Cardiac Failure in Children

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Summary

In children, cardiac failure is most often caused by congenital heart disease and cardiomyopathy. These causes are significantly different from those usually responsible for the condition in adults, which include coronary artery disease and hypertension.

Literature searches were undertaken using a variety of search engines including PubMed, the Cochrane Library, BMJ Clinical Evidence and the National Guideline Clearinghouse to identify evidence for the management of cardiac failure. There is a large amount of research published on the management of heart failure in adults, which has given rise to significant changes in management in the last decade. However, there are far fewer studies in children and those which do exist are often small, retrospective and use a diverse range of measures to assess efficacy.

As a result, the management of cardiac failure in children has largely evolved based on clinical experience and the application of adult data, supported by the more limited paediatric literature. Given the significant differences in aetiology of heart failure between the adult and paediatric populations, this is not ideal. However, clinical experience in paediatrics with the drugs which have been proven to be beneficial in adults provides some re-assurance that the outcomes may be similarly beneficial.

On this basis, it is recommended that the EMLc is expanded to include additional treatment options for children with cardiac failure, namely an ACE inhibitor and a beta-blocker.

In the case of ACE inhibitors, the two supported by the greatest paediatric data are captopril and enalapril. The former has the advantage of greater stability in liquid formulation and the latter the advantage of requiring less frequent dosing. It should be noted that there is very limited published data on the paediatric use of those ACE inhibitors most widely used in adults (such as ramipril, lisinopril and perindopril) and none at all in children with heart failure. Captopril is proposed for addition to the EMLc, as the representative of the ACE inhibitor group.

In terms of beta-blockers, the vast majority of evidence in paediatric cardiac failure is with carvedilol, which is supported by findings from the trials in adults, where it has been consistently shown to improve outcomes. Carvedilol should therefore be considered the beta-blocker of choice in children with cardiac failure and be considered for inclusion on the EMLc.

The EMLc already includes a number of drugs used in management of cardiac failure in children: frusemide, digoxin, spironolactone and dopamine. Although this review considers it appropriate to retain these four drugs in the EMLc at the current time, it should be noted that there is a lack of robust research to support the use of these drugs in the paediatric heart failure population; in particular digoxin, which appears to remain widely used based solely on long-standing clinical practice.

Although Angiotensin Receptor Blockers (ARBs) are increasingly used in cardiac failure in adults, especially where there is intolerance to ACE inhibitors, there is no published evidence supporting their use in children with the condition. Consequently, it is not considered appropriate to include an ARB in the EMLc at the current time.

Whilst there is data emerging for a range of other therapy options, this is not sufficiently robust to warrant their inclusion in the EMLc at the current time.
By adding an ACE inhibitor and beta-blocker to the EMLc, a greater number of those children worldwide who have cardiac failure should be able to benefit from improved outcomes.

There is also a pressing need for improved research into the treatments used in paediatric cardiac failure, as well as extension of product licenses where appropriate; and greater availability and standardisation of the formulations required for effective delivery of these treatments.

In addition to work around the drugs used to treat heart failure, continued efforts to reduce the burden of malnutrition and malaria which may exacerbate heart failure through anaemia and other causes; are essential in developing nations.

Introduction

The subcommittee of the Expert Committee on the Selection and Use of Essential Medicines identified Cardiac Failure as an area where more information was required to inform their decision for future meetings.

The aim of this review was to address the following questions that came out of the initial meeting.

1. What is the burden of disease from cardiac failure in children under 12 years of age?
2. What medicines are essential for treatment?
3. Are these already on the EMLc in an appropriate dosage form and strength?
4. If not, what needs to be added?

In order to address the above questions, a search and review of existing literature was undertaken, as outlined in Appendix 1.

Burden of disease from cardiac failure in children

Cardiac failure is a clinical syndrome where the heart is unable to provide the output required to meet the metabolic demands of the body; however, the causes and mechanisms of cardiac failure are significantly different between adults and children (1).

In adults, cardiac failure usually involves failure of the left ventricle, with the most common causes in developed nations being coronary artery disease; hypertension-induced cardiac stress, arrhythmias and valvular disease. In developing nations, it has been reported that other causes are frequently implicated, including rheumatic heart disease (20.1%) and cardiomyopathy (16.8%) (2).

In children, the causes of cardiac failure are significantly different and many cases are due to congenital malformations, such as left-to-right shunts. In these patients the function of both the right and the left ventricles will be affected and these children suffer from high-output cardiac failure. Other significant causes of heart failure in children are cardiomyopathy (3) and anthracycline toxicity, which lead to low- output cardiac failure. In developing nations, many cases are caused or exacerbated by anaemia, often secondary to malaria and malnutrition (4). It has also recently been identified that infants in ethnic minority groups in
developed countries may be at risk of heart failure linked with hypocalcaemia and vitamin D deficiency (5).

There is also a much higher proportion of children with heart failure who have undergone cardiac procedures (61.4%) compared to adults with heart failure (0.28%); this reflects the incidence of congenital defects, frequent surgical intervention to correct this, and the subsequent and eventual deterioration in cardiac function that is seen in many of these children.

Accurately estimating the incidence of cardiac failure in children is problematic. Congenital heart disease occurs in around 8 per 1000 live births; however, many of these children receive early surgical intervention and it has been estimated that the yearly incidence of heart failure as a result of congenital defects is between 1 and 2 per 1000 live births (6). As a result, cardiomyopathy contributes significantly to the number of paediatric patients who present with the symptoms of cardiac failure. Data from the United States (7) and Australia (8) suggests the incidence of cardiomyopathy to be 1.13 per 100,000 and 1.24 per 100,000, respectively. Nonetheless, it should be recognised that not all patients with cardiomyopathy have heart failure, which is supported by data from the UK (9), which reports the incidence of heart failure assessed at first presentation to hospital to be around 0.87 per 100,000. Data from Nigeria suggests that 7.02% of emergency paediatric admissions to a tertiary centre hospital are for cardiac failure, with over 90% of cases being from lower socio-economic groups (4). In general the prognosis for children with cardiomyopathy is poor, with 5-year mortality reported at around 80% (10) and many cases progress to requiring heart transplantation when drug therapy proves insufficient.

What medicines are essential for the treatment of cardiac failure in children?

Current status of the EMLc and guidelines

The October 2007 cardiovascular medicines section of the WHO Essential Medicines List for Children (EMLc) contains digoxin, frusemide, spironolactone and, on the complementary list, dopamine. Clinical practice in the management of cardiac failure in children uses a wider range of medicines than those currently on the EMLc; consequently, the sub-committee requested this review.

