, in particular where significant left ventricular outflow tract obstruction has developed, as well as transcatheter muscle ablation procedures are recognised forms of therapy in specialised units.

##### Restrictive cardiomyopathy

The standard strategy is careful observation with ongoing estimates of pulmonary artery pressure including cardiac catheterisation and early listing for transplantation if pulmonary artery pressures are elevated.

##### Unclassified cardiomyopathy

As for DCM and HCM.

##### Inborn error of metabolism - IEM

When an IEM is suspected or diagnosed on initial screening, discussion with and referral to a specialist paediatric metabolic unit is appropriate. This allows for the consideration of specialist diets (restrictions and supplementations), 'chaperone' therapy and enzyme replacement strategies either by direct replacement or using bone marrow transplantation.

##### Cardiac transplantation

In the event of medical therapy failing, the final option for treatment is cardiac transplantation with or without a mechanical bridge. It is important to remember that cardiac transplantation is not a cure and comes with well-known complications arising from chronic immunosuppressive therapy. However, when significantly symptomatic on maximal medical therapy, the improved quality of life offered by cardiac transplantation can

## Suggested Investigations

Investigation	Indications & comments
Echocardiogram	For ventricular morphology and to exclude structural heart disease especially anomalous left coronary in DCM Consider screening of family members
Electrocardiogram	Voltage criteria for chamber enlargement Arrhythmia, giant complexes & short PR interval in Pompe Any degree of conduction disturbance possible in IEM. Low voltages and ST segment changes in acute myocarditis
24 hour tape	Arrhythmia (aetiology and secondary complication of cardiomyopathy)
Chest x-ray	Heart size
Full blood count	Neutropaenia with Barth syndrome & organic acidaemias. Megaloblastic anaemia in B1 & B12 deficiency
Erythrocyte sedimentation rate & C reactive protein	Consider if inflammatory disorder suspected
Vacuolated lymphocytes	Lysosomal storage disorder (mucopolysaccharidoses, mucopolipidoses, Pompe) only if patient <2 year of age
Urea, creatinine, Na, K	Baseline pre treatment
Glucose	Infant of diabetic mother. Hypoglycaemia common in fatty acid oxidation defects, glycogen storage disorders & mitochondrial cytopathies
<b>Liver function tests</b>	
Brain natriuretic peptide	Inborn error of metabolism and baseline pre treatment
Creatinine kinase	More useful for monitoring progress Elevated in muscular dystrophies and with myocardial insult
Lactate & Ammonia	Raised in mitochondrial disorders, fat oxidation defects, organic acidaemias. Also raised in low cardiac output states
Serum & ionised calcium	Vitamin D deficiency
Parathyroid hormone	Breast fed infants in dark skinned families if Ca low
Vitamin D levels	Do only if Ca low and PTH raised, breast-fed infants in dark skinned mothers
Micronutrients eg selenium	Very rare, only if in area of endemic deficiency or patient on parenteral nutrition or severely malnourished
Thyroid function tests	Free T4, thyroid stimulating hormone
Thiamine	if megaloblastic anaemia
Carnitine	Very low in carnitine transporter defect. May be secondarily low in multiple other IEM
Acyl carnitine profile (Guthrie card)	Abnormal in fat oxidation disorders
Transferrin electrophoresis	Abnormal in congenital disorders of glycosylation
Plasma amino acids	Inborn error of metabolism
Antinuclear antibodies (ANA)	Screen for connective tissue disorders especially systemic lupus erythematosus
Anti DNA Antibodies	
Rheumatoid factor	
Viral studies including IgG, IgM, PCR, NPA for rapid immunofluorescence (respiratory viruses)	Liase with local virology laboratory – for Enteroviruses including coxsackie group, adenovirus, parvovirus, echovirus Consider VZV, EBV Serum for acute and convalescent titres Raised in mucopolysaccharidoses Mucopolipidoses Abnormal profile in organic acidaemias & mitochondrial disorders. Dicarboxylic aciduria in fat oxidation defects. Methylglutaconate raised in Barth syndrome
Urine glycosaminoglycans	
Urine oligosaccharides	
Urine organic acids	
<b>Second line investigations</b>	
Skeletal muscle biopsy, endomyocardial biopsy, mitochondrial respiratory chain analysis, skin fibroblasts	These investigations are dictated by the clinical scenario and used for histological diagnosis as well as genetic and enzyme analysis

The above table is by no means comprehensive and serves only as a guide. Acknowledgement: Dr M Cleary for her guidance on metabolic investigations. DCM, dilated cardiomyopathy; PCR, polymerase chain reaction; NPA, nasopharyngeal aspirate; VZV, varicella-zoster virus; EBV, Epstein-Barr virus.

**Table 2**

be dramatic with increasing graft longevity and a current mean patient survival of 15 years. ♦

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## Practice points

- Cardiomyopathies are a heterogeneous group of disorders arising from both genetic and non-genetic causes
- Ventricular morphological classification provides the best idea as to how to manage individual patients
- Cardiomyopathies remain an important cause of death, sudden death and cardiac transplantation in both children and adults
- Management is best carried out by paediatric cardiologists with access to genetic and metabolic teams but shared care remains an important and necessary resource



# Management of asymptomatic heart murmurs in infants and children

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## Abstract

Murmurs heard in neonates and older children may be innocent or signify heart disease. The neonatologist or general paediatrician must decide which infants and children need specialist referral, and if so, the urgency of referral. Neonates with clinical features suggesting heart disease should be referred urgently. Neonates with murmurs and no other pathological features must be reviewed regularly during the first few weeks of life if they are not referred to a cardiologist. Older children with asymptomatic murmurs should be referred routinely to a cardiologist if the paediatrician or parents are concerned about the possible significance of the murmur.

**Keywords** children; congenital heart disease; murmur; neonate

## Introduction

In the past 25 years, echocardiography has revolutionised the management of heart murmurs in infants and children. Prior to this, the only resources available to the general paediatrician to aid management were his or her clinical acumen, chest x-ray and electrocardiography, and referral to a paediatric cardiologist. The latter were few in number and apart from greater clinical experience and expertise the only added resource they had to offer was cardiac catheterisation. Since subjecting asymptomatic children with murmurs to the latter often seemed disproportionate, paediatricians undertook responsibility for clinical management of many such children. This often involved periodic review, not only of children with innocent murmurs, but also of some with a clinical diagnosis of asymptomatic and uncomplicated heart disease, such as ventricular septal defect.

This practice demanded of paediatricians that they maintained their clinical skills, offered continuity of family care, and

provided gate-keeping access to scarce paediatric cardiology resources. The practice carried several disadvantages, however. Difficulty in categorically excluding heart disease led to children with innocent murmurs being subjected to unnecessary outpatient review, inappropriate advice concerning antibiotic prophylaxis and possibly even more harmful constraints. In contrast, diagnosis of significant heart disease may have been delayed in some children.

The advent of echocardiography appeared, at first glance, to solve these problems. It permits prompt diagnosis of most types of congenital heart disease. It can help to exclude heart disease in children with innocent murmurs, thus obviating the need for inappropriate outpatient review and unnecessary precautions. Echocardiography is not a panacea, however. It demands considerable training and ongoing practice to maintain skills. Undue reliance on echocardiography may supplant the clinical skills that older paediatricians had to maintain. A normal scan does not always provide the expected reassurance to parents. Finally, incidental findings, in particular persistent patent foramen ovale, may not only induce parental anxiety but also mandate further review, thus defeating the purpose of conducting a 'therapeutic' scan. Paediatricians, therefore, must continue to exercise clinical judgement in determining which children and families need specialist referral, and when. This paper is written from the perspective of the general paediatrician or neonatologist, working in a climate of possibly increasing pressure to refer all infants and children with murmurs to a specialist.

## Objectives in the assessment and management of murmurs

The paediatrician must consider several issues when faced with an infant or child with an asymptomatic murmur. The first priority is the prompt recognition of structural heart disease. The second is the reasonably confident exclusion of such disease, and reassurance of the child and family. These objectives must be achieved by the judicious use of specialist resources, that is, paediatric cardiology and echocardiography. Since resources do not currently permit specialist referral of all such children, these objectives may conflict with one another. Thus, in some children, the pronouncement that a murmur is innocent is made on the balance of probabilities, and parents and clinicians may have to accept some uncertainty. The probability of identifying significant heart disease is greater in neonates than in older children and uncertainty is less acceptable. We will, therefore, outline the management of murmurs in neonates separately from their management in older children.

## Asymptomatic murmurs heard in the neonatal period

### Prevalence

The reported prevalence of murmurs in the neonatal period varies from 0.6 to 1.9 per 1000 infants.<sup>1-4</sup> This variation may depend on the timing of examination, whether preterm infants and infants with other cardiovascular symptoms and signs are included, and on the size of the population studied. In general, there is an inverse association between population size and the prevalence of murmurs.<sup>1</sup>

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### Pathological associations

Many types of congenital heart disease can be associated with an asymptomatic murmur. The most common association is ventricular septal defect (VSD); and patent ductus arteriosus (PDA) if preterm infants are included.<sup>5</sup> Many VSDs identified in the neonatal period are small and close spontaneously.<sup>3</sup> Murmurs can also, however, be associated with obstructive or cyanotic congenital heart disease, in which early identification and treatment are essential.<sup>2,6,7</sup>

### Innocent (functional) murmurs

Non-pathological murmurs in the neonate are generally related to blood flow through the ductus arteriosus or to turbulent flow in the pulmonary arteries.<sup>1</sup> Arlettaz *et al.* conducted serial clinical and echocardiographic review of 50 neonates with 'innocent murmurs' and 50 controls.<sup>8</sup> All infants with murmurs had a patent foramen ovale (PFO) compared with 82% of controls, 50% with a murmur had pulmonary branch stenosis (PBS) compared with less than 12% of controls and 60% of infants with a murmur had a PDA, compared with 6% of control infants. In all cases the duct had closed by 6 weeks, and the PBS had resolved by 6 months. Patency of the foramen ovale persisted in 66% of infants.

### Investigation and management: referral or review?

Careful clinical examination for other cardiovascular findings is mandatory, and should be repeated daily if the infant remains in hospital. Measurement of blood pressure in all limbs is often done, but its variability in normal neonates casts doubts upon its reliability in identifying or excluding duct-dependent heart disease.<sup>9</sup> Chest x-ray is unlikely to be of value as it may be normal in asymptomatic infants with heart disease. Electrocardiography may be of value, as an abnormal axis or changes suggesting ventricular hypertrophy raise the possibility of heart disease. Pulse oximetry is receiving increasing attention as a possible screening tool for congenital heart disease.<sup>10</sup> It should be conducted in all neonates found to have a murmur. It may detect subtle or evolving hypoxaemia, and differences between upper and lower limb oxygen saturations may point to a duct-dependent lesion.<sup>11</sup>

The challenge facing the clinician is to decide whether to refer a neonate with a murmur for urgent cardiological assessment and echocardiography. In infants who have any other cardiac symptoms or signs, who have dysmorphic features or congenital abnormalities, who have a harsh or a loud murmur, or who show hypoxaemia on pulse oximetry this decision is straightforward. Whether to refer infants who are otherwise asymptomatic and have normal oxygen saturation is more problematic. Proponents of early referral dispute the frequency of innocent murmurs in neonates and cite the challenges posed by physiological changes in the circulation after birth and early discharge of neonates.<sup>1,2,7</sup> They argue that routine neonatal examination is insensitive at detecting congenital heart disease, and that identification of a murmur at least gives an opportunity for targeted investigation of infants at particularly high risk. In support of this case is the extensive experience of infants presenting critically ill, or dying, with obstructive left heart malformations, before diagnosis and timely treatment.<sup>1,7</sup>

The number of units with a paediatrician or neonatologist with a special interest in cardiology is increasing and in these

units early echocardiography of all infants with a murmur may be feasible. There are issues relating to quality control, accumulating experience and maintaining skill. Also, the findings on echocardiography conducted by a non-specialist may need to be confirmed later by a cardiologist. Some lesions, such as anomalous pulmonary venous drainage, can be very difficult to identify, even by experienced practitioners.

Many units do not have this facility and the general paediatrician or neonatologist must still decide which infants to refer and which may safely be reviewed. For an otherwise well infant, with no symptoms or signs other than a medium to low intensity murmur, recent experience suggests that careful and timely clinical review is safe and effective, and may reduce the need for cardiological referral of all such infants. Patton and Hey reported their experience in a maternity unit where routine neonatal examination was conducted by advanced neonatal nurse practitioners.<sup>4</sup> About 10% of all neonates were found to have a murmur. They were discharged if otherwise clinically well and if pulse oximetry was normal. The parents were given verbal and written advice concerning murmurs and significant symptoms. The infants were reviewed during the first and second weeks of life. If the murmur was still present at 2 weeks of age, the infant was referred to a paediatric cardiologist. One-third of the latter were found to have a structural heart defect. During the 8-year period of audit, the number of infants with congenital heart disease diagnosed after discharge declined. In the past 4 years, only 6% of cases were identified after discharge, and none were life-threatening.

A similar recent study reported the performance of senior house officers in evaluating murmurs heard on routine examination.<sup>3</sup> During a 2-year period, 112 such infants were identified. Infants with significant clinical features were referred for immediate senior assessment. The rest were reviewed in a dedicated clinic run by a consultant neonatologist with experience and training in echocardiography. All 12 infants referred for immediate cardiological assessment because of clinical concern had significant pathology – 11 had structural heart disease and one had pulmonary hypoplasia. The remaining 100 infants were referred to the 'murmur clinic'. Of the 78 who attended, only 16 infants still had a murmur. Three of these had a normal echocardiogram, seven had pulmonary branch stenosis and six had minor heart lesions (VSD, PDA and pulmonary valve stenosis (PS)). Pulmonary branch stenosis resolved eventually in all infants. Of the 22 who defaulted, none were known to have presented to the hospital, or elsewhere, with heart disease.

These studies were relatively small and the findings cannot be used to guarantee that clinical review is always as safe as urgent cardiological referral. They do suggest, however, that a carefully structured system, with appropriate training, provision of appropriate information to parents, facility for review of infants during the first weeks of life and audit of outcomes is likely to be safe for the many infants who have either an innocent murmur or non-life-threatening heart disease. It also provides substantial, although not absolute, safeguards that may identify infants with evolving symptoms or signs of serious heart disease.

Depending on local facilities and arrangements, regular review of neonates with a murmur in the first few weeks may be no less draining on resources than early cardiological referral. In such instances, the latter approach may be preferable.

## Management of asymptomatic murmurs beyond the neonatal period

In evaluating the older infant or child found to have a murmur, the same general principles should inform the paediatrician's practice – appropriate referral if the clinical features suggest pathology and reassurance if they do not. There are, however, differences in emphasis compared with the evaluation of neonatal murmurs. First, identification of life-threatening heart disease is less likely in an older child presenting with a murmur. Second, compared with neonates, murmurs first heard in older infants and children are more likely to be innocent. In contrast, the prevalence of asymptomatic murmurs (up to 70% of children) is greater in older children than in neonates, so the obligation to 'gate-keep' remains. Finally, echocardiography does not always provide definitive reassurance in the evaluation of asymptomatic murmurs. McCrindle reported that, even after children with murmurs were reported to have a normal heart following echocardiography, 10% of parents still had anxieties and misconceptions, often still conflating a murmur with heart disease.<sup>12</sup> Liberal use of echocardiography does not replace the need for careful clinical management and communication with parents.

