Medical cardiovascular support in acute viral myocarditis in children

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There are insufficient data to support a diagnostic standard for this topic.

Guidelines

Inotropic support with beta-agonists such as dobutamine and phosphodiesterase inhibitors such as milrinone are indicated for patients with severely compromised ventricular function and symptoms of low oxygen delivery. More severe cardiogenic shock states may require additional inotropic support with low-dose epinephrine. The need for blood pressure support in the setting of acute viral myocarditis should merit discussion of the need for mechanical support. Noninvasive ventilation may be effective in treating pulmonary edema and reducing left ventricular afterload.

Options. In patients with acute viral myocarditis, poor ventricular function, and maintained oxygen delivery and hemodynamics, the use of beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) should be considered.

Overview

Pediatric patients with acute viral myocarditis have myocardial injury mediated by viral damage to heart muscle and depression of function due to the effect of cytokine release. The use of inotropes, although helping to support blood pressure and cardiac output, may be associated with increased myocardial oxygen consumption and with being proarrhythmogenic. Alternatives are the use of intravenous vasodilators or beta-blockers in an attempt to mitigate ongoing myocardial injury. There is also a rationale, based on studies done in adults with congestive cardiomyopathy, that nonpharmacologic afterload reduction with the use of noninvasive ventilation may augment cardiac performance.

Process

MEDLINE database searches were conducted to find published data regarding the use of inotropic agents, vasodilators, ACEIs, angiotensin receptor antagonists, beta-adrenergic blockers, calcium channel blockers, and noninvasive ventilation in pediatric myocarditis. Because few studies were expected to meet these criteria, studies of adults with myocarditis or dilated cardiomyopathy were also examined. Finally, studies of children and adults with acute viral myocarditis, wherein the primary objective of the study was a treatment or outcome other than one involving medical cardiovascular support, were studied to see if there was pertinent information regarding such support. The level of evidence for each study was classified as class I (randomized, controlled trials), class II (uncontrolled trials, historical controls, etc.), and class III (case series, case reports). The data gathered from this comprehensive review were then used to generate clinical recommendations regarding pharmacologic and ventilatory support of pediatric patients with acute viral myocarditis.

Scientific Foundation

Trials of Medical Therapy for Low Cardiac Output Syndrome/Heart Failure in Pediatric Acute Viral Myocarditis (Class I). There have been no trials specifically designed to examine management of low cardiac output syndrome (LCOS) or heart failure in pediatric patients with myocarditis.

Trials of Medical Therapy for LCOS/Heart Failure in Adult Acute Viral Myocarditis (Class II). There is one published class II study of acute treatment for heart failure in acute viral myocarditis in adult patients. Popovic et al. (1) treated 11 subjects with biopsy-proven acute viral myocarditis with metoprolol and nitroglycerin during cardiac catheterization. The acute hemodynamic effects of metoprolol included a decrease in heart rate and end-systolic pressure and an increase in end-diastolic volume without increasing end-diastolic pressure. The net result was an increase in ejection fraction, thought to be largely due to the decrease in heart rate and therefore a longer period of diastole. Addition of nitroglycerine lowered end-diastolic pressure and decreased arterial elastance. There were no measurements of oxygen delivery reported, and it was thus unclear if the increase in ejection fraction combined with the decrease in heart rate ultimately led to an increase in overall cardiac output.

Reports of Medical Therapy for LCOS/Heart Failure Included in Trials of Other Aspects of Treatment of Acute Viral Myocarditis (Class I, II, or III for Agent Under Study but Class III for Heart Failure Treatment in Myocarditis). The vast majority of clinical literature concerning treatment for acute viral myocarditis has been centered on potential anti-inflammatory or immunomodulatory therapy or on mechanical support. Several of these articles contain summary information regarding the type of support used for the treatment of heart failure or LCOS in subjects enrolled in these trials or case series (2–5). The prevailing theme is that

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management in most cases is likely dictated by the specific circumstances of the situation and by common sense. Agents used for acute cardiac support include dopamine, dobutamine, epinephrine, milrinone, and in >50% of cases in such reports, mechanical ventilation (6–8). Unfortunately, these types of articles do not generally contain hemodynamic information presented in a way that allows one to determine the indications for any of these types of therapy. It therefore remains unclear whether consensus from these types of studies support routine use of beta-adrenergic agents or intravenous vasodilators for myocardial support in the absence of overt symptoms of LCOS or hemodynamic instability.