Management of cardiac failure in adults is covered by a number of national guidelines (11-15). In contrast, although there are many reviews of the management of cardiac failure in children (6, 16-23), there are no national or international guidelines to steer consistent evidence-based practice.

The approach to the management of cardiac failure in children has consequently developed from a combination of clinical experience, small scale studies in paediatric populations and the application of adult trial data to the paediatric population. Given the significant differences in the causes of cardiac failure between the adult and paediatric populations, caution is required when applying evidence in this way and it may be misleading (6).

Most of the drugs used in paediatric cardiac failure are not licensed for use in children and are not routinely available in suitable formulations, which introduces additional complications in terms of practical dose administration and potential bioavailability and bioequivalence (24).
This review seeks to summarise the evidence which is available and provide a basis on which the committee can formulate guidance on the management of cardiac failure in children, supported by an appropriate EMLc.

**Diuretics**

<table>
<thead>
<tr>
<th>Rational for use of Diuretics:</th>
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</thead>
<tbody>
<tr>
<td>Diuretics have two main effects which may be beneficial in heart failure:</td>
</tr>
<tr>
<td>• increased water loss</td>
</tr>
<tr>
<td>• increased sodium loss</td>
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</tbody>
</table>

Diuretics have been widely used in cardiac failure in both adults and children for many years, providing rapid relief from the symptoms of fluid overload; however, the effects of diuretics on disease progression and survival have been unclear.

Most patients with heart failure who require diuretic therapy are treated with loop diuretics, rather than thiazides, as they are more powerful agents (11). However, the use of loop diuretics has been questioned on the basis of the lack of randomised clinical trials and the potential for undesirable effects on intracellular and extracellular magnesium and calcium ion concentrations, and thiamine deficiency (23, 25).

A Cochrane systematic review specifically considered the risks and benefits of diuretics in heart failure and found a limited number of studies which met their criteria. Based on 14 trials, with 525 participants, this review drew the conclusion that diuretics appeared to reduce risk of death and deterioration of cardiac failure compared to placebo, and improved exercise capacity when compared to other active treatments (26).

One review of paediatric heart failure has specifically laid out a treatment pathway, which positions diuretics, including frusemide, as a first step (alongside digoxin) (20). Consistent with this approach, many of the trials looking at ACE inhibitors and beta-blockers in cardiac failure in children have reported their use was in addition to standard therapy, which where specified, has without exception included diuretics, particularly frusemide.

Of the available loop diuretics, frusemide is the most widely used in cardiac failure and is already included in the EMLc, in a range of presentations. Bumetanide is also available and used in paediatrics, although there is limited published data on the use of this alternative loop diuretic in heart failure amongst children (27).

Research in adults with heart failure has suggested that torasemide, a longer-acting loop diuretic, is at least as effective as frusemide (28). More recently, a small study specifically in children with cardiac failure concluded that torasemide was safe and effective in this group, with significant improvements in heart failure index measurements amongst newly-diagnosed patients (29).

As highlighted above, the loop diuretics have been the most widely used in heart failure, although in some situations other types of diuretics have a role. In adult patients with mild heart failure, thiazide diuretics may be effective as monotherapy. In refractory oedema, sometimes referred to as braking, there is an apparent decrease in the urine volume produced by standard diuretic therapy and this occurs in children and infants, as well as adults (30). In this situation combinations of drugs with different sites of action have been used, most commonly a thiazide (or thiazide-type) diuretic with a loop diuretic. One small study in children with frusemide-resistant oedema, reported that the combination of
frusemide with metolazone (a thiazide-related diuretic) produced significant improvements in urinary volume and sodium excretion (31) in the absence of chronic renal insufficiency. A review of the same approach in adults reported that there were few studies, but based on these and an additional observational study, concluded that use of low dose metolazone (≤5mg) added to loop diuretics is effective and relatively safe for adult outpatients with refractory heart failure (32), although significant electrolyte disturbances were reported.

Hydrochlorothiazide is included on the essential medicines list for adults as an option in both hypertension and heart failure. A review by the European Medicines Evaluation Agency (EMEA) has identified a need for the indications for hydrochlorothiazide, including heart failure, to be extended to all age groups, as well as the development of an age-appropriate formulation (33). The same review makes no reference to metolazone.

The role of those diuretics which are aldosterone antagonists is discussed separately, as their application in heart failure is different to that of the thiazide and loop diuretics.

Based on the existing inclusion of frusemide in the EMLc, its widespread use, availability in formulations suitable for paediatric administration and the lack of any compelling data showing specific advantages of other loop diuretics, it is considered appropriate to retain frusemide as the loop diuretic of choice in the EMLc.

The need for an additional diuretic, of the thiazide (or thiazide-type), is less clear. Whilst the limited evidence supports use of metolazone, the EMEA appears to consider hydrochlorothiazide as the preferred option. At this point in time there is insufficient evidence to argue for their inclusion on the EMLc.

**Digoxin**

<table>
<thead>
<tr>
<th>Rational for use of Digoxin:</th>
</tr>
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<tbody>
<tr>
<td>Digoxin has a number of effects which may be beneficial in heart failure:</td>
</tr>
<tr>
<td>• inotropic effects</td>
</tr>
<tr>
<td>• slowed heart rate, improving balance of oxygen supply and demand</td>
</tr>
<tr>
<td>• inhibition of sympathetic nervous system</td>
</tr>
<tr>
<td>• inhibition of renin release</td>
</tr>
</tbody>
</table>

Cardiac glycosides have been used in the management of cardiac failure for over 200 years. Whilst digoxin and related drugs are still considered to have a role in the presence of atrial fibrillation, their place in the therapy of patients with cardiac failure without atrial fibrillation has been increasingly questioned, particularly given the significant changes in heart failure management over the last 20 years.

There is a dearth of research published evaluating the role of digoxin in children with cardiac failure. However it is notable that many of the trials looking at other therapies in paediatric cardiac failure have referred to standard treatment, which has almost without exception included digoxin, indicating that it remains widely used, despite the lack of trial evidence.