### Pathological associations

Pathological murmurs may be associated with a jet effect due to blood flowing through a stenotic valve (e.g. aortic stenosis) or through a left to right shunt (e.g. VSD), or to increased pulmonary blood flow (e.g. atrial septal defect (ASD)). Table 1 lists the common types of congenital heart disease that may be associated with an asymptomatic murmur, along with possible associated clinical features. Less commonly, a murmur may point to cardiomyopathy,

### Common types of congenital heart disease that may present with an asymptomatic murmur beyond the neonatal period

Type of congenital heart disease	Clinical features
Atrial septal defect	Wide, fixed splitting of second heart sound
Ventricular septal defect	Discrete blowing or harsh murmur Thrill
Aortic stenosis	Harsh murmur that may radiate to neck Ejection click Thrill
Pulmonary stenosis	Ejection click
Patent ductus arteriosus	Murmur heard over upper precordium or back Diastolic murmur in older children Prominent pulses
Aortic coarctation	Low volume or delayed femoral pulses Hypertension

Table 1

or rheumatic valvular disease. Some of the associated clinical features, such as ejection clicks and wide splitting of the second heart sound, may be difficult for the non-specialist to identify or exclude, and their absence does not exclude pathology.

### Innocent murmurs

Four types of innocent murmur are generally recognised in children.<sup>13</sup> Table 2 lists these types and summarises their characteristic features. McCrindle's review offers a comprehensive account of the clinical features of innocent murmurs for interested readers.

### Clinical evaluation and investigation

With the exception of the venous hum, innocent murmurs are exclusively systolic in timing, with an ejection quality such that the heart sounds are heard easily. They are typically of low to medium intensity. Some innocent murmurs vary in intensity with respiration, posture and physical manoeuvres such as valsalva or compression.

Obviously, the presence of any cardiovascular symptoms or signs points to the likelihood of a murmur being pathological. Other clinical features suggesting pathology include high intensity, harsh quality, and diastolic or pansystolic timing. Some of these characteristics, such as intensity and quality, are subjective, and evaluation of their significance depends on the experience and skill of the clinician. Also, many heart lesions, such as ASD, mild PS and a small PDA, may be associated with a low-intensity, ejection systolic murmur and no other clinical signs. How can the clinician distinguish such lesions from an innocent murmur?

In the pre-echocardiography era, paediatricians frequently relied on chest x-ray and electrocardiography in this situation. Extensive evidence, however, suggests that these investigations are unhelpful in distinguishing innocent from pathological murmurs.<sup>14,15</sup> They may, indeed be misleading and yield false-positive

### Common innocent murmurs in children

Innocent murmurs	Characteristic features
Carotid bruit	Ejection systolic Heard best above clavicles and over upper precordium
Venous hum	Heard best above clavicles Systolic and diastolic components Accentuated by sitting forward Diminished by pressure, supine posture
Still's murmur	Vibratory ejection systolic Localised to left sternal edge Accentuated by fever, activity
Pulmonary outflow murmur	Ejection systolic Heard best at upper left sternal edge Peak incidence in late childhood

Table 2

results. Right bundle branch block, for example, which is commonly seen on the electrocardiograph of healthy children, may be interpreted as suggesting an ASD.<sup>14</sup> Also, non-specialists may misinterpret chest x-ray findings as suggesting increased pulmonary vascularity or cardiomegaly.<sup>14</sup>

If further investigation is considered necessary, therefore, echocardiography is the investigation of choice. At present in the UK, referral for this entails referral to a paediatric cardiologist. Indications for such referral include the presence of clinical features suggesting pathology as outlined above, parental anxiety, and lack of confidence on the part of the clinician that a murmur is benign.<sup>16</sup> Other indications, which may overlap with the latter two, include the finding of an apparently new murmur in an older child, a family history of heart disease such as cardiomyopathy, or the finding of a murmur in a child undertaking strenuous physical activity. Some of these indications are not clearly defined, and much depends on the clinician's and the family's tolerance of uncertainty. Echocardiography should not, however, be assumed to be a panacea, a reassurance tool.<sup>12</sup> It may not alleviate disproportionate parental anxiety, which should be investigated and managed holistically. The authors have anecdotal experience of several children who were referred repeatedly from primary care with parental 'cardiac neurosis' that was not alleviated by normal findings on echocardiography. Also, incidental findings may engender even further anxiety, in particular the finding of a persistent PFO. There is increasing concern that this may be associated with an increased risk of stroke in adult life.<sup>17</sup> Its identification in young infants now often generates the need for repeat scanning to confirm closure. What if it is identified in an older child who is being scanned largely to reassure the family or the referring clinician? Surely the cardiologist must inform the child or family, and give some account of its possible significance? Clearly, avoiding referral in the first place does not solve this problem, but the point is that liberal use of echocardiography for reassurance may in some cases be counterproductive.

If the clinician is confident, based on clinical assessment, that a murmur is innocent, he or she should say so, explain the grounds for this opinion to the parents and discharge the child. With the availability of echocardiography, there is now no place for the old practice of bringing such children back for indefinite clinical review and advising antibiotic prophylaxis and other inappropriate constraints. If the clinician cannot be so confident, the child should be referred.

### Conclusions and future developments

Paediatric cardiology and echocardiography are finite resources that at present cannot extend to the evaluation of all infants and children with asymptomatic murmurs. The responsibility of the paediatrician is to decide which infants and children need referral, and which can be managed safely and appropriately in secondary care. Neonates with murmurs and other symptoms or signs, or those in whom the murmur sounds pathological, should be referred urgently. Neonates with no such accompanying features may be managed locally provided carers are given comprehensive relevant information and advice, and provided the infant is reviewed regularly by senior clinicians during the first few weeks of life. If the murmur persists beyond this time, or if other symptoms or signs develop, they should be referred.

Older infants and children with asymptomatic murmurs can be managed at greater leisure. If the clinician and parents are happy with the clinical diagnosis of an innocent murmur, no further investigation or follow-up are needed. This practice is necessary in order to 'gate-keep' paediatric cardiology resources, but it cannot guarantee the exclusion of a minor asymptomatic heart lesion.<sup>18</sup> If the clinician or parents are not confident that a murmur is innocent, the child should be referred. Again, a normal echocardiogram does not always provide full reassurance and incidental findings, such as a PFO, may engender further anxiety.

If further evaluation of screening pulse oximetry in the newborn confirms its promise, its introduction may complement the practice of careful clinical management of young infants with clinically innocent murmurs. This practice demands a clear pathway for such management, including audit of the unit's experience. The increasing introduction of paediatricians with a special interest in cardiology will hopefully support safe local management of children with innocent murmurs or minor heart disease, and enhance efficient utilisation of tertiary paediatric cardiology services.<sup>19</sup> ◆

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### Practice points

- Neonates with significant-sounding heart murmurs, symptoms or associated congenital abnormalities should be referred urgently for cardiological assessment
- Neonates with innocent-sounding murmurs and no symptoms should be reviewed regularly during the first few weeks of life
- Older infants and children should be referred routinely to a cardiologist if the paediatrician or parents are not confident that the murmur is innocent
- Echocardiography may aggravate parental anxiety if it identifies incidental, possibly significant, findings such as persistent patent foramen ovale



# Diagnosis, evaluation and treatment of cardiac arrhythmias

Edmund J Ladusans

## Abstract

Paediatric cardiac arrhythmias commonly occur in the absence of structural heart disease, and are classified according to their cardiac site of origin. Although a detailed history and examination are invaluable, a correct diagnosis cannot be made unless the ECG is analysed, taking into account features specific to this age group. A 24-hour ECG recording may also be helpful. As many of these conditions have a genetic basis, a careful family history should be taken. For patients presenting acutely with haemodynamic collapse, paediatric life support measures should be instigated. For others, there is more time to undertake investigations prior to treatment. A relatively small number of agents, described here, are used in therapy, and in older children, radiofrequency ablation or fitting of a pacemaker offers a more permanent treatment. Advances in genetics suggest the chance of improved screening and treatment for those conditions which are inherited.

**Keywords** adenosine; amiodarone; atrioventricular node; beta-blockers; cardiac arrhythmia; digoxin; ECG; flecainide; genetics; radiofrequency ablation; tachycardia

## Introduction

The term 'arrhythmia' refers to the absence of normal sinus rhythm. Cardiac arrhythmias can occur at any time in the paediatric population. At all ages we can classify arrhythmias according to the presence or absence of structural heart disease, and according to whether the heart rate is too fast or too slow. This review is concerned predominantly with tachycardias occurring in the structurally normal heart.

Arrhythmias are further classified according to site of origin above, at, or below the atrioventricular (AV) junction. The term 'supraventricular tachycardia' (SVT) is usually applied to tachyarrhythmias that have a narrow QRS complex width and a regular rapid rate. Nomenclature is flawed in that these tachycardias are most commonly caused by AV re-entry with an accessory pathway. They, therefore, require atrium, AV node, His bundle and ventricle to be maintained. The only arrhythmias that are truly supraventricular are those confined to the atrium (i.e. atrial tachycardia, flutter and fibrillation).

An important principle in the management of arrhythmias is not to commence treatment without electrocardiogram (ECG)

documentation. It is impossible to make a rhythm diagnosis on history and physical examination alone and incorrect drug treatment can have grave consequences.

## Clinical features

A detailed history is invaluable in the assessment of possible arrhythmia. Symptoms in children will vary with age and in the very young, accounts from parents and carers are essential. In infants, parents may report poor feeding, breathlessness and irritability but often diagnosis is delayed until heart failure and collapse occurs. In the toddler, vivid descriptions may be forthcoming but only in the older child can palpitations, heart racing, breathlessness, chest pains and dizziness be elicited. Observers may note pallor and alteration of consciousness and syncope. Life-threatening arrhythmia may present as seizures.

It is important to note the onset and termination of symptoms. Most arrhythmias start and stop suddenly. Children may discover simple vagal tricks such as handstands, which can terminate an attack. Occurrence of very rapid heart rates at rest is suggestive, whilst it may be difficult to differentiate normal sinus tachycardia in those that only occur on exercise. Documentation of the timing of events is helpful in differentiating secondary sinus tachycardias from primary arrhythmias.

Many arrhythmias have a genetic basis and a family history of arrhythmia, fits, syncope or premature sudden death should not be forgotten.

Physical examination, whilst important, is usually normal in between attacks. Attention should be directed to the cardiovascular system to exclude structural heart disease but also to general examination to detect systemic disorders, such as anaemia and thyrotoxicosis.

## Investigations

All children suspected of arrhythmia should have an echocardiogram to exclude structural heart disease, including Ebstein's anomaly and mitral prolapse. Attention is paid to chamber size and ventricular function and the exclusion of dilated and hypertrophic cardiomyopathy. Almost invariably cardiac structure is normal.

The ECG and demonstration of the relation of atrial to ventricular activity during tachycardia is the key to diagnosis. Measurements on the 12-lead ECG are age-dependent and tables of age ranges for intervals and wave axes are available.<sup>1</sup> Remember that heart rates of over 200 bpm can be seen in sinus tachycardia in the neonate. The mean frontal QRS axis should be inferior until late childhood and normal QRS duration at all paediatric ages should be less than 0.09 seconds. Thus, what is considered to be narrow complex in the adult can be broad complex in the child.

The ECG is often normal in between symptoms. A 24-hour ECG recording is useful in documenting the frequency of ectopy and heart rate variations. Unless symptoms are very frequent it seldom captures an attack.

External event recorders can either be applied to the chest during symptoms or worn with electrodes on a belt. When fixed with electrodes they have the advantage that a period of ECG before the attack is recorded and the onset of tachycardia can

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be demonstrated. They allow transtelephonic transmission of the ECG and printout remotely.

For infrequent symptoms that are of a potentially sinister significance or if there is syncope so manual activation is impossible, there are implantable devices that allow automatic recording of events. The loop recorder is usually placed in a pre-pectoral pocket. It can be activated manually and auto-activated to detect heart rates above and below programmed limits. Battery life is up to 14 months and will store a period of ECG before and after the activation.

Exercise testing is useful in the assessment of premature ventricular extrasystoles. In children with normal hearts, suppression of extrasystoles on exercise indicates a benign outlook. This is not necessarily the case in those with structural disease. Exercise testing has also been used to assess changes in the QT intervals that normally shorten as exercise increases. Occasionally it precipitates arrhythmia where exercise provocation is a feature.

## General treatment principles

In the acute presentation with haemodynamic collapse, treatment is guided by the principles of advanced paediatric life support. Electrical cardioversion starting at 2 J/kg should not be delayed.

In situations where the arrhythmia is tolerated and the child is stable there is time to assess the situation and obtain an ECG diagnosis. A full 12-lead ECG is essential, as is a paper recording of the ECG during all treatment interventions. This is invaluable as how a tachycardia starts and terminates can reveal the arrhythmic substrate to the expert.

Urea and electrolytes should be checked and correction given to ensure normal levels of potassium, calcium and magnesium. Magnesium intravenously is a very effective anti-arrhythmic agent in its own right.

Adenosine is the first-line drug for acute termination of supra-ventricular tachycardias. It is an endogenous purine nucleoside, which pharmacologically acts on the sinus and AV nodes. The principal effect is to slow AV conduction and produce AV block. It has a very short half-life, which limits its toxicity of hypotension, bradycardia, asystole, flushing and bronchospasm, but also limits efficacy in maintaining sinus rhythm. Adenosine is given by rapid injection into a central vein where possible, starting with 100 µg/kg in children and 200 µg/kg in infants to a maximum of 300–500 µg/kg.<sup>2</sup>

Adenosine is an important diagnostic tool. It will have no effect on the rate of ventricular tachycardia (VT) but may by slowing the atrial rate reveal AV dissociation and confirm the diagnosis. It does not produce any haemodynamic deterioration in VT.

Adenosine can differentiate the mechanism of SVT. It may unmask pre-excitation by blocking the AV node and increasing conduction down an accessory connection where previously not apparent. Alternatively it may show changes in PR interval indicative of dual AV nodal pathways. In atrial tachycardias and atrial flutter with rapid ventricular response where the diagnosis is not obvious, the increased AV block and slowed ventricular rate after adenosine will reveal the underlying atrial rhythm.

Where tachycardias have responded to adenosine it is logical to start a nodally active drug when recurrence requires treatment. Digoxin still has a role but requires monitoring and it has

a narrow therapeutic range. It is contraindicated where there is overt pre-excitation on the ECG in sinus rhythm since it may increase the speed of conduction of an accessory pathway. Beta-blocking drugs are safe and there is no contraindication in Wolff-Parkinson-White syndrome (WPW). Long-acting preparations, such as nadolol, are particularly important in the treatment of life-threatening arrhythmia. Verapamil although very effective in adults and older children, is absolutely contraindicated in infancy where ventricular function is very calcium-dependent and deaths have been reported.

For arrhythmias where membrane stabilising activity is important or refractory arrhythmias, flecainide has been the mainstay in many institutions. It should not be used where there is structural heart disease or impaired ventricular function. It does require monitoring and drug levels have to be measured early after starting treatment to exclude values in the toxic range. As with many drugs, therapeutic efficacy may be achieved with low drug concentrations. Flecainide is useful in combination with digoxin in AV nodal tachycardias in older children.<sup>3</sup>

Amiodarone is a very powerful drug with class III action and a degree of beta-blocking action. It acts on atrial myocardium, the AV node and ventricular myocardium and is minimally negatively inotropic. The drawback is a potential for serious long-term adverse effects including hepatotoxicity, thyroid dysfunction and photosensitivity. It also causes corneal microdeposits, which are, however, reversible. Pulmonary toxicity, seen in adults, has not been a problem in children.<sup>4</sup> It is effective intravenously with a very long half-life and builds up in the myocardium. It can be used in combination with digoxin for added AV nodal effect and as with flecainide, amiodarone increases the level of digoxin and maintenance doses need to be reduced.