Several drugs used for chronic heart failure are also reported in these types of studies. Diuretics are used almost universally, and ACEIs are also used commonly, even at the time of acute presentation. Use of digoxin is somewhat controversial, although there are no clinical reports in humans directly indicating or contraindicating its use specifically in acute viral myocarditis. Beta-blockade is reported in about one third of cases, which suggests not all subjects in these types of studies have LCOS or shock because initiation of beta-blockade is contraindicated under such circumstances. Use of anticoagulation is common, and anti-arrhythmic drugs are frequently used to treat arrhythmias associated with acute viral myocarditis.

Expert Opinion from Review Articles/Chapters. There are numerous articles and chapters that include recommendations for treatment of patients with acute viral myocarditis (6, 7, 9–13). In general, these recommendations are again based on common sense and rarely, if ever, cite specific supporting evidence. Most authors suggest inotropic support with adrenergic agonists (most commonly dobutamine, dopamine, or milrinone), afterload reduction with vasodilators unless the patient is hypotensive, and anticoagulation. Specific indications are usually not mentioned, but it is apparent that the degree of support is often dependent on the goal of therapy. For example, beta-adrenergic agonists or phosphodiesterase inhibitors might be used to acutely increase cardiac output to improve overall perfusion and perhaps help establish diuresis for a patient who has symptoms of heart failure but who seems hemodynamically stable. Potent vasoconstrictors such as epinephrine may be required to maintain adequate blood pressure for a hypotensive patient in cardiogenic shock while alternatives such as mechanical support are being considered or implemented. Similarly, mechanical ventilation is indicated for frank respiratory distress or to decrease transmural left ventricular pressure and thus reduce afterload for patients in distress.

Recommendations regarding transition to oral medications and treatment of chronic heart failure mostly consist of use of ACEIs, beta-blockade, and diuretics (10). Several authors suggest that digoxin may be contraindicated in acute viral myocarditis (10–13) and that amlodipine and captopril might be particularly advantageous (9). These recommendations, however, are largely based on either anecdote or on the results of animal research using a murine model of acute viral myocarditis.

Acute Heart Failure Trials (Class I Trials for Acute Heart Failure in Adults and Children with No Specific Reference to Acute Viral Myocarditis). There have been few randomized, controlled trials of medical management of acute heart failure in dilated cardiomyopathy. Two class I studies that may be relevant to pediatric acute viral myocarditis are the PRIMACORP trial and the LIDO study. The PRIMACORP trial examined the use of prophylactic milrinone for prevention of LCOS after reparative cardiac surgery in infants and children (14). The study found that high-dose milrinone (0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was effective in preventing LCOS and that low-dose milrinone (0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) showed a tendency in the same direction but not at a level that reached statistical significance. Clearly, there are likely to be important differences between postoperative myocardial dysfunction and acute viral myocarditis, but this remains the only large-scale, randomized, placebo-controlled trial for acute low cardiac output in children.

Levosimendan, a novel inotropic agent that increases the sensitivity of the myofilaments to calcium, was studied in the LIDO trial (15). This study compared levosimendan with dobutamine in adults hospitalized with congestive heart failure and low cardiac output from all causes. A positive response to the study drug was defined as an increase in cardiac output of ≥30% with a decrease in pulmonary artery occlusion pressure of ≥25%. Subjects receiving levosimendan met end point more frequently than those receiving dobutamine (27% vs. 15%). Survival at 180 days was also significantly higher in the levosimendan group (74% vs. 62%). Although there have been a few published reports of use of levosimendan in children from outside of North America, there are still few data on its effects in a pediatric population or for patients with acute viral myocarditis. One recent uncontrolled, nonrandomized study (class II–III) of levosimendan use in 15 children with either end-stage or acute heart failure included two subjects with acute viral myocarditis. Use of levosimendan was associated with weaning of dobutamine and with an increase in left ventricular ejection fraction in subjects with acute heart failure (16). Due to the small number of patients in this study and the lack of a control group, results should be interpreted with caution. Levosimendan is not yet approved by the Food and Drug Administration for use in the United States.

Chronic Heart Failure Trials (Class I Trials for Chronic Heart Failure in Adults and Children with No Specific Reference to Acute Viral Myocarditis). There have been several large, multiple-center, randomized, placebo-controlled trials of a variety of drugs used to treat heart failure in adult populations. None of these trials has attempted to separate out patients with a history of acute viral myocarditis, and none published to date have been conducted specifically in children. Nevertheless, many clinicians regularly use drugs studied in these trials, particularly ACEIs and beta-blockers.