A Cochrane systematic review sought to clarify the evidence in adults with heart failure who were in sinus rhythm and identified thirteen articles which met their criteria and reported endpoints including mortality, clinical status and hospitalisation. This review concluded that the data shows no evidence of a difference in mortality between treatment and control groups, but that digitalis therapy is associated with a lower rate of hospitalisation and of clinical deterioration (34).
There is no equivalent systematic review looking at the role of digoxin in paediatric cardiac failure and the significance of the conclusions of the Cochrane review for children is unclear, especially given the differing aetiology. Those reviews and discussions which have focussed on paediatric cardiac failure vary in their assessments, with some suggesting use of digoxin is controversial (22) whilst others position it as a first line treatment alongside diuretics (20).

At a time when beta-blockers are being more widely used, it is important to note that a clinically significant interaction has been documented between carvedilol and digoxin. This can result in significant increases in digoxin levels, which necessitates a reduction in the digoxin dose to avoid the risk of digoxin toxicity (35). It would be prudent to highlight this in any guidance on management of heart failure where these two drugs may be given concurrently.

Digoxin in a range of formulations is already included in the EMLc and, given its application in other indications, it is considered appropriate for it to be retained. However, the specific inclusion of digoxin for cardiac failure would appear to be based on long established clinical practice rather than on robust evidence and this should be noted by the committee.

**Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)**

**Rational for use of angiotensin converting enzyme (ACE) inhibitors:**
ACE inhibitors reduce the effects that result from the activation of the renin-angiotensin-aldosterone (RAA) system which often occurs in heart failure. The beneficial effects of ACE inhibitors in heart failure may therefore include:
- reduced Angiotensin II mediated vasoconstriction
- reduced Angiotensin II mediated potentiation of sympathetic nervous system activity
- reduced Angiotensin II mediated aldosterone release and therefore
  - reduced sodium and water retention
  - reduced myocardial fibrosis
  - reduced inhibition of nitric oxide release
- reduced breakdown of vasodilatory bradykinin

A number of angiotension converting enzyme inhibitors have been studied in large randomised trials in the management of cardiac failure in adults, with generally consistent findings of reduced symptoms, morbidity and mortality. Of those studied enalapril, lisinopril and ramipril have the greatest weight of evidence in heart failure. There is no data directly comparing the different ACE inhibitors on which any conclusions about the superiority of one over another can be drawn. Based on studies and reviews of various ACE inhibitors in other conditions, such as post-MI (36), hypertension (37, 38), stroke (39), diabetes (40) and renal disease (41), and the generally favourable outcomes seen, there has been a tendency to consider that ACE inhibitors exhibit a class effect. Consequently, other drugs in the group such as perindopril, captopril and trandolapril are also widely used in adults.

In children with cardiac failure, the ACE inhibitors which have been most studied are captopril and enalapril, with more modest data for cilazapril. Whilst there is some data supporting ramipril and lisinopril in children with hypertension (42, 43), there is no published data on the use of these drugs in children with heart failure and no published studies on the use of perindopril in children for any indication.
The key studies on the use of ACE Inhibitors in children with cardiac failure are summarised in Table 1. It should be noted that many of the studies have been retrospective and assessed surrogate markers for clinical outcomes.

In common with experiences in adults, a number of children treated with ACE inhibitors experienced deterioration in renal function and hypotension. In many cases discontinuation of the ACE inhibitor or reduction in dose was effective in reducing these problems; however, some of the studies reported renal failure and death in a small number of cases. It should, however, be noted that as many of the patients included in these reports were already significantly haemodynamically compromised, the exact role of the ACE inhibitor in the development of these adverse outcomes is unclear. Other adverse effects were reported in one of these trials and included one case of neutropaenia and one case of cough, both of which resolved on discontinuation of the ACE inhibitor (44).

On the basis of the available data, a recent review of use in paediatric practice concluded that myocardial dysfunction should be treated with ACE inhibitors, mild-moderate valvular insufficiency is effectively treated with ACE inhibitors and large left to right shunts should be surgically treated, unless surgery is not appropriate, when an ACE inhibitor should be used (45).

There is currently not an ACE inhibitor included on the EMLc; based on the evidence and current clinical opinion, this needs to be addressed. Enalapril and captopril account for the majority of the evidence from studies in children; consequently, any ACE inhibitor to be included in the EMLc would most rationally be one of these two.

A recent review has concluded that the lack of definitive data comparing individual drugs makes it inappropriate to recommend a specific ACE inhibitor for use in children (45); however, for practical purposes the inclusion of one ACE inhibitor on the EMLc would be desirable. In the absence of compelling clinical reasons to select a specific ACE inhibitor, it is appropriate to consider other factors which may affect the practical administration of these drugs. It is recognised that the preparation of enalapril in a liquid formulation is challenging, whereas in some countries a licensed liquid formulation of captopril is available, to supplement the tablet formulation which would be appropriate for older children. However, the shorter duration of action of captopril necessitates more frequent administration, usually three times per day compared to once or twice per day for enalapril and the latter is already included in the essential medicines list for adults. The relative merits of these factors needs to be carefully considered in any decision which is made regarding inclusion of an ACE inhibitor in the EMLc.
Table 1. Summary of studies on ACE inhibitors in Paediatric Cardiac Failure and related conditions
(DCM=dilated cardiomyopathy, LVD=left ventricular dysfunction, VSD=ventricular septal defect)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population treated with ACE inhibitor</th>
<th>ACE Inhibitor used</th>
<th>Key findings and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(46)</td>
<td>27 with DCM</td>
<td>Captopril (0.9-3.9mg/kg/day)</td>
<td>Significantly improved survival over first two years, trend towards this continued thereafter.</td>
</tr>
<tr>
<td>(47)</td>
<td>18 LVD post doxorubicin</td>
<td>Enalapril (mean 18mg/day)</td>
<td>Left ventricular function improved over the first six years, deteriorating between 6 and 10 years.</td>
</tr>
<tr>
<td>(48)</td>
<td>12 with DCM</td>
<td>Captopril</td>
<td>Improvements in haemodynamic effects.</td>
</tr>
<tr>
<td>(44)</td>
<td>63 with LVD (congenital &amp; acquired)</td>
<td>Enalapril (mean 0.3mg/kg/day)</td>
<td>58% of patients improved, 30% had no improvement and 12% had side-effects. 3 patients died with cardiac / renal failure.</td>
</tr>
<tr>
<td>(49)</td>
<td>8 with CM and HF</td>
<td>Enalapril (0.5mg/kg/day)</td>
<td>Persistent clinical improvement after one year, with decreased heart size reported.</td>
</tr>
<tr>
<td>(50)</td>
<td>6 with VSD and HF</td>
<td>Enalapril (0.12-0.43mg/kg/day)</td>
<td>Clinical improvements in all patients, improvements in body weight and feeding</td>
</tr>
<tr>
<td>(51)</td>
<td>8 with VSD and HF</td>
<td>Enalapril (0.16mg/kg/day)</td>
<td>Clinically effective and well tolerated in all patients</td>
</tr>
<tr>
<td>(52)</td>
<td>20 with left to right shunts and HF</td>
<td>Captopril (0.9-2.5mg/kg/day)</td>
<td>Clinical improvement in most patients, four developed renal failure or hypotension. Improvements in weight gain and respiration rate reported.</td>
</tr>
<tr>
<td>(53)</td>
<td>20 with aortic regurgitation</td>
<td>Captopril (1.15mg/kg/day)</td>
<td>Left ventricular dilatation and hypertrophy were reversed.</td>
</tr>
<tr>
<td>(54)</td>
<td>13 with DCM and post-surgical</td>
<td>Cilazapril (0.04mg/kg/day)</td>
<td>Treatment reduced left ventricular afterload and increased LV shortening.</td>
</tr>
</tbody>
</table>
Angiotensin Receptor Blockers (ARBs)