Radiofrequency ablation has been more widely applied in children since the 1990s. Although possible in infancy, it is reserved for refractory and life-threatening arrhythmia in the very young. There is still concern in the small heart as to long-term complications of the lesions produced. In the older child, it offers the prospect of cure of the arrhythmia and avoidance of drug associated side effects. Success rates for ablation of accessory pathways are as high as 95%.<sup>5</sup> Caution has to be employed where pathways are close to the AV node and when considering ablation for AV nodal re-entry tachycardia. Ablation is applicable to some VTs and has a special role in the treatment of arrhythmias after surgery for congenital heart disease.

## Specific arrhythmias

### Tachycardias confined to the atrium

Atrial tachycardias are common in the foetus and neonate and then diminish in frequency until adult life. They are important arrhythmias in children and adults with corrected congenital heart disease where there has been atrial dilatation or surgical suture lines in the atrium.

### Atrial flutter

This is not uncommon in the foetus and neonate. The rapid AV conduction at this age can result in very high ventricular rates, causing hydrops and heart failure in the newborn. Flutter waves are usually apparent or made obvious after adenosine. The ventricular rate can be reduced by drugs that increase AV block. Flutter can be termi-

nated pharmacologically with amiodarone or flecainide in association with digoxin to prevent paradoxical increase in ventricular rate as the flutter rate is reduced. Cardioversion is effective and once sinus rhythm is attained the arrhythmia very rarely recurs.

### Atrial ectopic tachycardia

Atrial ectopic tachycardia is caused by an aberrant focus of excitation. ECG shows an abnormal P wave axis, the morphology of which depends on the site in the atrium the focus arises. The ventricular rate can vary with accelerations and deceleration. In infancy, spontaneous resolution is common; in older children they often are incessant and cause secondary impairment of ventricular function and clinical heart failure. The impaired ventricular function resolves when the tachycardia is abolished, and this may require radiofrequency ablation.<sup>6</sup>

### Chaotic ectopic atrial tachycardia

This arrhythmia is very rare in children and adults. It is characterised by multiple P wave morphologies producing varying ventricular rates in tachycardia. The baseline is isoelectric between P waves. It is usually asymptomatic and, in most infants, arrhythmia resolves by 1 year of age. Treatment may not be necessary. Amiodarone has been used in symptomatic patients with varying success.

### Atrial fibrillation

In contrast to adult practice, this arrhythmia is rarely seen in childhood and usually associated with congenital heart disease

leading to atrial dilatation and previous cardiac surgery. The surface ECG shows the typical fine irregular baseline between irregular ventricular complexes.

An important association is with WPW. Theoretically patients with accessory pathways are at increased risk of atrial fibrillation as the atrium may be excited prematurely in a vulnerable phase that induces fibrillation. This is thought to be the mechanism of rare sudden death in WPW where rapid anterograde conduction down the accessory pathway leads to rapid irregular broad complex tachycardia (Figure 1) and ventricular fibrillation.<sup>7</sup>

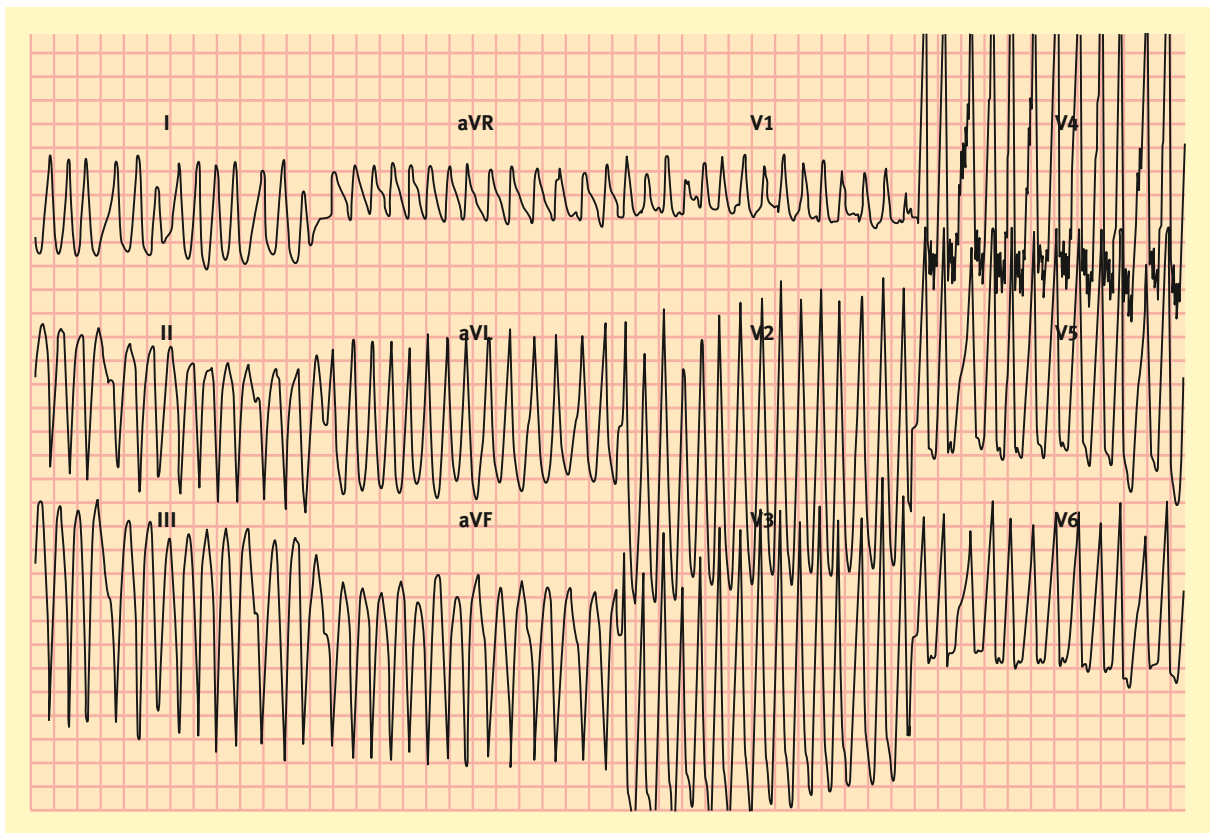
### Tachycardias involving the AV junction

There are two common types of tachycardia arising at the AV junction: AV re-entry tachycardia involving an accessory pathway and AV nodal re-entry tachycardia.

### Re-entry tachycardia secondary to accessory pathway

This is the most common type of SVT overall in childhood and has a peak incidence in infancy then diminishing to rise again in adolescence.<sup>8</sup>

An accessory pathway is a microscopic bridge of muscle between atrium and ventricle that bypasses the normal electrical insulation of the AV ring. Accessory pathways can occur anywhere in the AV junction and can be close to the AV node or more commonly lie in a left lateral position. In sinus rhythm, if the accessory connection can conduct from atrium to ventricle, pre-excitation will be manifest on the ECG as a slur on the QRS upstroke ( $\delta$ -wave) and a short PR interval. When pre-excitation



**Figure 1** Atrial fibrillation in Wolff-Parkinson White syndrome. Irregularly irregular broad complex tachycardia is seen with ventricular rate in excess of 300 b.p.m.

is associated with episodes of SVT it is termed Wolf-Parkinson White syndrome. The degree of pre-excitation will depend on the degree of conduction down the AV node and down the accessory connection. Accessory pathways may be 'concealed' and only able to conduct retrogradely from the ventricle to atrium. They will not then be visible on the ECG during sinus rhythm.

In the usual form of SVT, impulses pass down the AV node to the ventricles and then re-enter the atrium via the accessory pathway cycling again down the AV node. This 'orthodromic' tachycardia is narrow complex as ventricular activation is via the normal conduction tissue. An inverted P wave will be seen usually mid-way between the QRS complexes in a lateral pathway reflecting the delay in impulses reaching the site of the connection (Figure 2). The P wave will be closer to the QRS complexes when the site of atrial insertion is near the AV node. Less commonly in 'antidromic' tachycardia conduction is down the accessory connection and back up the AV node. This produces a broad complex tachycardia, which has to be differentiated from ventricular tachycardia.

Recurrent SVT can be controlled usually by beta-blockers, flecainide, amiodarone or a combination in refractory cases. The tendency to SVT will resolve in most infants. In older children and in those where the accessory pathway can conduct very rapidly, RF ablation is curative.<sup>5,9</sup>

#### AV nodal re-entry tachycardia

AV nodal re-entry is the predominant mechanism of SVT in older children. This is caused by dual pathways in the AV node. One pathway has a fast conduction time and a short refractory period

whilst the other is slow but with a long refractory period. Typically during re-entry tachycardia, conduction proceeds down the slow pathway and returns up the fast pathway to reactivate the atrium and AV node. These pathways are now known to be anatomically distinct, the slow pathway activating the ventricle near the mouth of the coronary sinus and the fast pathway entering in the region of the normal AV node insertion.

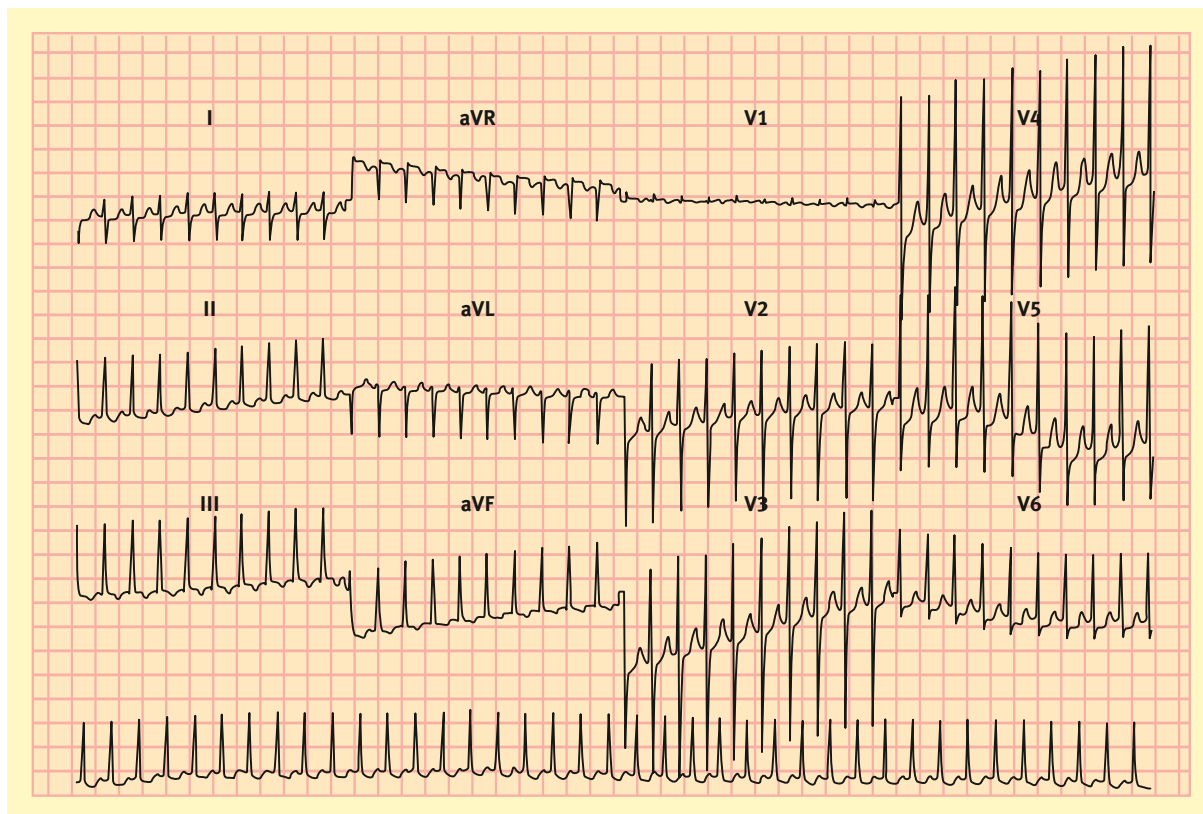
In sinus rhythm, the ECG is normal without pre-excitation. In re-entry tachycardia the atrial activation occurs simultaneously with the ventricles and the P wave is buried in the QRS complexes and not visible on the surface ECG.

Medical treatment with nodal drugs such as beta-blocking agents or digoxin may be effective but usually the combination of flecainide and digoxin is required. Ablation, whilst often curative, in our practice is deferred if possible for older children and teenagers where they can give fully informed consent to the procedure. This is because of the rare risk of the order of 1% of heart block leading to permanent pacemaker insertion.<sup>5,10</sup>

#### Incessant junctional reciprocating tachycardia

In this condition the heart rate is relatively slow and children do not present because of the acute increase in heart rate but from symptoms of congestive cardiac failure resulting in a rhythm-related cardiomyopathy. Some come to light on routine examinations when a tachycardia is noted.

The underlying basis is a concealed accessory pathway, which has much slower conduction than usual. This allows both AV node and the accessory pathway to recover excitability in between depolarisations and leads to the incessant nature. On



**Figure 2** 12-Lead ECG showing typical orthodromic re-entry tachycardia in Wolff-Parkinson syndrome. Inverted P waves are clearly visible between QRS complexes, best seen in Lead III.

ECG, the retrograde P wave is close to the following QRS complex giving a long RP interval. Medical treatment is difficult but ablation is usually possible.<sup>11</sup>

### Junctional ectopic tachycardia

The anatomic basis of this arrhythmia is thought to be a small focus of abnormal automaticity in the AV node or bundle of His. It accounts for 8% of all SVTs seen in children. ECG shows narrow complex morphology because of the site of origin. There is usually no retrograde activation of the atrium and typically there is complete AV dissociation with the atrium activated by the normal sinus impulses at a much slower rate.

Most commonly, junctional ectopic tachycardia (JET) occurs after cardiopulmonary bypass especially with suturing near the AV junction. Postoperative JET develops within hours of discontinuing bypass and the high ventricular rate with AV dissociation lead to haemodynamic decompensation. JET also occurs as a congenital arrhythmia first described by Coumel as His bundle tachycardia. It usually presents in the neonatal period or infancy with incessant tachycardia.

In the postoperative situation, surface cooling is effective in reducing the ventricular rate and improving haemodynamics. Electrolyte imbalance has to be corrected and use of inotropes minimised. Atrial pacing at a faster rate may lead to capture and restoration of AV synchrony. Amiodarone is the drug usually chosen to minimise negative inotropic side effects. Postoperative JET usually resolves after these supportive measures.

In congenital JET, treatment is directed to improving the ventricular rate and various drugs have been used alone or in combination, such as sotalol, flecainide and propafenone. Amiodarone is probably the most effective.<sup>12</sup> Radiofrequency ablation is associated with a high degree of complete heart block and lifelong pacemaker requirement.

### Ventricular arrhythmias

Ventricular arrhythmias are defined as originating distal to the bundle of His. VT comprises less than 5% of tachycardias in children and symptoms depend on the ventricular rate. Ventricular arrhythmias and sudden death are well-documented to occur after cardiac surgery for complex congenital heart disease and this has been extensively studied in long-term follow-up after repair of tetralogy of Fallot. VT may also arise secondary to metabolic disturbance, drug toxicity (tricyclic antidepressants, solvent abuse), myocarditis or cardiomyopathy.

