Health Policy & Clinical Effectiveness Program

Evidence-Based Care Guideline

Inotropic Support with Phosphodiesterase Inhibitors After Repair of Tetralogy of Fallot

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(see Development Process section)

Target Population

Inclusions: These guidelines are intended for use in infants and children who have undergone complete repair of Tetralogy of Fallot (TOF).
Exclusions: The guidelines do not address all considerations needed to manage those with the following:

- Significant hypotension.

Target Users

Include, but are not limited to (in alphabetical order):

- Clinicians caring for infants and children with Tetralogy of Fallot (TOF)
- Patient Care staff, including:
  - nurse practitioners
  - nurses
  - pharmacists
- Residents

Introduction

References in parentheses ( ) Evidence strengths in [ ] (See last page for definitions)

Challenges in the management of infants and children following TOF repair include: right ventricular hypertrophy.

The objectives of this guideline are to:

- improve cardiac output following TOF repair
- decrease length of stay required in cardiac intensive care unit (CICU)

Right ventricular hypertrophy, a hallmark of Tetralogy of Fallot (TOF), causes what has been termed "restrictive physiology" and diastolic dysfunction in some patients in the early period after TOF repair. A poorly compliant, restrictive right ventricle is thus a common cause of low cardiac output after TOF repair. Restrictive physiology after TOF repair is defined by the need to maintain high central venous pressure (CVP) to maintain cardiac output. The high CVP causes third space accumulations of fluid in the pleural and peritoneal cavities as well as peripheral edema. Because of the limited cardiac output, this fluid is not easily removed by diuretic agents and can interfere with mechanical ventilation and organ function. Restrictive physiology has been specifically associated with clinical evidence of low cardiac output, slower post-operative recovery and persistent pleural effusions. although it may predict a more favorable long-term outcome. *(Norgard 1996 [C], Cullen 1995 [C]).*

Inamrinone and milrinone are phosphodiesterase inhibitors (PDEI). They prevent the breakdown of cyclic AMP and thereby increase activity of a number of cellular systems that are crucial for calcium handling and cardiomyocyte contraction and relaxation. Clinically, PDEI improve myocardial contractility, diastolic relaxation, and cause a decrease in afterload through vasodilation. These agents therefore improve cardiac index and lower left ventricular filling pressure after cardiopulmonary bypass, even in comparison to other inotropes or vasodilators. *(Hamada 1999 [B], Laitinen 1999 [B], Kikura 1998 [C], Bailey 1997 [C], Chang 1995 [C], Lynn 1993 [C], Berner 1990 [C]).*

Of particular interest in the post-operative TOF patient is the potential effect of these agents on right ventricular relaxation and therefore the CVP needed to maintain cardiac output. The effects of PDEI on the right ventricle have not been well-studied, but PDEI improve right ventricular contractility and improve left ventricular diastolic function in some animal models of cardiac disease and dysfunction. *(Saal 1994 [C], Werner 1995 [F], Pagel 1993 [F]).* A randomized controlled trial of the effects of inamrinone on right ventricular diastolic function after repair of TOF is currently underway at CHMC.

Because of the potential improvements in right ventricular diastolic function, and pending further data, phosphodiesterase inhibition is considered potentially useful treatment restrictive right ventricular physiology after TOF repair. These recommendations are based on

the most current scientific information and are subject to update at the conclusion of our current study.

In developing this guideline, we recognize the paucity of large-scale studies with direct bearing on this particular focus population. The specific recommendations in this guideline are drawn from directly applicable studies where possible, but are largely extrapolated from smaller studies, and from studies more indirectly related to the present issues.

Guideline Recommendations

Clinical Assessments

1. It is recommended that cardiac index be supported to maintain normal to minimally elevated right atrial pressure or CVP (5-15 mmHg) with evidence of adequate tissue and organ perfusion as defined by physical exam, urine output >1cc/Kg/min and no ongoing metabolic acidosis or lactic acidemia.
   Note 1: Ongoing metabolic acidosis caused by the continued production of lactic acid has been associated with a poor outcome following cardiac surgery in infants and children. *(Charpie 2000 [C], Munoz 2000 [C])*
   Note 2: Continuous monitoring of arterial blood pressure via an arterial line is recommended. *(Local Expert Consensus [E]).*
   Note 3: Continuous monitoring of right and left atrial pressures with transthoracic or internal jugular/subclavian vein catheters is recommended