Rationale for use of Angiotensin Receptor Blockers (ARBs):
Angiotensin Receptor Blockers (ARBs) reduce some of the effects that result from the activation of the renin-angiotensin-aldosterone (RAA) system which often occurs in heart failure. The beneficial effects ARBs in heart failure may therefore include:
- reduced Angiotensin II mediated vasoconstriction
- reduced Angiotensin II mediated potentiation of sympathetic nervous system activity
- reduced Angiotensin II mediated aldosterone release and therefore
  - reduced sodium and water retention
  - reduced myocardial fibrosis
  - reduced inhibition of nitric oxide release

Three ARBs have been studied in adults with heart failure - candesartan, losartan and valsartan.
Although an initial small trial with losartan was encouraging, a subsequent larger study failed to confirm that it was as effective as an ACE inhibitor (55). Candesartan (56) and valsartan (57) have, however, been shown in subsequent trials to provide beneficial outcomes in adults with heart failure; although they have not been shown to be superior to ACE inhibitors. As regards the inclusion of heart failure as a licensed indication for these two ARBs, there is international variation.

In view of the more established evidence base for ACE inhibitors in cardiac failure and the lower cost of the latter, some guidelines for adult heart failure recommend that ARBs are only used as an alternative to ACE inhibitors where patients are intolerant to these, usually as a result of a persistent dry cough (11).

There is very little published data on the use of ARBs in children. The pharmacokinetics of irbesartan in hypertensive children have been reported (58), as has the effectiveness of losartan in hypertensive children (59); however, no published studies specifically on the use of ARBs in children with cardiac failure were identified. It should be noted that heart failure data for these two specific ARBs is either lacking or sub-optimal.

A recent review has concluded that as there is no efficacy data on ARBs in children with heart failure, they should only be used where there is intolerance to an ACE inhibitor (21), which is in line with general practice in adults. In line with this, it is not considered appropriate to make recommendations to add an ARB to the EMLc at the current time or to include an ARB in guidance on management of cardiac failure in children.

Aldosterone antagonists

Rationale for use of aldosterone antagonists:
Aldosterone antagonists reduce some of the effects that result from the activation of the renin-angiotensin-aldosterone (RAA) system which often occurs in heart failure. The beneficial effects of aldosterone antagonists in heart failure may therefore include:
- Reduced sodium retention
- Reduced water retention
- Reduced myocardial fibrosis
- Reduced inhibition of nitric oxide release
- Slowed heart rate, improving balance of oxygen supply and demand
- Reduced myocardial apoptosis and fibrosis
- Anti-arrhythmic effects

There has been renewed interest in the role of aldosterone antagonists in heart failure following research in adults demonstrating that the addition of spironolactone at low doses (25mg per day) to standard care was beneficial in terms of symptoms and hospital admissions (60). Use of spironolactone had previously waned as a consequence of concerns over potential carcinogenicity and an adverse effect profile which included anti-androgenic effects which could be problematic for male patients, especially when the drug was used at the higher doses required in liver disease.

The literature supporting the role of spironolactone in paediatric heart failure is however limited. One study in heart failure reported that it enhances the effect of digoxin and thiazide diuretics (61). The second (62), in a paediatric population with heart, lung and other pathologies, reported that spironolactone can be added to loop and/or thiazide diuretics, although it highlighted the need for close monitoring of potassium levels and recommended that further research is needed to look at pharmacokinetics and the most appropriate dosing interval in children.

Eplerenone is a newer, more specific aldosterone antagonist which has been studied in the post-MI setting in adults and has been shown to reduce the onset of heart failure in this setting (63). It has also been used in patients requiring an aldosterone antagonist who are intolerant to spironolactone. There is no published evidence on the role of eplerenone in the management of paediatric heart failure. One review commented that eplerenone is one of the few newer drugs for which paediatric dosing has been established (64), although it should be noted that this refers to the manufacturer’s data on file rather than published studies.

Spironolactone is already included in the EMLc and although the available evidence specifically in paediatrics is modest, it remains appropriate for it to be retained. In the absence of any clear advantages for eplerenone from adult studies and the lack of published data on its use in children, it is not considered appropriate to include this in the EMLc at the current time.

**Beta-blockers**

**Rationale for use of beta-blockers:**
Beta-blockers counter the activation of the sympathetic nervous system which is often seen in heart failure. The beneficial effects of beta-blockers in heart failure may therefore include:
- Slowed heart rate, improving balance of oxygen supply and demand
- Reduced myocardial apoptosis and fibrosis
- Anti-arrhythmic effects
- Synergism with ACE inhibitors

A number of beta-blockers have been studied in large randomised trials in the management of cardiac failure in adults, with generally consistent findings of reduced symptoms, morbidity and mortality. Of those studied, bisoprolol (65, 66), carvedilol (67, 68), metoprolol (69) and, most recently, nebivolol (70)
have the greatest weight of evidence and are the most widely used in clinical practice in adult heart failure.

Although the adult data for bucindolol is less favourable than that for other beta-blockers in terms of outcome data (89), findings from the research with this agent may have significance for paediatrics, given the recurrent concern about applying adult data to paediatrics where the aetiology is usually different. One of the bucindolol trials in adults included patients with cardiomyopathy, a major cause of heart failure in children and the benefits of beta-blocker treatment were significant in this group (90).