ECG shows a wide complex tachycardia. QRS duration for a neonate greater than 0.075 seconds and greater than 0.09 seconds in older children is prolonged. The presence of AV dissociation is diagnostic and may be unmasked after the administration of adenosine. VT can occur, however, with 1:1 retrograde conduction to the atrium and it then has to be differentiated from antidromic AV re-entry tachycardia in WPW or SVT with aberrant conduction, which is usually of right bundle branch morphology. Other suggestive features on ECG are a superior QRS axis in tachycardia, capture beats where an atrial impulse passes through the AV node and manages to excite the ventricle producing an interpolated narrow complex. Fusion beats are where partial activation occurs from the sinus node and an intermediate complex is produced.

Idiopathic monomorphic VT in infancy and childhood carries a good prognosis in general if intra-cardiac structure is normal.<sup>13</sup> If the ventricular rate is slow, treatment may not be required. An incessant form of VT can be seen in infancy, which arises from the left ventricle and has right bundle branch block with superior QRS axis. This condition is thought to be due to small ventricular hamartomas. Suppression can be achieved with flecainide or amiodarone if necessary combined with a beta-blocker. Spontaneous resolution is usual.

A similar morphology, monomorphic VT occurs in older children and teenagers in the absence of structural cardiac abnormality. This left posterior fascicular tachycardia can be responsive to verapamil. Ablation has been successful and curative in refractory cases. Idiopathic right ventricular outflow tachycardia is also described.

### Genetic conditions associated with ventricular arrhythmia and risk of sudden death

These conditions have an importance which outweighs their incidence since they can result in the tragic sudden death in otherwise fit and normal children. They are increasingly recognised and the molecular genetic basis defined. This will give the opportunity of mutation specific therapy and automated mutation analysis will in the future simplify screening.

### Long QT syndrome

Congenital prolonged QT syndrome is a disorder of ventricular repolarisation characterised by prolongation of the QT interval on the ECG. The autosomal dominant Romano-Ward syndrome is the most common form. The Jervell-Lange-Nielsen syndrome is associated with congenital deafness and inherited as an autosomal recessive condition with a poor prognosis.

The mutations cause defects in various ion channels that affect myocardial repolarisation. This causes predisposition to ventricular arrhythmia – the hallmark of which is a polymorphic VT known as ‘torsades de pointes’. This arrhythmia is often self-limiting but can deteriorate to ventricular fibrillation and lead to sudden death. Typically, patients present with syncopal episodes precipitated by exercise, intense emotion or loud noises and startle. Hypotension can cause secondary hypoxic seizures and diagnosis is not uncommonly delayed and initially mistaken for epilepsy. Most patients present between 9 and 15 years of age but cases have been described in infancy and even presenting in the foetus.

Eleven mutations have now been detected. For the most common phenotype-genotype correlations have been described and some have therapeutic implications.<sup>14</sup> LQT1 and LQT2 are associated with mutations of genes KCNQ1 and KCNH2 (HERG), respectively. These genes code for subunits of potassium channels. LQT3 is associated with mutations affecting the SCN5A gene, which codes for a cardiac sodium ion channel. LQT1 generally is associated with a broad T wave, LQT2 with low amplitude and often double peaked T waves and LQT3 with a very delayed symmetrical T wave. Syncopal episodes and torsades typically are triggered on exercise and especially swimming with LQT1. LQT2 patients typically are provoked by auditory stimuli and attacks in LQT3 often occur at sleep or resting situations.

Therapy of choice is beta-blockade and a long-acting agent such as nadolol is preferred. Studies have shown that mortality is reduced considerably in treated patients.<sup>15</sup> Theoretically, sodium

channel blockers such as mexilitine may be effective in LQT3. Syncope despite beta-blockade is an indication for an automated implantable cardiac defibrillator (ICD). Small units are now available that can allow implantation in young children, although the effects of growth on the electrodes and requirement for repeated revisions is a problem. Trials are underway of a 'leadless' ICD that should eventually improve this concern. Treatment with beta-blocking drugs is still required and inappropriate defibrillator activation can occur and cause psychological disturbances.

#### Catecholaminergic polymorphic ventricular tachycardia

Coumel described this familial condition in a series of children who developed syncope secondary to exercise, stress, or startle. There is a typical pattern of a bidirectional ventricular tachycardia (Figure 3) – it can deteriorate to polymorphic VT and sudden death. An autosomal dominant form is related to mutations in the cardiac ryanodine receptor gene and a less common autosomal recessive variety associated with mutations in the calsequestrin 2 gene.<sup>16</sup> Both genes are involved in intra-cardiac calcium transport. Treatment with beta-blocking drugs is effective but poor compliance and syncope despite treatment are indications for consideration of implantation of an ICD.

#### Arrhythmogenic right ventricular dysplasia

The clinical features of arrhythmogenic right ventricular dysplasia are an abnormal resting ECG with T wave inversion in the right precordial leads and ventricular tachycardia with typical left bundle branch block morphology. The condition is associated with fibro-fatty replacement of myocardium in the right ventricle.<sup>17</sup> It is one of the major genetic causes of juvenile sudden death

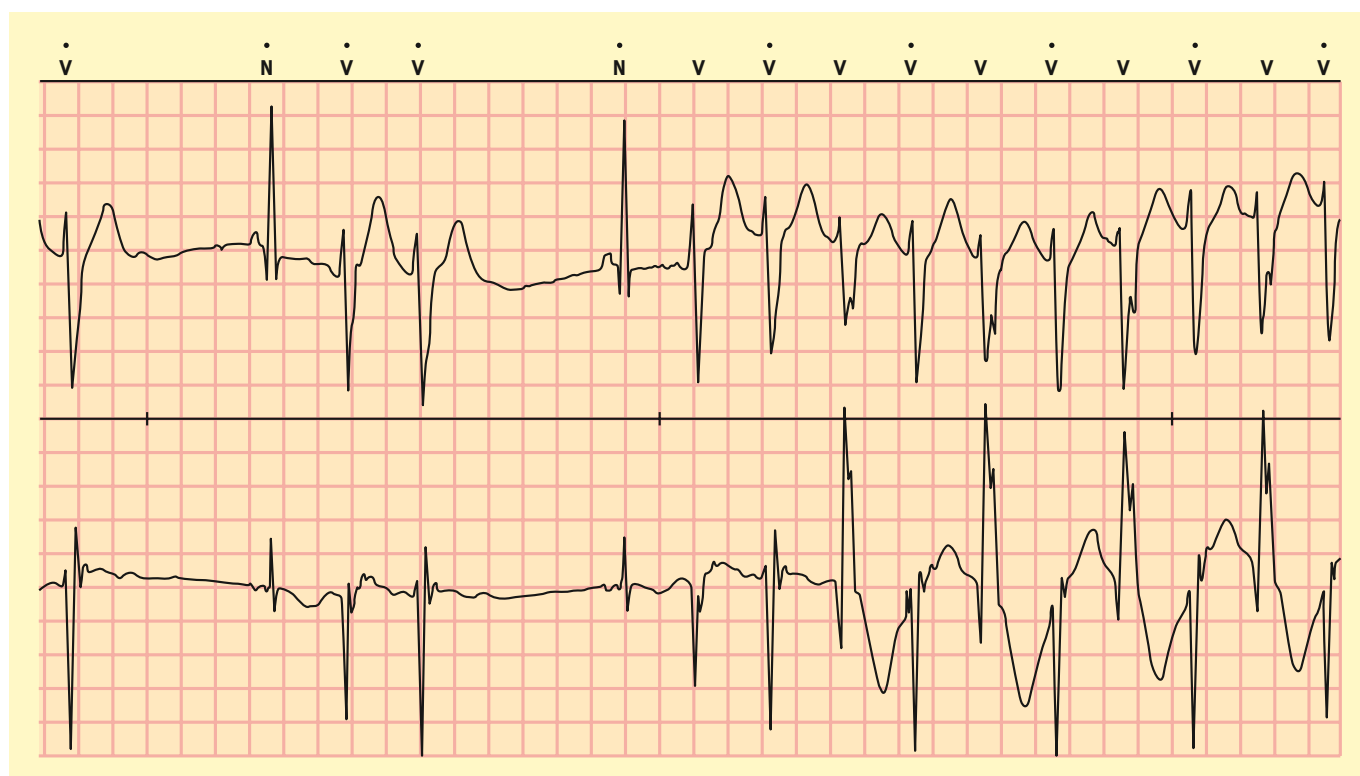
and inherited as an autosomal dominant condition with variable penetrance. Several different loci have been demonstrated in this condition including a ryanodine-receptor mutation.

#### Brugada syndrome

In this condition syncope occurs due to idiopathic ventricular fibrillation. It is associated with typical ECG changes consisting of right bundle branch block pattern and variable ST segment elevation in the right precordial leads. It is considered mainly a disease of young adults but was first described in children and events are commonly associated with febrile illnesses in the young and often occur at night.<sup>18</sup> The ST elevation has a coved or 'saddle type' appearance and may be revealed after the administration of sodium channel blocking drugs such as mexilitine or flecainide, which can be used as a diagnostic test. Spontaneous presence of the typical pattern is a risk factor for sudden death. There is autosomal dominant inheritance and mutations have been found in the SCN5A gene in 20–30% of patients.

#### Summary

The spectrum of arrhythmias in children is now well-defined. Correct diagnosis and management depends on the capture and analysis of an ECG during symptoms. Most arrhythmias can be controlled successfully with a relatively small range of drugs. Treatment is given until either there is spontaneous resolution or the age is reached where ablation and pacemaker therapies have the least risk. Refractory arrhythmias require multidisciplinary collaboration from paediatric cardiologists, cardiac surgeons, electrophysiologists, and geneticists. Genetic advances offer the



**Figure 3** Holter recording showing simultaneous ECG channels demonstrating an episode of bidirectional VT in a patient with history of syncope. Alternating different morphologies of ventricular complex are seen during tachycardia. This is diagnostic of Catecholaminergic polymorphic VT.



prospect of improved screening and specific treatment for life-threatening inherited conditions. ♦

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## Practice points

- Cardiac arrhythmias can be classified as supraventricular, nodal or ventricular, and in terms of whether or not they are occurring secondary to structural damage
- The correct diagnosis and management of a cardiac arrhythmia depends on the analysis of an ECG during symptoms, as well as on a detailed history and examination
- Most arrhythmias can be controlled successfully with a relatively small range of drugs
- Treatment is given until either there is spontaneous resolution or the child is old enough to undergo radiofrequency ablation or pacemaker therapies with least risk
- Refractory arrhythmias require multi-disciplinary collaboration from paediatric cardiologists, cardiac surgeons, electrophysiologists, and geneticists
- Genetic advances offer the prospect of improved screening and specific treatment for life threatening inherited conditions

# Long-term outcome of the child with congenital heart disease

Damien Kenny

A Graham Stuart

## Abstract

The incidence of congenital heart disease is 6–8 per 1000 live births and has remained unchanged for many years. Congenital heart defects occur with similar frequency throughout all ethnic groups and regions of the world. It is estimated that 1600 patients requiring long-term care will enter adulthood every year in the UK – many of whom have complex disease. The majority have survived as a consequence of innovative cardiac surgery. Their management offers an insight into the surgical, medical, social and psychosocial therapies that have been introduced in recent years.

**Keywords** congenital heart disease; morbidity; mortality; re-intervention; surgery

## Introduction

There have been huge advances in the treatment of children with congenital heart disease (CHD) in the past 20 years. Thus, surgical mortality has decreased from an average of 15% in 1990 to an average of 5% in 2000.<sup>1</sup> Although mortality remains a necessary definition of outcome, it is insufficient and significant morbidity also needs to be considered. This includes neuropsychological impairment, exercise limitation, need for re-intervention, problems during pregnancy, the need for long-term medications especially anticoagulation, and impaired functional status and quality of life. Defining outcome (including morbidity) will require multicentre inter-specialty collaboration and accurate data collection and interpretation.<sup>2</sup> Greater involvement and understanding of the disease process by the patient is also required and this may be assisted by the development of effective transitional care from paediatric to adult services. Similarly, there needs to be further subspecialty development of adult congenital services with the specialist services for imaging, transcatheter intervention, electrophysiology and cardiac surgery. To achieve this there must be continued financial commitment at a central level as well as constant re-evaluation of strategy to take into account the rapid increase in number of children reaching the adult service. Future

services should be designed to predict identifiable future needs. This review will focus on these points and will consider how such developments might affect the long-term outcome of the patient with CHD.

## Who has long-term problems?

Patients with CHD are a heterogeneous group. Even within the same diagnostic group, there may be a wide spectrum of severity. The inherent heterogeneity of this patient population has made it virtually impossible to develop randomised controlled trials to guide management. Consequently, clinical decision-making has to be individualised. Most guideline documents are based on clinical consensus rather than a strong research base.

Some general comments can be made about long-term outcome in patients with CHD. Perhaps not surprisingly, patients with two functioning ventricles have a better long-term outcome than those with one. Similarly, those repaired or palliated in the early surgical era have more long-term problems than those operated in more recent years with the benefit of improved cardiopulmonary bypass techniques (including myocardial preservation) and postoperative intensive care. In part, however, this may simply reflect the longer period of follow-up. Similarly, irrespective of aetiology, pulmonary hypertension and systemic ventricular dysfunction are associated with a poor prognosis.

## Specific problems

Emergency admission of the adult patient with CHD carries a worrying prognosis. In many patients it heralds deterioration and in-hospital mortality is high. Common presentations include: heart failure, arrhythmias, pulmonary hypertension and non-cardiac complications related to coagulation or infection. Other common reasons for hospital admission are outlined in [Table 1](#) and include the need for re-intervention.

### Heart failure

Heart failure is present in over 30% of patients with either univentricular circulation or a systemic right ventricle (atrial switch operations for transposition of the great arteries (TGA) and congenitally corrected TGA).<sup>3</sup> Mortality is significantly higher in symptomatic patients (47%) compared with those without symptoms (5%).<sup>3</sup> Classical assessment tools for heart failure have not been adapted to CHD patients and symptoms may be difficult to discern in patients who are not active or those with significant psychosocial problems. However, certain predisposing correctable risk factors for heart failure can be identified and include older age at operation, severe atrioventricular valve regurgitation, duration of cyanosis, and pregnancy.

Although impaired ventricular function on echocardiography may precede symptoms, the reproducible and accurate assessment of ventricular function, particularly in patients with a single ventricle, can be difficult. Similarly, although cardiopulmonary exercise testing can provide useful prognostic data,<sup>4</sup> it may be difficult to interpret if motivation is low. High levels of brain natriuretic peptide and chronotropic incompetence may also be prognostic. Standard medical treatments particularly with angiotensin-converting enzyme inhibitors have not been shown to be effective in patients with systemic right ventricular failure.

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### Common reasons for hospital admission

Problem	Example
Cardiac arrhythmias	Cardioversion Electrophysiology study/ablation Pacemaker implantation Defibrillator implantation
Cardiac failure	Inotrope therapy Cardiac resynchronisation therapy Commencement of pulmonary vasodilator therapy
Cardiac surgery	Primary repair Conduit replacement Valve replacement Fontan conversion Arrhythmia surgery
Transcatheter intervention	Atrial septal defect closure Ventricular septal defect closure Coarctation stent Pulmonary artery stent
Endocarditis	IV antibiotics Emergency surgery
Pregnancy	Peripartum care Anticoagulation management
Non-cardiac surgery	Cholecystectomy in cyanotic patient Dental extraction
Non-cardiac medical problem	Thyroid dysfunction on Amiodarone Acute gout

**Table 1**

Cardiac resynchronisation therapy has demonstrated benefit in selected groups and may delay the need for heart transplant. It is estimated, however, that 10–20% of patients with CHD will eventually require heart or heart–lung transplantation at some point in their life. Congenital heart patients are a small proportion of transplant referrals (only 2% of all heart transplants in adults in the past two decades). Traditionally, it has been thought that adult patients with CHD carry a worse early prognosis than most non-congenital referrals, however, recent data have shown the outcome can be improved with careful patient selection. Overall, approximately 50% of adult CHD transplant patients survive 11 years.<sup>5</sup>

#### Arrhythmias and sudden cardiac death

Arrhythmias account for up to 37% of emergency admissions in adult patients with CHD.<sup>6</sup> These include atrial and ventricular dysrhythmias and late onset heart block. Arrhythmias may be difficult to recognise in patients with complex disease where there are pre-existing conduction abnormalities or abnormal p wave morphology. Many postoperative arrhythmias are ‘scar’ related and may be refractory to anti-arrhythmic medication. Modern three-dimensional mapping techniques are invaluable in the assessment of arrhythmias in the adult with CHD. This can enable transcatheter ablation to be carried out. Cardiac arrhythmias may both cause and be caused by underlying haemodynamic abnormalities. The new onset of a cardiac arrhythmia should prompt

a full haemodynamic assessment. Patients with impaired systemic ventricular function or a single ventricle tolerate atrial arrhythmias poorly and should be promptly electrically cardioverted, due to the risk of deterioration into ventricular fibrillation.