Two of the largest and most well-known ACEI trials have been the Studies of Left Ventricular Dysfunction (SOLVD) and the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I). The SOVLD trials were conducted in adults with an ejection fraction of <35% and have shown a 22% reduction in mortality from progressive heart failure and a 26% reduction in hospitalization in the enalapril group compared with placebo (17–22). There are numerous publications showing specific benefits of enalapril compared with placebo in terms of measurements of left ventricular size and function that have also resulted from the data gathered in this trial (23–27). The CONSENSUS I study showed similar results (28). Currently, enalapril has essentially become standard of care for treatment of adults with congestive heart failure (29) and is frequently used as such in pediatrics. There are limited data from controlled studies of enalapril use in chil-

dren, largely limited to studies in cardiomyopathy resulting from anthracycline use. The data are somewhat indeterminate, with one study showing improvement in left ventricular end-systolic wall stress at up to 5 yrs of follow-up (30), and another showing no benefit beyond 6 yrs (31).

The role of beta-agonists and antagonists is of interest and concern to those who care for children with acute viral myocarditis in the critical care unit. Beta-agonists are frequently used to improve contractility and oxygen delivery in critically ill patients with low cardiac output. Nevertheless, a large amount of literature has accumulated in recent years suggesting that overall survival is better with beta-antagonists as opposed to beta-agonists in severe heart failure. Carvedilol, metoprolol, and bisoprolol have all been subject to at least one large-scale trial and shown to be effective in reducing mortality in adults. The most effective beta-blocker, assuming there is one, has yet to be determined, although the Carvedilol or Metoprolol European Trial (COMET) suggested that carvedilol was superior to metoprolol (23). This conclusion has been contested by some who suggest that the dose of metoprolol did not result in a level of receptor antagonism comparable with that induced by carvedilol in this particular trial (24). Pediatric trials of beta-blockade have been limited to small case series and case reports with the exception of work by Bruns et al (25). This study evaluated the use of carvedilol in addition to standard therapy in 46 pediatric subjects at six centers. New York Heart Association class improved in 67% of subjects, and fractional shortening improved from 16.2% to 19%. Shaddy et al. (26) have shown similar improvements in a smaller group of subjects who were administered metoprolol. The only randomized, placebo-controlled, large-scale trial of heart failure treatment in pediatrics is a recently concluded multiple-center trial conducted by Shaddy and colleagues of carvedilol for the treatment of pediatric heart failure (personal communication). The results suggest that children may respond differently to heart failure treatment than adults. There was no statistically significant effect of carvedilol on pediatric heart failure. Left ventricular ejection fraction improved in both the carvedilol and placebo groups, although the trend was for a higher left ventricular ejection fraction in the carvedilol group. There were also trends toward lower all-cause mortality and heart failure hospitalization in the carvedilol group, but the p value in each case was $>.5$ (32). The results of this study suggest the need for more rigorous testing of heart failure treatment in pediatric patients.

Other cardiovascular drugs that have been shown to be of benefit in chronic heart failure include angiotensin receptor antagonists, aldosterone antagonists, diuretics, and digoxin. Numerous studies have demonstrated reduction in mortality or morbidity with the angiotensin receptor antagonists losartan (27), valsartan (33), and candesartan (34). In general, this class of drugs is considered an acceptable alternative for patients unable to tolerate ACEIs because of side-effects related to kinin reduction such as cough or angioedema (29). Spironolactone can produce better long-term inhibition of aldosterone than ACEIs or angiotensin receptor antagonists and has also demonstrated a beneficial effect on morbidity and mortality in adults with chronic heart failure and depressed left ventricular function (35). Diuretics have not been shown to affect survival, but they are the most effective agents to rapidly reduce the acute respiratory symptoms associated with heart failure and for reduction in total body water (36, 37). They are generally considered first-line, standard-of-care agents for all heart failure patients (29). Digoxin has been shown to improve symptoms and quality of life among heart failure patients, but it is not clear that there is a beneficial effect on mortality (36, 38). Some have suggested that the use of digoxin in the setting of myocardial inflammation may be pro-arrhythmic, although there is no literature to support this. Calcium channel blockers are considered contraindicated in patients with reduced ventricular function, largely based on expert opinion (29). They may be even more disadvantageous in neonates due to the relatively larger dependence of the neonatal heart on extracellular calcium.

The use of anticoagulation for patients with heart failure and very low ejection fraction is common, presumably to prevent thromboembolic events brought about by a low flow state. The data to support this practice are largely anecdotal and not supported by most retrospective studies of adults with heart failure (39, 40).