One study in adults directly compared carvedilol and metoprolol and indicated superior effects from carvedilol (71), although it has been suggested that the formulation of metoprolol used in this study may have contributed to these findings; otherwise, there is no data from which firm conclusions about the specific advantages of one beta-blocker over another can be drawn.

In children with heart failure and related conditions, carvedilol has been the most widely studied beta-blocker. Table 2 summarises the studies carried out to date. Beyond these studies, experience has been gained with beta-blockers in children with a variety of other conditions, such as migraine. However, few of these have much significance for the management of heart failure, with the possible exception of a recent evaluation of metoprolol as an antihypertensive in children (72). No published data on the use of nebivolol in children with heart failure was identified.

Reviews have commented that children with severe CHF who are started on beta-blockers are unlikely to tolerate the reduction in sympathetic drive (23), although this observation may be less relevant to those with earlier stage disease. Concern has also been raised that whilst beta-blocker therapy in adults reduces sudden cardiac death, the effect of beta-blockade in children does not appear to reduce the QT interval in the same way (91), the significance of this is not yet known.

In addition to the studies shown in Table 2, other work has assessed the systemic exposure to carvedilol amongst paediatric heart failure patients and has indicated that higher doses relative to body weight are required to provide exposure comparable to adults. It was suggested that paediatric carvedilol doses should subsequently be: 1mg/kg/day for adolescents, 2mg/kg/day for children aged 2 to 11 years and 3mg/kg/day for infants (aged 28 days to 23 months) (73). It should be noted that the doses of carvedilol used in many of the studies summarised in Table 2 have been lower than these recommendations, in some cases significantly lower.

The recently published randomised trial with carvedilol (74) has prompted significant debate and comment. The authors and subsequent reviews have commented that these findings may have been due to an unexpected level of improvement in the placebo arm, the low dose of carvedilol used and the study being underpowered (75-77). It has been suggested that, on this basis, the findings of this trial may not mean there is no role for beta-blockers in this population (76) and that it is likely beta-blockers will continue to be used based on the evidence from adults (75).

There is currently no beta-blocker included on the EMLc; based on the evidence and current clinical opinion, this needs to be addressed. Although a number of beta-blockers have been studied in heart failure, the greatest weight of evidence is with carvedilol both in adults and paediatrics; it is therefore considered appropriate to recommend this beta-blocker is added to the EMLc.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population treated with beta-blocker</th>
<th>Beta-blocker used</th>
<th>Key findings and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(78) Retrospective</td>
<td>46 with cardiomyopathy or congenital heart disease</td>
<td>Carvedilol (mean 0.46mg/kg)</td>
<td>Three month follow-up showed 67% of patients had improved NYHA class. 54% had side-effects, mainly dizziness, hypotension and headache which were generally tolerated. Adverse outcomes (death, transplantation and ventricular-assist device) were reported in 30% of patients. Improvements were sustained in 25 children who continued therapy for 12 months.</td>
</tr>
<tr>
<td>(79) Placebo controlled double-blind RCT</td>
<td>14 with HF awaiting transplant</td>
<td>Carvedilol (0.2mg/kg/day)</td>
<td>Nine were removed from transplant list with improvements in LVEF and NYHA class, four died and one underwent transplant. Amongst the 8 receiving placebo, two died, two were transplanted and there was no significant improvement in LVEF.</td>
</tr>
<tr>
<td>(80) Open label prospective</td>
<td>15 with DCM and congenital heart disease</td>
<td>Carvedilol (0.7mg/kg/day)</td>
<td>Evaluated effect amongst those not responsive to standard therapy including digoxin, diuretic and ACE inhibitor. In this study all patients achieved target dose and at six month follow-up significant improvement in Ross Score and ejection fraction was reported.</td>
</tr>
<tr>
<td>(81) Retrospective</td>
<td>23 with DCM congenital heart disease, anthracycline induced cardiac damage</td>
<td>Carvedilol (median maximum 0.9mg/kg/day)</td>
<td>Assessed effect in children on treatment with ACE inhibitors, diuretics, spironolactone and digoxin. This reported improvements in ejection fraction and allowed 3 patients to be removed from transplant list. Benefits were most significant in those who started carvedilol at an early age.</td>
</tr>
<tr>
<td>(82) Retrospective</td>
<td>24 with DCM</td>
<td>Carvedilol (mean 0.98 mg/kg/day)</td>
<td>Another study where added to therapy with ACE inhibitor, digoxin and diuretic. 22 patients continued for 2 years, with 15 patients (68%) had improvement in the NYHA class; there was one death and three required transplant. Adverse effects occurred in 5 patients (21%) and carvedilol was stopped in 2 patients (8%).</td>
</tr>
<tr>
<td>(83)</td>
<td>20 with DCM and congenital heart disease</td>
<td>Carvedilol (max 0.8mg/kg/day)</td>
<td>Significant improvement in ejection fraction amongst those with DCM treated for 6 months, with a trend towards delay in need for transplant and death. Carvedilol was stopped in three patients during the study.</td>
</tr>
<tr>
<td>(74) Placebo controlled double-blind RCT</td>
<td>103 with ventricular systolic dysfunction</td>
<td>Carvedilol (max. 0.4mg/kg)</td>
<td>Carvedilol patients randomised to one of two arms, one receiving 0.2mg/kg and the other 0.4mg/kg. Of all those on carvedilol, 58 improved (56%), 25 worsened (24%) and 20 were unchanged (19%), this was not significantly different to those on placebo.</td>
</tr>
<tr>
<td>Study</td>
<td>Population treated with beta-blocker</td>
<td>Beta-blocker used</td>
<td>Key findings and comments</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------------------</td>
<td>-------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>(84).</td>
<td>3 with doxorubicin cardiomyopathy</td>
<td>Metoprolol (max 25-75mg bd)</td>
<td>Improved NYHA class and ejection fraction in all patients and enabled two of three patients to be removed from transplantation waiting lists.</td>
</tr>
<tr>
<td>(85)</td>
<td>15 with DCM</td>
<td>Metoprolol (max 2.3mg/kg/day)</td>
<td>Improvements in systolic ventricular function followed the addition of metoprolol to long standing conventional therapy with diuretics, digoxin and ACE inhibitor.</td>
</tr>
<tr>
<td>(86)</td>
<td>11 with Duchenne’s cardiomyopathy</td>
<td>Metoprolol and Bisoprolol</td>
<td>Reported improvements in symptoms and ventricular function after 6 months therapy, effects sustained for 2 to 5 years.</td>
</tr>
<tr>
<td>(87)</td>
<td>6 with left-to-right shunts</td>
<td>Propranolol (max 3mg/kg/day)</td>
<td>Added to existing therapy with diuretics and digoxin, improvements in heart failure score noted, reduced aldosterone and renin levels, 5 of 6 patients stopped diuretics.</td>
</tr>
<tr>
<td>(88)</td>
<td>10 with left-to-right shunts</td>
<td>Propranolol (max 2mg/kg/day)</td>
<td>Added to existing therapy with diuretics and digoxin, compared to control patients those receiving propranolol had improvements in heart failure scores and reduced aldosterone and renin levels.</td>
</tr>
</tbody>
</table>
Antiarrhythmic Medication