Although rare, sudden cardiac death is a devastating complication and may occur in apparently asymptomatic individuals – in particular, in patients with single ventricles, complex TGA, aortic stenosis, tetralogy of Fallot and pulmonary atresia.<sup>7</sup> Risk stratification with appropriate insertion of implantable cardiac defibrillators has been shown to be effective in preventing sudden cardiac death in this subgroup.

#### Pulmonary hypertension

Up to 10% of adult patients with CHD develop pulmonary hypertension. The extreme manifestation of this is reversal of a long-term left-to-right shunt due to pressure-induced changes in the distal pulmonary vascular bed (Eisenmenger’s syndrome); however, poor ventricular function, cyanosis and thromboembolism, and long-term abnormality in flow dynamics also contribute. Increased pulmonary vascular resistance is particularly poorly tolerated in single ventricle circulation and has been implicated in protein-losing enteropathy, which may be fatal. Treatment options for pulmonary hypertension were previously limited to heart and lung transplantation, however, a myriad of new medical therapies – including endothelin receptor antagonists and phosphodiesterase inhibitors such as Sildenafil – offer improved medical palliation.<sup>8,9</sup>

#### Non-cardiac and vascular complications of CHD

A total of 25% of acute admissions to hospital in adults with CHD are due to non-cardiac complications such as infection, systemic or cerebral thromboembolism, syncope, or rarely aortic dissection. Long-term cyanosis with associated polycythemia and iron deficiency promotes thrombosis. Prophylaxis with warfarin is not without complication and significant haemorrhage is an important cause of death. Aortic dissection can occur in patients with coarctation of aorta and tetralogy of Fallot. This is secondary to progressive aortic dilatation and is due to innate abnormalities in the aortic tissue – usually cystic medial necrosis.

#### Need for intervention/re-intervention

Many children with CHD will require re-operation in later life. One study demonstrated that of 2250 neonates operated on over a 27-year period, 27% required re-operation.<sup>10</sup> The majority of these operations were as part of a staged approach to complex lesions with the remainder mostly due to residual defects after the primary procedure. This is particularly prevalent in certain diagnoses including tetralogy of Fallot when late pulmonary valve replacement is necessary in up to 20% of patients undergoing primary repair in childhood.

Some patients will undergo their initial surgery as adults. This includes patients with conditions that increase in severity with the aging process (for example, increasing left to right shunt in partial atrioventricular septal defect) and those in whom the natural history is associated with gradual deterioration (for example, heart block in congenitally corrected TGA).

There is a rapid increase in the number of ‘surgical’ procedures that can now be carried out via the transcatheter route (Table 2). The transcatheter technique has the advantage of

### Examples of transcatheter interventions in adults with congenital heart disease

Lesion	Procedure	Operation replaced	Comment
Atrial septal defect	Device closure	Open heart repair	75% suitable for transcatheter closure
Ventricular septal defect	Device closure	Open heart repair	Some muscular and perimembranous defects
Patent arterial duct	Coil or plug occlusion	Thoracotomy – closed repair	>90% suitable for transcatheter closure
Coarctation and re-coarctation of aorta	Angioplasty or stent implantation	Closed or bypass repair	Open surgery carries high risk
Venous and arterial collaterals in complex disease	Coil or plug occlusion	Surgical ligation	>80% suitable for transcatheter repair
Tetralogy of Fallot – pulmonary regurgitation	Percutaneous stented valve	Surgical homograft	>90% suitable
Tetralogy of Fallot – branch pulmonary stenosis	Pulmonary artery stent	Surgical repair	Evolving – currently only suitable if adequate stenosis to anchor stent
Mustard/Senning baffle obstruction	Baffle stent	Open surgical repair	>90% suitable
Post Fontan surgery - fenestration	Plug or coil closure	Open heart repair	>90% suitable
Myocardial scar-related tachycardia	3D mapping and irrigated tip ablation	Medical therapy	Increasing frequency of scar-related tachycardia – success rate 75%

**Table 2**

reduced hospital stay and morbidity. In some conditions the surgeon and the interventionalist work together to achieve the desired outcome – so called, hybrid surgery. Hybrid surgery provides the interventionalist with direct access to the heart and avoids the need for cardiopulmonary bypass. Such co-operation is likely to provide a cornerstone of patient management in the future.

#### The specific problem of teenagers

Adolescents with CHD face unique problems during their transition into adulthood and 'transition clinics' are needed to address their needs. Care in the paediatric culture is family-centred but is often not focused on a teenager's growing independence and adult behaviour. Conversely, adult clinics are less family and developmentally centred but assume patient's autonomy. A gradual transition from the paediatric to adult congenital system is essential. This needs to be individualised and take into account the patients co-morbidity – in particular learning difficulties.

Many patients with CHD will have had multiple admissions to hospital and memories of painful procedures and surgery. They may have problems with low self-esteem and body image because of scars and altered body image.<sup>11</sup> As they develop emotionally, many will have questions about work, travel, exercise, insurance, inheritance and dying and will gradually be ready to take responsibility for their own health. This is a particularly difficult time for parents who will have spent many years caring for and protecting their child and will find it difficult to relinquish control. Teenagers are increasingly exposed to smoking, alcohol and drugs. They will begin to have relationships and it is vital that female patients receive appropriate contraceptive advice early. Although most patients with CHD should cope with the haemodynamic stresses of pregnancy well, unplanned pregnancy in patients with severe left ventricular outflow tract obstruction, pulmonary hypertension or cyanosis can be disastrous for both

mother and foetus. Indeed cardiac disease is now the most common cause of maternal mortality in the UK.<sup>12</sup>

### Specific conditions

#### Acyanotic lesions

##### Left-to-right shunts

These include atrial septal defects (ASD), ventricular septal defects (VSD), atrio-ventricular septal defects (AVSD) and persistent arterial duct (PDA).

Although most children with ASDs remain asymptomatic, untreated, up to 70% of adults demonstrate symptoms in the fourth decade of life secondary to arrhythmias and exercise intolerance due to right heart failure.<sup>13</sup> In adult life, there is a tendency for the left-to-right shunt to increase as a consequence of reduced left atrial compliance. Percutaneous closure with a range of commercially available devices is the technique of choice for most ASDs although surgery may be more appropriate if the defect is large or concomitant arrhythmia surgery is required. Large unrestrictive VSDs result in heart failure in infancy and require early surgical repair. Smaller restrictive defects present with murmurs and almost half will close throughout childhood.<sup>14</sup> Some defects will persist into adulthood and only 10% of these will close spontaneously. Indications for intervention include increasing left ventricular diameter, aortic regurgitation or endocarditis. Most patients who have undergone surgical repair and those who have a small VSD with normal pulmonary vascular resistance have a normal life expectancy. Rarely, right ventricular outflow tract obstruction, sub-aortic narrowing or aortic regurgitation develop and require intervention later in life. Patients with a residual VSD should be followed up throughout early adulthood. Patients with large defects that are untreated in childhood will inevitably develop Eisenmenger's syndrome, which carries a high risk of morbidity and early death.

AVSD is most commonly seen in patients with Down's syndrome. However, those without Down's syndrome often have a more dysplastic atrio-ventricular valve. Repair is normally carried out in infancy, however, re-intervention is frequently required. Long-term morbidity usually relates to residual regurgitation of the left atrio-ventricular valve, left ventricular outflow tract obstruction and complete heart block.

The long-term outlook for PDAs closed in childhood is excellent. If, however, pulmonary blood flow has been high for any length of time, pulmonary hypertension can develop. Large patent ducts that have been missed can cause Eisenmenger's syndrome and all patients are at risk of endarteritis. Percutaneous closure is the approach of choice in all age groups apart from premature infants.

### Left heart obstructive lesions

Left heart obstruction includes mitral stenosis, aortic valve stenosis, sub-aortic stenosis, supra-aortic stenosis and coarctation of the aorta. These lesions may occur together and in association with other left heart lesions.

Although congenital mitral stenosis may be treated with balloon valvuloplasty, surgery is usually required. Mitral valve repair is sometimes possible but eventually valve replacement is usually needed. Early valve replacement can lead to significant morbidity and mortality due to the need for repeated surgery (to upsize the valve) and complications secondary to anticoagulation.

Aortic valve stenosis may be treated in infancy with balloon valvuloplasty or surgical valvotomy with comparable rates of re-intervention at 5 years (50%).<sup>15</sup> Ultimately, aortic valve replacement is required. In young patients, the Ross operation is often used. In this procedure, the native pulmonary valve is transplanted to the aortic position, the coronary arteries are transplanted and a homograft is placed in the pulmonary position. This avoids the need for a prosthetic valve and anticoagulation, however, re-intervention at 10 years is 25%.

Coarctation of the aorta is the fourth most common congenital heart lesion. It is a diffuse disease of the vasculature and long-term complications include cerebral haemorrhage, early onset ischaemic heart disease, endocarditis and hypertension. There is a bimodal age presentation; infancy and early adult life. Most infants present in the first week of life and current surgical approaches lead to excellent results. There is, however, a 20% incidence of hypertension in adolescence leading to significant longer-term morbidity. The factors driving the hypertension are as yet unclear. Re-intervention may be necessary throughout childhood and balloon angioplasty is often the preferred approach although this may lead to aneurysm formation in up to 35% of patients with native coarctation.<sup>16</sup> In adolescence and early adult life, the usual presentation is with asymptomatic hypertension. Stent implantation is now the treatment of choice in most centres for native coarctation and re-coarctation in older children and adults. Covered stents may be used to treat aneurysm formation; however, the long-term results of these approaches have yet to be seen.

### Isolated right heart obstructive lesions

Isolated pulmonary stenosis is found in 7–10% of children with CHD. Severity may vary from haemodynamically insignificant valvar abnormalities to near atresia. Foetal intervention has been carried out for the latter with mixed results. Percutaneous

valvotomy is the treatment of choice at any age but surgery may be required for severe valvar dysplasia or in association with Noonan's syndrome. Repeat balloon valvuloplasty may be necessary in 10% of patients with increased risk of pulmonary regurgitation, which will require monitoring. The overall long-term prognosis is excellent. Ebstein's anomaly is a rare condition associated with a dysplastic, apically placed tricuspid valve. Like coarctation, it has a bimodal age presentation. Infants present with heart failure. There is a high mortality due to lung dysplasia and survivors may require a conversion to a single ventricle circulation. In older children and adults, patients usually present with arrhythmias or heart failure secondary to tricuspid regurgitation. There is a strong association with ASD and Wolf-Parkinson-White syndrome.

### Cyanotic lesions

#### Tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic heart defect presenting in early childhood. The prognosis for unrepaired tetralogy is poor with 86% patients dying by the age of 15 years.<sup>17</sup> Surgical correction is now routinely performed in the first year of life and patients have an excellent long-term outlook with over 98% 20-year survival. However, approximately 20% will require surgical re-intervention due to residual right ventricular outflow tract obstruction, VSD or progressive pulmonary regurgitation. Transcatheter pulmonary valve replacement (Figure 1) has been an important development that will reduce the need for open surgical replacement in the future. However, the optimal timing for pulmonary valve replacement is still unclear by either technique. There is an important subgroup of patients who suffer sudden late cardiac death, thought to be due to ventricular arrhythmia. Those with QRS duration of greater than 180 milliseconds are particularly at risk and, if symptomatic, an implantable defibrillator may be required.

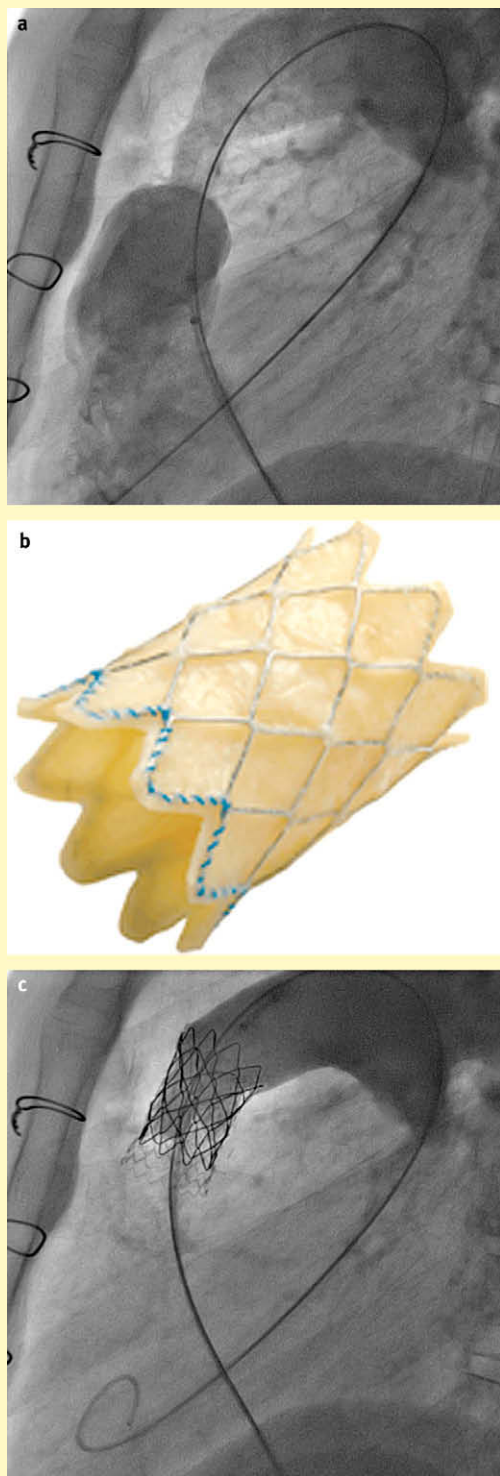
#### Transposition of the great arteries

Untreated TGA is lethal in over 90% of patients by 1 year of age. The current surgical approach to TGA is the arterial switch operation. Survival rates are excellent with an early mortality of less than 5%. Up to 10% of patients will require catheter intervention for branch pulmonary artery narrowing and 5–10% will require re-operation for coronary artery lesions or right ventricular outflow tract obstruction.<sup>18</sup> Some adolescents and most adults with TGA will have undergone an atrial redirection procedure (Mustard or Senning operation). Mustard and Senning operations fell into disuse due to the long-term complications of systemic ventricular failure, baffle leaks and stenosis, and the high rate of arrhythmias – including sudden death. This has resulted in a 25-year postoperative survival of only 64%.