Laboratory Studies

2. It is recommended that in order to monitor for metabolic acidosis and lactic acidemia a renal panel be obtained on arrival to CICU and every AM until transfer from the CICU and lactate be obtained every 4 hours for the first 24 hours.
   Note: Ongoing metabolic acidosis caused by the continued production of lactic acid has been associated with a poor outcome following cardiac surgery in infants and children. *(Charpie 2000 [C], Munoz 2000 [C])*

Treatment Recommendations

Medications

3. It is recommended that milrinone be considered for any patient following TOF repair to prevent the occurrence of low cardiac output due to restrictive right ventricular physiology after TOF repair.
   Note: There is no direct evidence to suggest that routine use of milrinone following TOF repair improves outcome, but this recommendation is based on evidence that restrictive right ventricular physiology is associated with increased morbidity after TOF repair and that PDEI improves left ventricular diastolic function. *(Hoffman 2003 [A], Hoffman 2002 [A], Norgard 1996 [C], Chang 1995 [C], Cullen 1995 [C], Berner 1990 [C], Werner 1995 [F], Pagel 1993 [F])*

4. It is recommended that milrinone be started for any patient with a right atrial pressure >15mmHg or with signs or symptoms of low cardiac output. The recommended loading dose of milrinone is 50 mcg/Kg over 30-60 minutes, followed by an infusion at 0.375-0.75 mcg/Kg/min.
   Note 1: : Direct comparison has failed to show any significant hemodynamic differences between inamrinone and milrinone. There are anecdotal reports of less thrombocytopenia with milrinone, so milrinone may be particularly useful for patients in whom phosphodiesterase inhibition is desired who are thrombocytopenic or following surgery *(Hamada 1999 [B], Rathmell 1998 [B]).*
   Note 2: If hypotension develops, blood pressure support with other inotropic/vaspressor agents may be necessary *(Lynn 1993 [C]).*

Members of Cardiac Clinical Pathway Team 2006

CHMC Physicians

Peter Manning , MD	(Cardiac Surgery)
Catherine Dent, MD	(Cardiac Intensive Care)
William Border, MD	(Cardiology)
James Spaeth MD	(Anesthesia)
Michael Alice Moga, MD	(Cardiology/Fellow)

Patient Services

Karen Uzark, PhD, CPNP	(Cardiology)
Susan Ryckman, MS, CPNP	(Cardiac Services)
Betsy Adler, MS, PNP	(Cardiac Services)
Christa Barlow, CNP	(Cardiac Surgery)
Karen Jones, MS, PNP	(Cardiac Surgery)
Melissa Magness, RN	(Cardiac ICU)
Tammy Lingsch, RN	(A6 Central)
Cynthia Wedekind, Pharm D	(Clinical Pharmacy)
Jenni Raake, RRT	(Respiratory Care)

Division of Health Policy & Clinical Effectiveness Support

Eloise Clark, MPH
Danette Stanko, MA, MPH, Epidemiologist
Kate Rich, Lead Decision Support Analyst
Carol Frese, RN, Medical Reviewer
Eduardo Mendez, RN, MPH, Dir. Evidence-Based Care

Development Process

The process by which this guideline was developed is documented in the Guideline Development Process Manual; a Team Binder maintains minutes and other relevant development materials. The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using the grading scale that follows, and examined current local clinical practices.

To select evidence for critical appraisal by the group for the update of this guideline, the Medline, EmBase and the Cochrane databases were searched. Evidence from 2000 and before was verified for inclusion in the guidelines. Evidence from 2001 through 2005 were reviewed to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to inotropic support with phosphodiesterase inhibitors following TOF repair and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. July, 2000 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

CCHMC Grading Scale			
M	Meta-analysis or Systematic Review	S	Review article
A	Randomized controlled trial: large sample	E	Expert opinion or consensus
B	Randomized controlled trial: small sample	F	Basic Laboratory Research
C	Prospective trial or large case series	L	Legal requirement
D	Retrospective analysis	Q	Decision analysis
O	Other Evidence	X	No evidence

A search using the above criteria was conducted for dates of January, 2006 through July, 2006. No relevant articles were found that would require changes to the January, 2006 version of the recommendations.