**Rationale for use of antiarrhythmic medication:**
Antiarrhythmic medication can reduce the incidence of cardiac arrhythmias and may potentially be useful in heart failure where ventricular tachyarrhythmias are a major cause of mortality.

Arrhythmias are a major cause of mortality and morbidity in children with cardiac failure (92). Over half of children with dilated cardiomyopathy who die have ventricular arrhythmias at the time of presentation and almost two-thirds of those awaiting transplantation have life-threatening arrhythmias (93, 94).

Antiarrhythmic medication has been used in children, although there is a lack of trial data looking at its role in paediatric cardiac failure. As with many other therapy options, there has been extrapolation from studies in adults. In addition, there are risks associated with some antiarrhythmic medications, in that they may have negative inotropic effects or have proarrhythmic effects. Two studies showed that Class 1c antiarrhythmic drugs increased mortality, the first in paediatrics with structural heart disease (95) and the second in adults post-myocardial infarction (96).

The role of beta-blockers in cardiac failure has been discussed elsewhere and it is likely that some of the benefits reported are likely to be due to antiarrhythmic properties. The specific antiarrhythmic properties of sotalol have been studied in children, with some success, but with side-effects affecting 20-30% of patients (97).

Amiodarone has been studied in children and whilst some studies suggested it was well tolerated (98), others have raised concerns that the intravenous formulation may be linked with hypotension or collapse (99).

Alternative approaches to the management of rhythm problems in children with heart failure have been evaluated and paediatric electrophysiology has the potential to provide beneficial effects with or without adjunctive drug therapy (92).

Given the limited role for anti-arrhythmics in heart failure and lack of studies in children showing beneficial outcomes, the inclusion of an antiarrhythmic to the EMLc is not considered appropriate.

**Inotropes**

**Rationale for use of inotropes:**
In severe heart failure, where cardiac output and blood pressure are low, inotropic drugs which stimulate cardiac contractility and/or produce peripheral vasoconstriction have been used to try and maintain tissue perfusion.

Management of the acute phase of cardiac failure has seen the use of inotrope (also referred to as inodilator) drugs to maintain perfusion of vital organs, and the existing EMLc includes dopamine on the supplementary list to fulfill this role.
A number of inotropes have been used in acute cardiac failure; amongst these are the catecholamines, dopamine and dobutamine, and the phospho-diesterase inhibitors, milrinone and amrinone.

It is recognised that acute cardiac failure is often complicated by deterioration in renal function that is associated with worsened outcomes and it has been suggested that this cardio-renal syndrome occurs in children (100). The application of dopamine in acute heart failure also aims to address this decreased renal function and evidence suggests that it is effective in achieving this in adults, although it is considered that further evaluation is needed (101).

In some situations, more than one inotrope has been given concomitantly, in an attempt to optimise the specific effects of the individual drugs. However, data from adults suggests that use of more than one inotrope in acute heart failure is associated with increased mortality (102).

The appropriateness of all inotropes in acute cardiac failure is controversial, based on the lack of robust evidence and lack of alternative options (103). Two recent reviews have advised that there is a limited role for inotropes in adults. One suggested that the use of inotropes should be restricted to patients who, despite a high left ventricular filling pressure, remain hypotensive (103). The second, that routine use in the acute setting is not indicated, but that there may be a role in those with hypoperfusion or shock and in those awaiting transplant or revascularisation (104).

In common with the chronic management of cardiac failure, many of the studies in the acute phase have been carried out in adults and the significance of their findings for children is unclear. In children, the catecholamines have been the drugs of choice, with their pharmacokinetics permitting titration to response and it is with dopamine that there is the greatest experience (105). The alternative phospho-diesterase inhibitors produce significant pulmonary vasodilation and have little effect on myocardial oxygen demand. Of the two available, milrinone is favoured on the basis of its shorter half-life and wider therapeutic index (105).

Children with acute cardiac failure generally fall into one of two groups, those with established cardiomyopathy and those who were previously healthy (106). In the former group, the acute phase may present where the patient has become refractory to existing treatment or when precipitated by co-morbid conditions such as anaemia or overwhelming infection. It is in situations such as these where inotropic support has been utilised. In the case of those patients with exacerbations, treatment of the underlying cause, where possible, should determine that the need for inotropic support is short-term.

In the case of children refractory to existing treatment, the options for long term treatment may be limited and are likely to include consideration for cardiac transplantation. Proceeding to transplant immediately will however often not be possible or appropriate, due to the instability of the patient, access to a transplant unit or availability of a suitable donor. Consequently, there may be a requirement for the use of additional supportive treatments for a period of several months. In this situation, inotropes have been used as a so called “bridging-therapy”, which has been delivered in both the in-patient and out-patient settings.

In one report, seven children with advanced chronic heart failure were given parenteral inotropic therapy (mean 10 weeks), in the out-patient setting. Six patients were successfully bridged to transplantation and one died. During the period of treatment, inotropes led to symptomatic improvements and reductions in hospital admissions and presentations at the emergency department (107).
In another similar study, 21 children awaiting transplant were given inotrope therapy (dobutamine, milrinone or dopamine) at home. Survival at 12 months was reported as 84%, with improved cardiac and renal function, and reduced hospitalisations (108).

A recent study has shown that amongst paediatric patients with acute heart failure due to cardiomyopathy or myocarditis, up to 96% will recover over a two-year period, during which time they will require a package of intensive support, which includes inotropes and extracorporeal membrane oxygenation (109).