#### Anomalous pulmonary venous drainage

Mortality after total anomalous pulmonary venous connection repair has decreased (postoperative 5-year survival for patients undergoing repair in the recent era is over 95%) but remains highest in young patients and in those with cardiac connection type or pulmonary venous obstruction.<sup>19</sup> Obstruction of an implanted vein may occur in up to 10% of patients postoperatively; however, new sutureless repair techniques may reduce this complication. Occasionally partial anomalous pulmonary venous drainage





Percutaneous pulmonary valve implantation. A patient with previous right ventricle to pulmonary artery conduit has developed severe conduit stenosis **a**. The Medtronic Melody valve **b** is inserted via the groin crimped onto a balloon catheter. In the case shown, the right ventricular outflow tract has been stented as part of the same procedure to provide support for the new pulmonary valve. The result is a non-stenotic, competent valve without the need for surgery **c**.

**Figure 1**

is diagnosed in adulthood in conjunction with a secundum ASD. The main long-term risk following surgery is atrial arrhythmias and most patients do not require long-term follow-up.

### Univentricular heart

This includes diagnoses such as tricuspid atresia, double inlet left ventricle and hypoplastic left heart. The longer term complications have been discussed above. The 15-year survival has been reported at 82% following palliation with the Fontan procedure with preoperatively impaired ventricular function and elevated pre-operative pulmonary artery pressures identified as risk factors for poor outcome.<sup>20</sup> Outcomes for hypoplastic left heart remain the lowest of the common univentricular circulation defects with 5-year survival of 65%. The steady increase in numbers of patients with complex CHD reaching adult life represents the biggest challenge facing adult congenital heart services. In childhood, many of these complex patients are extremely well. When they reach adulthood, the inevitable cardiovascular changes associated with aging and long-standing abnormalities of circulation take their toll. Cardiac arrhythmias, protein-losing enteropathy, heart failure and multi-organ dysfunction are common. Intensive follow-up with full medical and psychosocial support is essential.

### Summary and the future

The number of patients surviving with CHD is rising rapidly and life expectancy for many patients is almost normal although morbidity remains high. To improve upon this we must target three vital areas:

- Continued commitment to foetal screening and attention to neuroprotective strategies at primary neonatal repair will improve outcomes. We also need a greater understanding of the longer term impact of initial surgical intervention and approach (for example, suture lines in the right atrium) to improve the longer term problems we are seeing at present time (arrhythmias).
- The transition between childhood and adulthood must be carefully managed to prevent patients being lost to follow-up. Although, most patients are managed as outpatients, structured follow-up protocols and open-access clinics are essential to detect early maladaptive response and instigate prompt treatment.
- A new specialty of adult CHD is developing but more trained specialists and centres with appropriate facilities including appropriate funding for data collection and research are required.

The treatment of CHD is both challenging and rewarding, however, there is an ongoing responsibility to our patients to ensure that we continue to strive for the best possible anatomical, physiological, neurological and psychosocial outcomes. ♦

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# Features of respiratory syncytial virus

Roddy O'Donnell

## Abstract

Respiratory syncytial virus infects almost all of us in early childhood and causes most cases of bronchiolitis – the most common reason to be admitted to hospital under 1 year of age in the developed world. Each winter, paediatric wards are tested by predictable epidemics of unpredictable intensity. Trials of vaccination in the 1960s were associated with catastrophic enhanced illness leading to intense research that has enriched immunology and virology as a whole. Treatment is still supportive but with modern facilities and training survival rates are high even in severe disease. Post bronchiolitis wheeze is common and hard to treat but new therapies are being proposed. Possible links between severe bronchiolitis atopy and asthma are still under investigation.

**Keywords** allergy; bronchiolitis; cell mediated immunity; lymphocyte; respiratory syncytial virus

## History

Outbreaks of feverish respiratory illnesses have been described for many centuries and the word 'influence' (from which 'influenza' comes) was used from the 14th century to imply that the disease was affected by astrological events. Goodpasture published the first account of pneumonia in infants caused by epidemic virus infection in 1939 and Adams was probably the first to give a detailed description of an outbreak of RSV in 1941. He described a nosocomial infection in a newborn nursery that affected 32 children causing nine deaths and found cytoplasmic inclusions in the lung at post mortem. The virus itself was first isolated from a chimpanzee with a coryzal illness in 1956. The virus was cultured and shown to be able to infect other chimpanzees and was named 'chimpanzee coryza agent'. In the following year, Chanock and others isolated the same virus from a child with croup in Baltimore. The virus was renamed respiratory syncytial virus (RSV) to describe the site of infection and characteristic syncytium formation found in cell culture and infected tissues.

## Epidemiology

RSV is distributed worldwide with similar patterns of disease in all climates. Wherever it is found, children are the ones most likely to have the severe illnesses. Bronchiolitis is the single commonest

reason for a child under 1 year of age to be admitted to hospital in the developed world. Re-infections occur throughout life, in spite of good levels of neutralising serum antibody. As well as the very young, the very old are also at risk from RSV infection. Outbreaks of RSV pneumonia in the elderly are possibly as important as influenza in causing excess deaths. Annual outbreaks occur that are usually of sharp onset and follow regular predictable patterns. In temperate climates most cases of RSV infection are reported during the winter months. Most hospital admissions occur during a narrow peak period lasting only a few weeks. In the UK, the peak incidence is between the beginning of January and the end of March. In tropical climates such as in Hong Kong and Trinidad, epidemics are seen during the rainy season. Influenza epidemics also occur in the winter but do not usually coincide with the peak of the annual epidemic of RSV infection. Clinical isolates of RSV are rare in the UK during the summer months and it is not clear where the virus goes or how it re-emerges so rapidly during the next winter season. No animal reservoir for human RSV is known to exist.

Initial studies of strain variation in RSV came from monoclonal antibody typing into A and B strains. Both strains commonly co-circulate in one outbreak. There is little difference in the type or severity in clinical disease produced by A or B strains. The possibility still exists, however, that some strains, not defined by monoclonal studies, may cause more severe disease. Molecular biological techniques have allowed a more detailed study of sub-type variation within RSV, by classification according to genome sequences especially of the highly variable G protein gene. Interestingly, viruses sequenced from children all over the world fall into the similar lineage classifications although the relative frequency of each lineage differs. Unlike influenza virus, several strains of RSV commonly circulate locally alongside one another with similar frequencies. Some evidence of evolution of RSV strains has emerged, some strains becoming less common over the years and others increasing in frequency. This may be occurring through immune selective pressure and the common ancestor of the current B strains has been estimated to date back to around 1949. The divergence between A and B strains has been calculated to have occurred approximately 350 years ago.<sup>1</sup>

## Taxonomy: the mononegavirales

RSV belongs to the order mononegavirales, which consists of viruses with non-segmented negative-stranded RNA genomes. In this group, the entire virus is coded within a short length of fragile RNA written in a negative sense and which therefore needs first to be transcribed within the infected cell into positive sense mRNAs to allow protein transcription.

The order includes three families of virus: the filoviridae, paramyxoviridae and rhabdoviridae. All have similar genomic organisation and patterns of morphogenesis and are differentiated by their biological differences.<sup>2</sup> Paramyxoviridae, including RSV, are transmitted by contact or aerosols and isolated from warm-blooded vertebrates suggesting the family evolved relatively recently. They are generally associated with respiratory illnesses. Filoviruses have only been isolated in sporadic cases or outbreaks, and cause severe haemorrhagic illnesses in primates and man. Rhabdoviruses are widespread and infect both mammals and other organisms even some plants. They are mostly spread by arthropod vectors and, with the exception of rabies, cause only mild illness in humans.

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Paramyxoviridae (or paramyxoviruses) are divided into two subfamilies: paramyxovirinae, and the pneumovirinae, to which RSV (genus pneumovirus) belongs. In recent years, a second human pneumovirus, human metapneumovirus, has been discovered and found to be an important human pathogen especially in children. The paramyxovirinae can be further subdivided into three genera: rubulavirus (e.g. mumps), morbillivirus (e.g. measles) and paramyxovirus also known as parainfluenzavirus.

Mononegavirales share a pattern of 5–10 genes arranged linearly with the viral polymerase (L) at the 5' terminus. Some 95% of the gene sequence codes for polypeptides. Comparison of gene sequences from several paramyxoviruses, rhabdoviruses and the filoviruses Ebola and Marburg suggested that pneumoviruses were indeed a separate lineage. Intriguingly the L (polymerase) and N (nucleoprotein) of RSV has closer homology to Ebola and Marburg than to the other pneumoviruses.<sup>3,4</sup>

## Molecular biology

RSV virions are heterogeneous in size and shape with pleomorphic spherical or filamentous forms. Spherical particles are approximately 60–100 nm in diameter. The nucleocapsid contains the single strand of non-segmented negative sense RNA of about 15222 nucleotides in length.<sup>5</sup> Virions assemble at the plasma membrane of an infected cell, are released by budding and take a lipid bilayer membrane derived from the host cell. Infectious RSV may well be in a filamentous form like the filoviruses (Ebola and others). The envelope of the virus is covered by projecting spikes of 11–20 nm separated by 6–10 nm. These are made up of the three surface glycoproteins – G, F and SH.

## Proteins of RSV

RSV is tiny, neat and beautifully put together. It consists of only 10 coded proteins. Three are surface transmembrane proteins: G, F and SH (small hydrophobic). Two are non-glycosylated matrix proteins: M and M2. Three are associated with the viral genome and make up a nucleocapsid: N, P and L. Two further proteins are described as NS1 and NS2 (non-structural). RSV protein sequence diversity has been studied and it appears that the surface protein G is highly divergent with only about 50% amino acid sequence homology between strains and the internal proteins, such as N, highly conserved with greater than 90% homology.

The F (fusion) protein is closely related in structure and function to surface proteins found in other paramyxoviruses. It is involved in virus penetration into cells and syncytium formation. Efficient syncytium formation also requires the presence of the other surface proteins, G and SH.<sup>5</sup>

The G protein mediates attachment. It is highly serine threonine rich (31%) and extensively O glycosylated, an unusual feature in viral proteins. O-linked glycosylation is not found in any other paramyxovirus, orthomyxovirus or rhabdovirus. It is, however, described for the G protein of filoviruses again suggesting a possible common origin.

SH is a small hydrophobic protein of 64 amino acids. It has been suggested that as well as being important in syncytium formation it may play a role in blocking cell death through apoptosis and inhibition of TNF- $\alpha$  signalling.

## Infectious cycle

### In vivo

Transmission of RSV is by introduction of infected secretions onto the mucosa of the eyes or nose. Usually this is by self-inoculation with the hands after touching infected secretions or contact with virus on objects such as doors, surfaces or fomites. Aerosolisation seems to be a less frequent means of spread.<sup>6</sup> Infection through the eye alone has been shown to be sufficient to cause respiratory illness.

The virus is capable of remaining infectious for several hours on inanimate objects given optimal conditions. In hospitals this means so many items including stethoscopes, door handles, lift call buttons, computer keyboards, toys and telephones provide opportunities for nosocomial spread.

RSV infects the upper respiratory mucosa of the nose and the conjunctivae but not buccal and oral mucosa. The mechanism of spread to the lower respiratory tract is not known, but assumed to be via the respiratory epithelium or aspiration of infected secretions. The incubation period between inoculation and disease is about 4–5 days from studies in adults. Lower respiratory tract signs appear 1–3 days after the onset of rhinorrhoea. In post mortem studies, using immunofluorescence, RSV is only found in the superficial epithelial layer.

Viral antigens have been reported to be present on circulating mononuclear cells from some individuals. With the use of reverse transcriptase polymerase chain reaction, viral RNA has been shown to be present in cells in circulating blood in bronchiolitis suggesting a mechanism by which RSV might spread outside the respiratory tract.

Virus shedding is often for more than 2 weeks, after the peak of the illness during resolution. RSV can be detected by conventional methods even 4 weeks after the onset of bronchiolitis in immunocompetent children.

### In vitro

RSV grows best in cultures of human cells such as HEp-2 and HeLa cells. In culture, it is associated with a characteristic effect of syncytium formation with eosinophilic cytoplasmic inclusions. RSV is relatively labile: it is destroyed rapidly at 55°C, it does not tolerate freeze-thawing well and can be inactivated by ultraviolet light.

It is not known which cellular protein provides the site of attachment for RSV. However, *in vitro*, the cellular receptor or receptors appear to be very abundant on the cell surface. Cell penetration is by fusion and the viral envelope may become incorporated into the cell surface. After this, all the events of replication occur in the cytoplasm independent of the nucleus and with little effect on other cellular functions. The RSV genes are transcribed in their 3' to 5' order into a positive strand RNA by the transcriptase L from which the proteins are synthesised. Viral mRNAs and proteins can be detected 4–6 hours after infection.

Virion assembly occurs at the plasma membrane. Nucleocapsids preformed in the cytoplasm collect near plasma membrane sections containing concentrations of transmembrane RSV glycoproteins and virion formation occurs by budding. Budding occurs from apical surfaces in well-circumscribed cell surface regions perhaps suggesting a dependence on local host sub-membranous structures.

## The immune response to RSV

Infection by RSV does not provide long-lasting protective immunity against re-infection and individuals are regularly re-infected throughout life. However, it is only in the very young and elderly that infections are likely to cause severe illness. An intact immune system is important – children with either congenital or acquired immunodeficiencies are often unable to terminate the acute infection and can shed virus at high levels for many months.

## Humoral immunity

The role of antibody in protection against RSV is interesting. Serum antibody levels do not correlate well with protection from infection and children with specific humoral immunodeficiencies but with intact cell-mediated immunity do not appear to have more prolonged or severe illness after primary infection. Most infants are admitted to hospital with bronchiolitis at between 2 and 6 months of age during the period passive maternal antibody levels decline and total plasma immunoglobulin (Ig) levels reach a nadir.

Specific anti-RSV antibody levels in cord blood suggest that high levels confer some protection. By 1 year of age between 25% and 50% of children will possess antibody to RSV; by 4 years of age, 80% of children have serological evidence of RSV infection; and by adulthood everyone appears to have serum antibody.<sup>7</sup> Trials of prophylactic pooled anti-RSV globulin in high-risk children showed some protection. A humanised monoclonal antibody to RSV, palivizumab, was introduced at the end of the 1990s and is used in targeted prophylaxis for high-risk infants especially those born very prematurely. The use of palivizumab has sparked considerable debate about the costs, which far exceed any reduction in costs associated with decreased hospital admissions.

Mucosal IgA against RSV may also have some protective effect but IgA-mediated immunity appears to wane approximately 9 months after infection and re-infection is still possible despite high levels of local IgA. Secretory IgA in infants is often lower than in adults and has been found to neutralise the virus poorly *in vitro*.

## Cell-mediated immunity

The role of cell-mediated immunity in both clearance of RSV and immunopathology is fascinating and complex. Mice that are immunodeficient (either mice with genetic mutations causing severe combined immunodeficiency, or after irradiation) fail to clear RSV and shed high levels of virus.<sup>8</sup> Adoptive transfer of RSV-specific CD8-positive cytotoxic T lymphocytes clears infection but is associated with weight loss and enhanced lung pathology.

Mice clear RSV from the bronchoalveolar lavage by about day 8 after primary infection and become ill with tachypnoea, weight loss and ruffled fur. They develop lymphoid and monocytic infiltrates around the bronchovascular bundles and an increase in alveolar lymphocytes.

When both CD4+ and CD8+ lymphocytes are depleted before infection, mice have no signs of illness, weight loss or lung infiltrates and RSV persists at high levels in the lung.