For those interested in a far more extensive discussion of evidence-based management of heart failure, the recently published 2005 American College of Cardiology/American Heart Association guideline update for the diagnosis and management of chronic heart failure in the adult is an excellent reference (29).

Noninvasive Ventilation (Class II and III for Acute Heart Failure in Adults with No Specific Reference to Acute Viral Myocarditis). It is well known that positive pressure ventilation can benefit patients with congestive heart failure because it can reduce work of breathing, improve gas exchange, lessen pulmonary edema, and reduce afterload on the left ventricle (41–44). As discussed above, use of mechanical ventilation is indicated as part of basic resuscitation of acutely ill patients with shock due to acute viral myocarditis or cardiomyopathy, but noninvasive modes of ventilation such as continuous positive airway pressure and bilevel positive airway pressure may also be of benefit for less acutely ill patients. For those with acute heart failure and respiratory distress, both continuous positive airway pressure and bilevel positive airway pressure have been associated with improved indices of cardiac and respiratory function, including oxygenation, ventilation, cardiac output, heart rate, blood pressure, and pulmonary artery occlusion pressure (45–51). Use of these devices can also prevent or postpone the need for intubation (52–54). No studies to date, however, have been associated with an increase in 24-hr survival, and at least two have suggested that use of noninvasive ventilation is associated with significantly increased cardiac risk in patients with severe coronary artery disease (55, 56). No similar trials have been conducted in pediatric populations (57). Use of noninvasive ventilation in pediatric patients with acute viral myocarditis and acute heart failure is therefore of potential short-term benefit but unknown long-term benefit. It is unlikely the issue of coronary ischemia is important in the pediatric population.

Summary

Class I evidence for treatment of LCOS in pediatric patients with acute viral myocarditis is essentially nonexistent, as is any significant amount class II and class III evidence specific to treatment of heart failure and low cardiac output in adults with this disease. Implementation of a comprehensive, evidence-based treatment strategy for acute and chronic heart

failure in pediatric patients with acute viral myocarditis is therefore not possible. Recommendations are therefore based on information culled from studies of other aspects of pediatric and adult inflammatory heart disease and acute and chronic heart failure and should thus be applied with regard to the specific situation and the experience of the clinician. With this caveat, the following approach is supported by the literature:

For the Patient with Acute Heart Failure and Clinical Signs of Low Cardiac Output/Oxygen Delivery. Inotropic support with beta-agonists such as dobutamine and phosphodiesterase inhibitors such as milrinone is indicated. More severe cardiogenic shock states may require additional inotropic support with low-dose epinephrine, and the presence of hypotension may merit use of inotropic agents with more alpha-adrenergic activity such as dopamine or higher-dose epinephrine. The need for blood pressure support in the setting of acute viral myocarditis should merit discussion of the need for mechanical support.

Diuretics, particularly loop diuretics, should be used to decrease pulmonary edema and total body water, and addition of spironolactone may confer some added benefit. ACEIs should be started as soon as it is deemed safe with regard to renal function, and initiation of beta-blockade should be avoided until there has been a sufficient period of cardiovascular stability off of intravenous inotropic drugs. The use of digoxin is controversial and has most traditionally been avoided, although it is not clear that this is supported by the literature.

Respiratory compromise due to pulmonary edema and low cardiac output should be treated with positive pressure ventilation as indicated. Less severe respiratory distress may be managed with noninvasive forms of ventilation in some patients.

Anticoagulation is usually started to prevent intracardiac thrombus formation for those with poor ventricular function, but the evidence to support this practice is limited.

For the Patient with Suspected or Proven Acute Viral Myocarditis, Poor Ejection Fraction, and Maintained Oxygen Delivery and Hemodynamics Based on Clinical Assessment. Initiation of ACEIs and beta-blockers are indicated. The use of intravenous inotropic agents should be directed toward relief of symptoms of low cardiac output and treatment of cardiogenic shock, as above. Angiotensin receptor antagonists might be an acceptable alternative for patients who do not tolerate ACEIs. Again, the use of digoxin is controversial, with some laboratory and anecdotal evidence to suggest it might be harmful. Diuretics are generally indicated to reduce pulmonary edema and the increase in total body water associated with heart failure. Addition of spironolactone to a loop diuretic may confer added benefit.

Key Elements for Future Investigation

The traditional approach to the treatment of patients with decreased ventricular function due to acute viral myocarditis has been the use of inotropes. Although this may be an effective strategy to support blood pressure and cardiac output, the increase in myocardial oxygen consumption may be harmful to the injured myocardium. The use of beta-blockers and ACEIs warrants further investigation.

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