It should also be recognised that the use of non-pharmacological interventions has a significant and increasing role in the management of acute cardiac failure in children (110).

Based on the available adult data and the absence of paediatric evidence, the routine use of inotropes in acute cardiac failure in children cannot be recommended. In other scenarios, such as use short-term alongside treatment of exacerbating conditions and as a bridging therapy pending transplantation, it would appear appropriate to include an inotrope on the EMLc. In the absence of compelling evidence for change, it is suggested that the EMLc retains dopamine, as it possesses both the cardiac and renal effects that are useful in this clinical situation.

**Other therapies**

<table>
<thead>
<tr>
<th>Rationale for use of other medication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued burden of cardiac failure with significant morbidity and mortality despite the existing treatment options</td>
</tr>
</tbody>
</table>

A number of other therapies are under evaluation in the management of cardiac failure, many of these in the acute phase of the condition.

**Natriuretic peptides:** Nesiritide is a recombinant B-type natriuretic peptide approved for use in some nations for the treatment of decompensated heart failure in adults.

Three studies have evaluated the role of nesiritide in children with heart failure in an intensive care setting and have reported improvements in renal function and increased urine output (111-113). The authors of these studies and a further review (114) have all concluded that further work is needed to assess the role of nesiritide.

The strength of the evidence available to date does not warrant the inclusion of nesiritide in the EMLc for the routine management of cardiac failure in children at the current time.

**Calcium sensitisers:** Levosimendan is the first of this group to be evaluated. One study in children with severe heart failure refractory to dobutamine, showed encouraging signs in terms of ejection fraction, reduction discontinuation of catecholamine therapy and adverse effects (115). There are a number of other reports on beneficial effects in individual patients; however, a recent review commented that further experience and data is required (64).

On this basis, levosimendan is not considered appropriate for inclusion in the EMLc for the routine management of cardiac failure in children at the current time.
Endothelin receptor antagonists: A number of these, including bosentan, tezosentan, darusentan and sitaxsentan, have been developed and studied in a range of conditions, including pulmonary hypertension and heart failure. Evidence of efficacy to date is variable and there are concerns about the hepatotoxicity of bosentan. There is no data on efficacy or safety in children. Depending on findings, the ongoing work in adult populations may give rise to paediatric studies in due course (64).

Roles for endothelin receptor antagonists remain to be clarified and there is no place for these drugs in the EMLc for the routine management of cardiac failure in children at the current time.

Discussion

Treatment

Clinical practice in the management of cardiac failure in children currently uses some or all of the following drug treatments: diuretics, digoxin, spironolactone, ACE inhibitors, beta-blockers and inotropes.

There are no national or international guidelines on the management of cardiac failure in children and, consequently, the approach to treatment is based on a combination of clinical experience amongst those involved in management, application of findings from many studies in adults with cardiac failure and the modest data from studies in children.

The data from studies in children is sub-optimal and when considered in isolation provides a poor basis for making decisions and wider recommendations. There are several reasons for this, including the small size of many studies, reliance on retrospective studies, the variation in causes of cardiac failure and age range amongst study participants, the doses of drugs used and variation in measures used to assess outcomes.

There is, however, reasonable evidence that some children with cardiac failure do benefit from treatment with drugs which have a proven evidence base in adults, in particular ACE inhibitors and beta-blockers.

Unanswered Questions

In compiling this report there are a number of recurrent themes which require consideration when developing the EMLc and guidelines on the management of cardiac failure in children. These fall into four main areas.

Paediatric practice based on adult evidence

Although the available paediatrics literature provides grounds for optimism in the use of drug therapy for cardiac failure, there remain questions about clinical practice in children being driven primarily by studies carried out in adults, where the underlying pathology of paediatric heart failure is significantly different.

Specific drug issues

Questions have been asked about the metabolic and electrolytic effects of loop diuretics, which may have potentially deleterious effects on the underlying pathology of heart failure. However, given that the presentation of cardiac failure is associated with oedema, which
invariably responds rapidly and significantly to diuretics, resolving these issues will be challenging.

The role of digoxin also remains somewhat unclear, based on the lack of robust evidence.

**Dosage**

The literature provides ample evidence of a wide disparity of dosing regimens being used in paediatric practice and it needs to be considered that these may have had significant effects on the outcome of some of the studies referred to. There is a need for further evaluation of the pharmacokinetics of many drugs used in heart failure in children to confirm both the dose and dosing interval that is required for optimal clinical benefit.

**Use of products outside of license**

In common with many other areas of paediatric clinical practice, the management of heart failure currently uses unlicensed drugs and licensed drugs outside of their product license. There are several inherent problems associated with this.

- To obtain a marketing authorisation to treat a specific condition in a specific patient group, the manufacturer is required to submit data to the licensing authorities to support claims of efficacy and an acceptable balance of risks and benefits. Consequently, when using an unlicensed drug or a licensed drug outside of its license, healthcare professionals and patients/carers are required to formulate their own judgments as to appropriateness based on sub-optimal information.

- Prescribers and others involved in the delivery of unlicensed drugs or licensed drugs outside of their license to the patient, carry greater legal responsibilities should harm be caused, than would be the case if prescribing was of a licensed product within the terms of its license.

- Unlicensed products are not as readily available as licensed products, which can introduce barriers to the timely delivery of medication to patients.

- Unlicensed products are not required to conform to the same consistent standards of manufacture as licensed products and there may be greater variation in the bioavailability of the active ingredient between different unlicensed formulations than there would be between different licensed formulations for the same drug.

In an ideal situation, all the drugs which are required would be licensed for use in children for the management of cardiac failure and be available in formulations which were appropriate for administration to children at the doses required. It has been suggested that where the required drugs are not available as licensed products, they should not be used and that greater pressure should be exerted on manufacturers and other organisations to invest in the research necessary to show the effectiveness (or otherwise) of the drugs involved, thus establishing the evidence base necessary to enable license applications to be made. This, however, would create a dilemma in that children would continue to present with heart failure whilst this research was undertaken and those outside of the trials would be denied treatments which, based on the limited data available already, may have had a significant probability of improving their outcome.
There is without doubt a need for a greater evidence base in the management of cardiac failure in children and the development of this through research should be encouraged. In the meantime the risks associated with the use of unlicensed and off label medications could be reduced by the requirement for greater standardisation in their manufacture to provide patients, carers and healthcare professionals greater confidence in their stability and bioavailability. The development of a prescribing reference to guide the appropriate off label use of medication in children would also assist in reducing the risks associated with this necessary practice. The WHO should give consideration to these two areas as medium and short-term priorities, to improve the management of heart failure in children.