CD4+ lymphocyte depleted mice become mildly ill following RSV infection, have less weight loss and clearance of the virus is delayed. CD8+ depleted mice also have less severe illness and delayed virus clearance. Both CD4+ and CD8+ lymphocytes are important in the clearance of RSV and they are also associated with illness and weight loss. Despite clearance from the bronchoalveolar lavage data from mouse and guinea pig models suggest persistence may occur after primary infection in privileged sites in the lung.<sup>9,10</sup>

## Formalin inactivated vaccine

In the 1960s there were a series of trials of vaccines containing formalin inactivated preparations of RSV precipitated with alum. Vaccinees developed high levels of serum antibody to RSV but were not protected when subsequently exposed to natural infection during the RSV season. Tragically, when the vaccinees became infected with RSV, they experienced augmented disease with severe pulmonary disease and a number of children died. Admission rates compared with controls were increased from less than 5% to almost 80%. One of the findings noted at post mortem examination in some of the vaccinees was the presence of pulmonary eosinophilia, suggesting a Th2 type immune response.

Openshaw and others have indicated that different T helper subsets may be being primed by different RSV proteins leading to either a Th1 or Th2 phenotype and enhanced disease.<sup>11</sup> Using the BALB/c mice model and vaccinia recombinant constructs encoding single proteins it was found that those mice primed to the G protein, F protein or N protein all developed enhanced pathology reflected by weight loss, pulmonary neutrophil efflux and pulmonary haemorrhage when subsequently challenged with RSV. Fascinatingly, mice sensitised to the G protein also developed pulmonary eosinophilia. From these studies it appears that subunits of RSV can prime for different T lymphocyte immune responses. In particular, the G protein of RSV may be capable of stimulating a different subset of T cells to produce a Th2 type response. Th2 responses had previously not been associated with virus infection but more classically were associated with responses to extracellular pathogens such as helminths and in atopy.<sup>11</sup>

## Clinical features

RSV causes between 50% and 90% of the cases of bronchiolitis admitted to hospital each year. Around 2% of the infants born in the UK each year will require admission because of bronchiolitis or viral pneumonia. It is also associated with 10% of the cases of croup and up to 25% of the cases of pneumonia under 1 year of age and with a number of clinical presentations such as: upper respiratory tract infections (coryza); acute pharyngitis; acute tonsillitis; acute laryngotracheitis (croup); otitis media; and bronchitis.

It is believed that primary infections with RSV are always symptomatic but may range from a very mild 'cold' to severe bronchiolitis with respiratory failure. The most serious illnesses associated with RSV occur in infants and the elderly. Even though a small proportion of RSV-infected infants require admission to hospital, a retrospective study from the United States covering



the period 1997–2000 suggested emergency department visit costs were \$202 million and that total hospital charges for RSV over the 4-year period were more than \$2.6 billion.<sup>12</sup>

RSV spreads rapidly through susceptible populations such as children in crèches and kindergartens and elderly people in residential institutions. Almost 100% of infants in childcare during their first RSV season become infected.<sup>5</sup> Spread within families is also common and having older siblings increases the risk of infants having bronchiolitis. Autumn or winter birth increases the risk of severe illness with RSV.

Children most at risk for severe illness include those who were born prematurely whether or not they have recognised chronic lung disease of prematurity. These infants are increasingly likely to survive the immediate neonatal period because of great advances in neonatal intensive care and bronchiolitis represents a serious threat to them. Children with congenital cyanotic heart disease are also at risk; in early studies these infants had up to 44% mortality with bronchiolitis where pre-existing pulmonary hypertension was present. Advances in paediatric intensive care, especially in ventilation and fluid balance, have improved the outlook considerably. Today the mortality rate in this group is nearer 9%. Another group of special importance are children with congenital or acquired immunodeficiencies in particular children with human immunodeficiency virus, undergoing chemotherapy or with congenital severe combined immunodeficiency. Other risk factors for severe bronchiolitis include parental smoking, lower socioeconomic group and other causes of lung disease such as cystic fibrosis. Breastfeeding may have a protective influence against severe RSV bronchiolitis but this may be short-lived.<sup>5</sup>

## Bronchiolitis

Infants with bronchiolitis present with symptoms of a non-specific viral illness with rhinorrhoea, cough and sometimes a low grade fever. Cough is usually prominent but not always especially in young infants. The child may be irritable, feed less well and may sometimes vomit. Young infants especially those below 48 weeks post conceptual age may present with life-threatening apnoeas. The respiratory rate is increased, exceeding 60 breaths per minute with subcostal, intercostal or suprasternal recession. Inspiratory crackles with or without expiratory crackles and wheezes are usually heard. The child may have signs of mild or moderate dehydration. Pulse oximetry is an essential, sensitive non-invasive technique and may show evidence of oxygen desaturation. However, increased respiratory rate is a more sensitive indicator of impaired gas exchange and frank cyanosis is relatively uncommon. A number of extrapulmonary manifestations may also occur such as rash, hyponatraemia and rises in liver transaminases.<sup>5</sup> Lymphopenia in the peripheral blood, which is more pronounced in critically ill infants, is a common feature and there is some data suggesting this may be through lymphocyte apoptosis.<sup>13</sup>

Radiographic manifestations of bronchiolitis are non-specific. There is usually diffuse hyperinflation of the lungs with flattening of the diaphragms. Patchy or peribronchial infiltrates suggesting interstitial pneumonia are usually present, but pleural thickening and fluid are very rarely seen and minimal if present. However, the chest x-ray may be normal.

## Pathophysiology

Airway oedema, occlusion and perhaps some bronchial muscle spasm all result in abnormal respiratory mechanics. Inflamed oedematous lung means the potential for ventilation to reach closing volumes is reached and gas trapping occurs. Infants with bronchiolitis breathe at high lung volumes and the lung is stiffer. Compliance is decreased because of uneven ventilation of different regions of the lung with areas of atelectasis and hyperinflation. Ventilation-perfusion mismatch produces hypoxia. Airway resistance is increased both in inspiration and expiration; however, the obstruction is usually more marked during expiration. Particularly in younger infants, hypercapnia can be seen secondary to hypoventilation as the work of breathing increases. Initially, therefore, infants will have evidence of a mild to moderate respiratory acidosis but later metabolic acidosis is more common.

## Diagnosis and treatments

The diagnosis of infection with RSV is still usually made by direct immunofluorescence of nasopharyngeal aspirates and virus culture. Reverse transcriptase polymerase chain reaction, often multiplex, is now becoming much more widely available clinically. Once the diagnosis is confirmed the mainstays of treatment are supportive: to ensure adequate oxygenation and hydration. In severe cases, positive pressure ventilation is required. The widespread availability of non-invasive nasal continuous positive airway pressure and bi-level positive airway pressure may now be reducing the need for intubation and ventilation. In the UK, these tools are widely available in local hospitals and help to reduce the need to move an infant even further away from home to a large paediatric intensive care facility.

Ribavirin, which is a synthetic nucleoside resembling guanosine, has potent antiviral activity against RSV *in vitro*. However, clinically it has shown very modest benefits and its use is usually limited to relatively small groups at very high risk or with severe disease. With the exception of oxygen and carefully prescribed fluids, which may be life-saving, the evidence of benefit in acute bronchiolitis of any of the pharmacological tools at the paediatrician's disposal has been lacking or disappointing. Neither antibiotics, corticosteroids, bronchodilators, immunoglobulin or physiotherapy have shown any clinically meaningful value although many are frequently prescribed.

## The delayed effects of RSV infection

Day care in the first year of life, which increases the chances of early primary infection with RSV, is known to increase the risk of a later asthma diagnosis. There is now solid evidence that infants who develop more severe clinical lower respiratory illness during primary infection with RSV have a much higher chance of developing chronic asthma-like respiratory symptoms during childhood. Sigurs has produced compelling data of longitudinal studies supporting the theory that early lower respiratory tract infection with RSV is associated with a higher rate of asthma and allergic sensitisation at 3, 7 and 13 years of age.<sup>14</sup> Evidence from the mouse model suggests that allergic sensitisation to protein antigens may be induced through the lung in the context

of an acute RSV infection.<sup>15</sup> It is also observed that previously allergically sensitised mice may experience more severe primary infection when then exposed to RSV. In terms of therapy, studies have shown that early inhaled corticosteroid use is of little value and does not alter later allergic asthma in these children. Current studies propose some beneficial effect from the use of leukotriene receptor antagonists in post-bronchiolitic wheezing.<sup>16</sup>

## Summary

RSV is a truly impressive little thing. We are all eventually infected. It could almost be described as part of us and may become persistent. Most active infections are of little clinical significance but for the young, the elderly and others with chronic lung disease or impaired cell-mediated immunity it can be a killer. In a century, we have identified it, started to understand its potential long-term effects and yet failed to develop an effective vaccine. The treatments are supportive and many commonly used medicines have proven at best disappointing but with modern paediatric care we can support almost all infants who become seriously ill during primary infection until they recover. ♦

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## Practice points

- RSV is a negative sense RNA paramyxovirus related to measles and parainfluenza
- Vaccination trials in the 1960s caused enhanced disease
- T-helper immunology both controls the virus and is associated with the illness
- The treatment is supportive
- Modern survival is excellent even in severe illness
- Severe bronchiolitis is associated with recurrent wheeze and may be associated with the development of allergic sensitisation and atopy

# Evaluation of chest pain

Andrew W Boon

## Abstract

Chest pain is a relatively common symptom in children. Evaluation is mainly clinical to exclude cardiac or organic causes of chest pain. Precordial catch syndrome is a benign cause of chest pain in children.

**Keywords** chest pain; precordial catch syndrome

## What do you do?

A 15-year-old boy is referred to the out-patient clinic with the following letter from his general practitioner.

‘Thank you for seeing Tim because of an 18-month history of chest pain. He had transposition of the great arteries repaired with a neonatal arterial switch and repair of coarctation at the age of 15 months. He is now complaining of recurrent left chest pain, which lasts for a few seconds and he feels he cannot breathe.

On examination he looks well, but he has a systolic murmur. I wonder if the pain is cardiac in origin. He is due to go on a skiing holiday in 2 months time.’

## Key points in the history

Does the pain have an organic cause? Is the pain caused by cardiac disease?

The type of pain reported, its position, radiation, relieving and exacerbating factors are useful in defining the aetiology of chest pain. Pain of sudden onset, pain that wakes the child from sleep and associated fever are excellent indicators of organic pain.

## When did the pain start?

A preceding history of trauma, such as a seatbelt injury from a road traffic accident or blunt trauma sustained in a contact sport, suggests the possibility of a rib fracture or bruising as the cause of the pain. Respiratory causes of chest pain usually present acutely. Pneumonia is the most common respiratory cause of chest pain. A painful pneumonia usually indicates pleural involvement, although excess coughing may cause musculoskeletal chest pain. Epidemic myalgia (Bornholm disease) is preceded by an upper respiratory tract infection. It typically affects adolescents and young adults.

## How long does the pain last?

Costochondritis (Tietze’s syndrome) produces a stabbing mid-sternal chest pain that is aggravated by deep inspiration and lasts from a few seconds to a number of minutes. Precordial catch syndrome typically produces a short, stabbing pain localised over the left anterior chest wall.

## Is the pain related to exertion?

Nearly all children will at some time experience ‘stitch’ – intercostal muscle strain, giving rise to lateral chest wall pain on exertion. Asthma is a common cause of exercise-induced chest pain, particularly in older children. The pain is usually retrosternal and improves with bronchodilators. Chest pain is an unusual manifestation of cardiac disease in children. It may be associated with breathlessness, pallor and sweating, implying cardiovascular compromise. Myocarditis is typically associated with an aching or stabbing chest pain on exertion. Ischaemic cardiac pain may be associated with exertion. It is classically described as gripping or crushing in nature and is localised to the precordium with possible radiation to the neck, arm or mandible. It may occur in hypertrophic cardiomyopathy, critical aortic stenosis, mitral valve prolapse, anomalous coronary arteries or following Kawasaki disease.

## Are there any aggravating factors?

Deep inspiration will aggravate pain secondary to chest trauma, costochondritis and pleuritic chest pain.

## Is the pain related to food?

Peptic ulcer disease and reflux oesophagitis produce a burning retrosternal pain, which may be provoked by eating food or bending down and relieved by antacids. A foreign body lodged in the oesophagus may also produce retrosternal pain, which may be associated with dysphagia or gagging with food.

## Are there any factors that point to a psychogenic cause?

A careful history will often elicit specific stressors such as bullying at school or family discord. The chest pain may be associated with hyperventilation or panic attacks. The child may also have symptoms of depression. Quite commonly another family member may have a history of heart problems or chronic chest pain.

## Findings from the history

On direct questioning, Tim’s pain was initially occurring about once a week but recently has become less frequent and is occurring about once a month. It occurs at any time and is not related to exertion. The pain is localised to the left precordium. It is described as a short, stabbing pain lasting for a couple of seconds. The pain tends to take his breath away. It does not radiate and he has never been woken by the pain. He has a normal exercise tolerance.

The history is strongly suggestive of the precordial catch syndrome. The lack of association with exertion and his normal exercise tolerance suggest that the pain is not cardiac in origin.

## Examination

The following features may be present on examination.

- Fever – this suggests an infective or inflammatory cause, such as pneumonia or myocarditis.

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- Tachypnoea – this points to a respiratory cause such as asthma or pneumonia.
- Dullness to percussion, reduced breath sounds, bronchial breathing and crackles – these point to pneumonia, with or without a pleural effusion.
- Expiratory wheeze – commonly found in asthma, although the child is often wheeze-free between attacks.
- Pleural rub – found in pneumonia with associated pleural involvement or effusion.
- Pericardial rub – this indicates pericarditis.
- Chest wall tenderness – look for this if there is a history of chest wall tenderness or history suggesting costochondritis where there is tenderness along the costochondral margin or below the clavicle at the site of insertion of pectoralis major.

### Examination findings

Tim is a well-looking boy. His height (166.0 cm) and weight (47.0 kg) are both between the 25th and 50th centiles. He has a weak left brachial pulse with easily palpable femoral pulses. His blood pressure is 90/60 mmHg. A grade 3/6 mid-systolic murmur is audible at the right upper sternal edge transmitted to the carotids. His chest is clear and there is no chest wall tenderness. The remainder of the examination is entirely normal.

Tim has clinical signs of aortic stenosis. His left brachial pulse is weak because of the previous subclavian flap repair of his coarctation of the aorta. Despite these cardiac findings it is unlikely that the pain is cardiac in origin.

### Investigations

In most cases, chest pain in children is benign and no investigations are required. However, because of his previous history,

Tim had an electrocardiogram (ECG), which was within normal limits and he was referred to a paediatric cardiologist who arranged echocardiography, which showed slight aortic stenosis with trivial aortic regurgitation.

### Case outcome

Tim and his parents were given strong reassurance that the precordial catch syndrome is entirely benign and that the pain was not cardiac in origin. He went on his skiing holiday uneventfully. ◆

### Practice points

- Chest pain in children is usually benign
- An acute onset of pain, particularly interfering with sleep, associated with fever, exacerbated by exercise and associated with breathlessness or cardiac signs, is an indication for further investigations, including a chest x-ray and ECG
- If the chest pain is thought to be cardiac in origin, cardiology referral is indicated in all cases
- The child with chronic chest pain who is well and has normal physical examination does not require any routine investigations. The most important part of the management in this situation is reassurance

# Self-assessment

## Questions

### Question 1

A 3-year-old boy presents with septic shock secondary to meningococcal septicaemia, and is treated in the regional paediatric intensive care unit (PICU). He is treated with 7 days of intravenous (i.v.) ceftriaxone 50 mg/kg daily. He required 180 ml/kg of fluid in the first 24 hours, received adrenaline and milrinone infusions until day 3, but was successfully extubated on day 4, and returned to the ward on day 5. He has not had a lumbar puncture.

It is now day 7, and his antibiotics are due to be discontinued.