**Conclusion**

The last twenty years have witnessed a significant advance in the evidence for and availability of drug therapies which can have a huge impact on the outcome for adult patients with heart failure. The situation with paediatric cardiac failure has followed a similar pattern, but has tended to be based on less robust evidence.

There is a compelling need for larger and higher quality studies on the drug treatment of cardiac failure in children to provide a more robust evidence base from which practice can develop. Alongside this is the need for greater availability and standardisation of products and formulations suitable for administration to children.

In the meantime, there is sufficient experience and evidence on which to base provisional recommendations affecting the EMLc. These would be for the addition of an ACE inhibitor and beta-blocker to the EMLc, (refer to accompanying applications for inclusion) to be used alongside those therapy options already included in the EMLc: frusemide, digoxin, spironolactone and dopamine, where they are clinically indicated.
Appendix 1: Search Strategy

Searches Performed

Initial:
Reviewed current EMLc
Search WHO website
Reviewed EMEA Assessment of the paediatric needs – Cardiovascular products, Oct 06
The Paediatric Cardiology Pharmacopeia, 2004 Update

PubMed:
Heart failure (title) AND Children (any field); Review – 16 found
Heart failure (title) AND Children (any field); Review – 65 found: looked at 2000+ only
Heart failure (title) AND paediatrics OR pediatrics (any field); Review; 2000-2008 – 22 found
Heart failure (title) AND paediatrics OR pediatrics (any field); Review; 2000-2008 – 3 found
Heart failure (title) AND Children (Title); 2000-2008 – 65 found
Heart failure (title) AND Children (Title) AND epidemiology (any field); 2005-2008 – 5 found
Heart failure (title) AND paediatrics OR pediatrics (title); AND epidemiology (any field); 2005-2008 – 0 found
Heart failure (title) AND Children (Title) AND epidemiology (any field); 2005-2008 – 1 found
Heart failure (title) AND paediatrics OR pediatrics (title); AND epidemiology (any field); 2005-2008 – 0 found
Heart failure (title) AND Children (any field) AND epidemiology (any field); 2005-2008 – 21 found
Heart failure (title) AND paediatrics OR pediatrics (any field); AND epidemiology (any field); 2005-2008 – 13 found
Heart failure (title) AND Children (any field) AND epidemiology (any field); 2005-2008 – 6 found
Heart failure (title) AND paediatrics OR pediatrics (any field); AND epidemiology (any field); 2005-2008 – 4 found
Heart failure (title) AND Children (any field) AND burden (any field); 2005-2008 – 3 found
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Heart failure (title) AND children (any field) AND beta-blocker (any field); 1995-2008 – 8 found
Heart failure (title) AND pediatric (any field) AND beta-blocker (any field); 1995-2008 – 6 found
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Acute cardiac failure (title) AND children (any field); 1995-2008 – 6 found
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Acute cardiac failure (title) AND pediatric (any field); 1995-2008 – 4 found
Heart failure (title) AND dopamine (any field); 1995-2008 – 127 found
Heart failure (title) AND dobutamine (any field); 1995-2008 – 333 found
Children (title) AND dopamine (any field); 1995-2008 – 273 found
Pediatric (title) AND dopamine (any field); 1995-2008 – 55 found
Children (title) AND dobutamine (any field); 1995-2008 – 37 found
Pediatric (title) AND dobutamine (any field); 1995-2008 – 23 found
Children (title) AND milrinone (any field); 1995-2008 – 12 found
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Heart failure (title) AND children (any field) AND inotropic (any field); 1995-2008 – 11 found
Cardiac failure (title) AND children (any field) AND inotropic (any field); 1995-2008 – 1 found
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Cardiac failure (title) AND pediatric (any field) AND inotropic (any field); 1995-2008 – 1 found
Heart failure (title) AND children (any field) AND dopamine (any field); 1995-2008 – 6 found
Cardiac failure (title) AND children (any field) AND dopamine (any field); 1995-2008 – 0 found
Heart failure (title) AND pediatric (any field) AND dopamine (any field); 1995-2008 – 5 found
Cardiac failure (title) AND pediatric (any field) AND dopamine (any field); 1995-2008 – 1 found
Heart failure (title) AND children (any field) AND dobutamine (any field); 1995-2008 – 3 found
Cardiac failure (title) AND children (any field) AND dobutamine (any field); 1995-2008 – 1 found
Heart failure (title) AND pediatric (any field) AND dobutamine (any field); 1995-2008 – 8 found
Cardiac failure (title) AND pediatric (any field) AND dobutamine (any field); 1995-2008 – 2 found
Heart failure (title) AND children (any field) AND nesiritide (any field); 1995-2008 – 3 found
Cardiac failure (title) AND children (any field) AND nesiritide (any field); 1995-2008 – 0 found

Cochrane Library:
Cardiac failure; no other limits – 25 items found
Heart failure; no other limits – 64 items found
Children cardiac failure; no other limits – 4 items found
Children heart failure; no other limits – 5 items found
Pediatric cardiac failure; no other limits – 18 items found
Pediatric heart failure; no other limits – 5 items found
BMJ Clinical Evidence
Cardiac failure; no other limits – 100 items found
Heart failure; no other limits – 153 items found
Children cardiac failure; no other limits – 7 items found
Children heart failure; no other limits – 9 items found
Pediatric cardiac failure; no other limits – 2 items found
Paediatric cardiac failure; no other limits – 3 items found
Pediatric heart failure; no other limits – 5 items found
Paediatric heart failure; no other limits – 2 items found

National Guideline Clearinghouse
Cardiac failure; no other limits – 313 items found
Heart failure; no other limits – 418 items found
Children cardiac failure; no other limits – 126 items found
Children heart failure; no other limits – 157 items found
Pediatric cardiac failure; no other limits – 67 items found
Paediatric cardiac failure; no other limits – 17 items found
Pediatric heart failure; no other limits – 78 items found
Paediatric heart failure; no other limits – 14 items found
References


15. Krum H JM, Stewart S, Sindone A, Atherton J, Hawkes A on behalf of. tCHFCPGEWP. Guidelines for the Prevention, Detection and Management of People with Chronic Heart Failure in Australia, 2006. 2006(National Heart Foundation of Australia and the Cardiac Society of Australia

and New Zealand ).