His mother reports he is less well in the past 24 hours – he is miserable and does not want to get out of bed. He says his leg is sore. The discharge summary from PICU shows that he had been afebrile since day 2. He had his urinary catheter and central venous line removed on the day of discharge from PICU.

On examination he has a temperature of 38.8 °C. He has a few maculopapular spots on his trunk and upper arms, and two of them appear blistered. There are no petechiae. The rash is new. His chest is clear, his abdomen soft and his heart sounds normal. He has no neck stiffness. He has a slightly swollen right knee, with slight restriction of flexion due to pain.

His blood results from this morning are as follows:

Hb	12 g/dl	Na	139 mmol/l
WBC	$22 \times 10^9/l$	K	3.2 mmol/l
Neutrophils	$17 \times 10^9/l$	Urea	5.3 mmol/l
Lymphocytes	$4 \times 10^9/l$	Creatinine	29 µmol/l
Platelets	$432 \times 10^9/l$		
CRP	89 mg/l (31 previous day)		

(a) What is the most likely diagnosis? Choose ONE of the following:

- Drug reaction
- Recurrent meningococcal septicaemia
- Septic arthritis
- Post-meningococcal immune complex mediated disease
- Incompletely treated meningitis

### Question 2

A 1-year-old boy weighing 11 kg has been transferred to PICU after presenting to his local hospital with a 48-hour history of lethargy, poor feeding and fever, culminating in a prolonged tonic seizure. He needed to be intubated and ventilated during the seizure after being treated with lorazepam, phenytoin and

paraldehyde. The seizure stopped as he was given thiopentone to induce anaesthesia. The total duration of seizure time was 55 minutes.

He is ventilated with pressures of 22/6cm H<sub>2</sub>O at 25 per minute and 40% oxygen giving a tidal volume of 90 ml, oxygen saturations of 100%. He has an area of right upper zone consolidation on his chest x-ray.

His heart rate is 125/min, blood pressure 90/45mm Hg, mean 60mm Hg, with a capillary refill time of 2 seconds. He has required three 20 ml/kg boluses of 0.9% saline in the past 4 hours and has not been started on inotropes. His i.v. maintenance fluid is running at 100% of normal requirements.

He had a computed tomography (CT) of his head with contrast, which showed a degree of meningeal enhancement, but is otherwise normal.

He is sedated with morphine and midazolam infusions. He has been treated with aciclovir and ceftriaxone.

Blood results are shown:

Hb	11.1 g/dl	Na	139 mmol/l
WBC	$16.4 \times 10^9/l$	K	3.7 mmol/l
Neutrophils	$11.9 \times 10^9/l$	Urea	2.6 mmol/l
Lymphocytes	$3.1 \times 10^9/l$	Creatinine	22 µmol/l
Platelets	$194 \times 10^9/l$		
CRP	142 mg/l	Arterial gas	
		pH	7.26
		pCO <sub>2</sub>	6.9 kPa
		pO <sub>2</sub>	18.4 kPa
		HCO <sub>3</sub>	21 mmol/l
		Base excess	-8.1 mmol/l
		Chloride	112 mmol/l
		Lactate	5.3 mmol/l

(a) Which of the following statements is true? Choose ONE of the following:

- Lumbar puncture should be performed now
- His ventilator settings should be changed
- Inotropes should be started
- His i.v. fluid requirements should be restricted
- He should have a bolus of 20 ml/kg 4% human albumin

He remains relatively stable for the next 48 hours. Blood culture results have been telephoned through from his original hospital, and show *Streptococcus pneumoniae*. His observation chart shows stable heart rate 120–130/min, blood pressure mean of 60 mmHg, stable and normal blood gases, urine output of 0.7 ml/kg/hour. His routine bloods for the day come back:

Hb	7.6 g/dl	Na	129 mmol/l
WBC	$12.4 \times 10^9/l$	K	4.3 mmol/l
Neutrophils	$8.5 \times 10^9/l$	Urea	14.5 mmol/l
Lymphocytes	$2.9 \times 10^9/l$	Creatinine	147 µmol/l
Platelets	$44 \times 10^9/l$	Phosphate	2.9 mmol/l
		Calcium (ionised)	1.03 mmol/l
CRP	98 mg/l	Magnesium	0.81 mmol/l

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PT	12 s
APTT	31 s
Fibrinogen	2.1 g/l

- (b) What investigation should you do now? Choose ONE of the following:
- Stool culture
  - Ferritin
  - Coombs test
  - Blood film
  - Renal ultrasound
- (c) A provisional blood culture result is phoned through the following day and reports Gram-positive diplococci. What is the likely diagnosis? Choose ONE of the following:
- Haemolytic uraemic syndrome – pneumococcal
  - Disseminated intravascular coagulation
  - Haemolytic uraemic syndrome – *Escherichia coli* H7:0157
  - Idiopathic thrombocytopenia
  - Primary bone marrow failure

### Question 3

An 11-year-old boy presents with a swollen left ankle. He had presented to Accident and Emergency 3 days ago after having hurt his ankle playing football. An x-ray at that time showed no fracture, and he was sent home. Since then his ankle has remained swollen and red, but his parents think it is no worse than at onset. The previous day he developed diarrhoea. He has also complained of aching arms and legs. A repeat x-ray does not demonstrate any fracture, and shows only soft tissue swelling. You have been asked to give a paediatric opinion.

His past medical history is unremarkable, and there is no family history of note.

On examination his temperature is 39.1 °C, and he appears flushed. His heart rate is 120/minute, his capillary refill time is 2 seconds and his blood pressure is 84/38 mm Hg. His respiratory rate is 24/minute. There is a 2 cm abrasion just above his medial malleolus, and his ankle is a little swollen and warm. It is painful to move, but he does have a full range of movement in the joint.

You suspect he has cellulitis, and admit him to the ward for intravenous penicillin and flucloxacillin after taking blood for culture, full blood count, urea and electrolytes, and C-reactive protein (CRP).

Over the next 12 hours he becomes more unwell. Nursing staff report him as being intermittently confused. His heart rate remains 120 per minute, and his systolic blood pressure is between 70 and 80 mmHg. He has developed a widespread erythematous rash which looks like sunburn, and has a bilateral conjunctivitis. His urine output is 0.3 ml/kg/hour.

His laboratory results from admission are below:

Hb	9.8 g/dl	Na	131 mmol/l
WBC	$4.8 \times 10^9/l$	K	4.2 mmol/l
Neutrophils	$1.0 \times 10^9/l$	Urea	10.2 mmol/l
Lymphocytes	$3.2 \times 10^9/l$	Creatinine	182 $\mu\text{mol/l}$
Platelets	$44 \times 10^9/l$		
CRP	256 mg/l		

- (a) Which of the following diagnoses is most likely? Choose ONE of the following:
- Septic arthritis
  - Kawasaki disease
  - Stevens–Johnson syndrome
  - Necrotising fasciitis
  - Toxic shock syndrome
- (b) In addition, discussing him with an intensivist, and giving him a 20 ml/kg bolus of fluid, which one of the following would you do? Choose ONE of the following:
- Treat with intravenous clindamycin
  - Treat with intravenous immunoglobulin
  - Start high dose corticosteroids
  - Obtain an ultrasound of his ankle
  - Obtain a paediatric nephrology opinion to arrange early dialysis

### Answers

#### Question 1

(a) Post-meningococcal immune complex mediated disease  
In meningococcal disease, type 3 hypersensitivity reaction, or immune complex associated complications (IAC), can present as arthritis, vasculitis, episcleritis, or pericarditis. Nephritis is very rare. It usually takes 4–10 days after the onset of disease for the first symptoms and signs of IAC to develop.<sup>1</sup>

The diagnostic features are:

Arthritis	Arthralgia, joint swelling and redness, limitation of movement Synovial fluid shows no bacteria, cultures remain negative
Vasculitis	Pustular, bullous, nodular lesions or rash
Pericarditis	Retrosternal pain, pericardial friction rub, ECG abnormalities, cardiac enlargement on x-ray/ultrasound
Pleuritis	Pleural effusion on x-ray. Pain on inspiration. Impaired percussion. Pleural rub

Up to 15% of children may show one or more of these features after severe meningococcal disease. There is typically a secondary fever (i.e. a fever occurs after the patient has been afebrile for some time), a raised CRP and a leucocytosis.

Although it is a diagnosis of exclusion, knowledge of its common incidence may prevent over-investigation of patients. Anti-inflammatory medication will relieve symptoms, and the course is benign and self-limiting in general. A pericardial effusion has the potential to cause more serious effects secondary to tamponade, but these features would be clinically manifest if significant.

Drug allergy (particularly penicillin) can cause this type of rash, but is often associated with an eosinophilia. It is much less common than IAC.

Partially treated meningitis, or recurrent meningococcal disease are unlikely as the patient has had appropriate antibiotic therapy. Patients can have meningococcal disease more than once in their life, as there are different serotypes, but it would

also prompt a search for defects in complement production or opsonisation, which are associated with recurrent meningococcal and pneumococcal infections.

### Question 2

(a) His ventilator settings should be changed

Cerebral blood flow is very closely associated with arterial partial pressure of carbon dioxide ( $p\text{CO}_2$ ). Increased  $p\text{CO}_2$  causes cerebral vasodilatation, and the increased cerebral blood flow can cause an increase in intracranial pressure if there is a lack of intracranial space to accommodate it, or a failure of normal cerebral circulatory autoregulation. In ventilated patients who are at risk of raised intracranial pressure, such as those with suspected meningitis, the target  $p\text{CO}_2$  is 4.5–5.0 kPa. This patient should have a change to ventilator parameters that reduce his minute ventilation, and his  $p\text{CO}_2$  re-checked 30 minutes after the change.

This presenting feature makes meningitis a possibility as an underlying diagnosis, especially given the appearances of meningeal enhancement. However, this patient was drowsy, and there is a possibility of raised intracranial pressure, which is a contraindication to lumbar puncture. Raised intracranial pressure may be present even if not demonstrated on a CT of the head.<sup>2</sup> It would be safer to treat for meningo-encephalitis and perform a lumbar puncture once the child's conscious level is shown to have improved – the biochemical and cellular changes within cerebrospinal fluid (CSF) will persist for 2–3 days after antibiotic treatment has started.<sup>3</sup>

His lactic acid levels are raised, but this is very common after a prolonged tonic clonic seizure, and his normal heart rate, perfusion and mean blood pressure would re-assure you that he does not have shock, and does not require inotropes. Likewise, there is no indication for a fluid bolus.

A popular misconception is that routine fluid restriction should be used in meningitis. This is not supported by published evidence – this patient will be started on routine fluid requirements, subsequently adjusted on the basis of clinical and laboratory information.

(b) Blood film

The striking feature of this set of blood results is renal failure and an acute drop in haemoglobin and platelet count. The latter two often occur in sepsis secondary to a dilutional effect from fluid resuscitation, and disseminated intravascular coagulation. However, his coagulation profile is not supportive of disseminated intravascular coagulation. Haemolytic-uraemic syndrome (HUS) has to be a strong possibility, and a blood film will demonstrate the red cell fragmentation typical of this microangiopathic haemolytic anaemia.

(c) Haemolytic uraemic syndrome – pneumococcal

Although *E. coli* H7:0157 is the most common cause of HUS in children, other bacteria such as *Shigella dysenteriae* produce the verocytotoxin (or shiga-like toxin) to produce HUS. The toxin acts on vascular endothelial cells to produce a multi-system vasculitis.

*Streptococcus pneumoniae* produces the enzyme neuraminidase. This cleaves N-acetylneuraminic acid from cell membrane surfaces exposing a cryptantigen, Thomsen–Freidenreich antigen (T-antigen), on red blood cells, platelets and glomerular capillaries. Most people possess a naturally occurring antibody to this antigen, and the cells are attacked and destroyed. Some hospital laboratories will perform a confirmatory test demonstrating the presence of T-antigen.<sup>4</sup> Pneumococcal HUS almost always occurs in children less than 2 years of age. The clinical course is more severe than non-pneumococcal, and the patients are more likely to require dialysis.<sup>5</sup>

### Question 3

(a) Toxic shock syndrome

Toxic shock syndrome (TSS) is caused by toxin-producing strains of *Staphylococcus aureus* or *Streptococcus pyogenes* (Group A streptococcus). Toxic shock syndrome toxin-1 (TSST-1) is best known in *S. aureus* infections, but other toxins are also produced and believed to function as 'superantigens', causing a powerful stimulatory effect on T-cell proliferation, and increased production of inflammatory cytokines like tumour necrosis factor and interleukin-1 (IL-1).<sup>6</sup>

Clinical criteria have been defined for the diagnosis. For staphylococcal TSS these are:

Negative blood throat and CSF cultures (if taken); blood culture may be positive for *S. aureus*.

Negative serology for measles, leptospirosis or Rocky Mountain spotted fever.

Major (all four must be met):

- Fever more than 38.9 °C
  - Rash – diffuse macular erythroderma
  - Hypotension – systolic blood pressure less than 5th centile for age
  - Desquamation –1 or 2 weeks after the acute illness
- Multi-system involvement (three must be met)
- Gastrointestinal: vomiting or diarrhoea at onset
  - Muscular: severe myalgia or creatine kinase level greater than twice upper limit of normal
  - Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperaemia
  - Renal: urea or creatinine more than twice the upper limit of normal
  - Hepatic: bilirubin, ALT or AST upper limit of normal
  - Platelets less than  $100 \times 10^9/\text{l}$
  - Altered consciousness when fever and hypotension not present

The definition of staphylococcal TSS does not require the isolation of *S. aureus*, but that for streptococcal TSS requires isolation of Group A streptococcus from a normally sterile site (e.g. blood, CSF) to make a definite diagnosis, or isolation from a non-sterile site (e.g. throat, skin) to make a diagnosis of a probable case.

Clearly, because of the requirement for desquamation, the definitive diagnosis cannot be made while treatment is being initiated, so management is based on clinical suspicion.

Although this patient had a suspected entry wound for infection, a positive site for primary infection is less common in staphylococcal TSS than it is in streptococcal.

This patient grew *S. aureus* from blood culture and had a desquamating rash shortly before discharge from the PICU where he was admitted.

Kawasaki disease is also believed to be a superantigen-mediated disease, so clinical features are similar. However, it is most common in children less than 1 year old and very rare over the age of 5 years.

Septic arthritis is usually associated with restricted joint movement. Necrotising fasciitis is characterised by severe pain around the infection site, and a rapidly spreading cellulitis – the degree of pain in the early stages is often disproportionate to the clinical appearances. Stevens–Johnson syndrome produces a characteristic rash with target lesions and mucosal ulceration.

#### (b) Treat with intravenous clindamycin

The general principles of caring for critically ill patients apply, suing fluid boluses and inotropes are necessary to maintain organ perfusion and oxygenation. Many patients will require to be treated in an intensive care unit.

At this stage in treatment, the likely diagnosis is TSS, although whether it is streptococcal or staphylococcal is not certain. Clindamycin is known to suppress toxin production in both types, and so is added in to the antibiotic regimen. Antibiotic treatment is continued for a minimum of 10 days, but may be longer if the source of primary infection requires it (e.g. osteomyelitis).

Intravenous immunoglobulin may have a role, but evidence is not compelling. It is currently recommended for cases of TSS that are not responding to conventional treatment.

There is no place for high dose steroids in this condition. Steroids may be used if there is inotrope resistant hypotension, but in physiological replacement doses in the manner recommended for treating septic shock.

The issue of whether this patient has a septic arthritis should be resolved, but it is not his most urgent problem, and will not change immediate management. Given the lack of impairment of joint mobility it is very unlikely. ♦

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