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline. Experience with the implementation of earlier publications of this guideline has provided learnings which have been incorporated into this revision. Hemodynamic stability and length of stay in the CICU are outcome measures that are monitored and reviewed quarterly. Once the guideline has been in place for four years, the development team reconvenes to explore the continued validity of the guideline. This phase can be initiated at any point that evidence indicates a critical change is needed.

Recommendations have been formulated by a consensus process directed by best evidence, patient and family preference and clinical expertise. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

The guidelines have been reviewed and approved by clinical experts not involved in the development process, senior management, Risk Management & Corporate Compliance, other appropriate hospital committees, and other individuals as appropriate to their intended purposes. The guideline was developed without external funding.

Copies of this Evidence-based Care Guideline (EBCG) and its companion documents are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm Examples of approved uses of the EBCG include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence-based care guidelines;
- hyperlinks to the CCHMC website may be placed on the organization's website;
- the EBCG may be adopted or adapted for use within the organization, provided that CCHMC receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any EBCG, or its companion documents, adopted, adapted, implemented or hyperlinked by the organization is appreciated.

Important Information

NOTE: These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

For more information about this guideline and the supporting evidence contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4770 or thc@cchmc.org .

REFERENCES

Note: When using the electronic version of this document, "☜" refers to journal articles that have a hyperlink to the abstract.

Bailey, J. M., B. E. Miller, et al.: A comparison of the hemodynamic effects of amrinone and sodium nitroprusside in infants after cardiac surgery. *Anesth Analg*, 84(2): 294-8., 1997, *[C]* ☜

Berner, M., C. Jaccard, et al.: Hemodynamic effects of amrinone in children after cardiac surgery. *Intensive Care Med*, 16(2): 85-8, 1990, *[C]* ☜

Chang, A. C., A. M. Atz, et al.: Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med*, 23(11): 1907-14., 1995, *[C]* ☜

Charpie, J. R., M. K. Dekeon, et al.: Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg*, 120(1): 73-80., 2000, *[C]* ☜

Cullen, S., D. Shore, et al.: Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot. Restrictive physiology predicts slow postoperative recovery. *Circulation*, 91(6): 1782-9., 1995, *[C]* ☜
output state in some patients after complete repair of tetralogy of Fallot.

Hamada, Y., K. Kawachi, et al.: Effects of single administration of a phosphodiesterase III inhibitor during cardiopulmonary bypass: comparison of milrinone and amrinone. *Jpn Circ J*, 63(8): 605-9., 1999, *[B]* ☜

Hoffman, T. M., G. Wernovsky, et al.: Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics. *Am Heart J*, 143(1): 15-21, 2002, *[A]* ☜

Hoffman, T. M., G. Wernovsky, et al.: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation*, 107(7): 996-1002, 2003, *[A]* ☜

Kikura, M., J. H. Levy, et al.: A bolus dose of 1.5 mg/kg amrinone effectively improves low cardiac output state following separation from cardiopulmonary bypass in cardiac surgical patients. *Acta Anaesthesiol Scand*, 42(7): 825-33., 1998, *[C]* ☜

Laitinen, P., J. M. Happonen, et al.: Amrinone versus dopamine and nitroglycerin in neonates after arterial switch operation for transposition of the great arteries. *J Cardiothorac Vasc Anesth*, 13(2): 186-90., 1999, *[B]* ☜

Lynn, A. M., G. K. Sorensen, et al.: Hemodynamic effects of amrinone and colloid administration in children following cardiac surgery. *J Cardiothorac Vasc Anesth*, 7(5): 560-5., 1993, *[C]* ☜

Munoz, R., P. C. Laussen, et al.: Changes in whole blood lactate levels during cardiopulmonary bypass for surgery for congenital cardiac disease: an early indicator of morbidity and mortality. *J Thorac Cardiovasc Surg*, 119(1): 155-62., 2000, *[C]* ☜

Norgard, G., M. A. Gatzoulis, et al.: Relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of Fallot. Implications for long-term outcome. *Circulation*, 94(12): 3276-80., 1996, *[C]* ☜

Pagel, P. S., D. A. Hettrick, et al.: Amrinone enhances myocardial contractility and improves left ventricular diastolic function in conscious and anesthetized chronically instrumented dogs. *Anesthesiology*, 79(4): 753-65., 1993, *[F]* ☜

Rathmell, J. P., R. C. Prielipp, et al.: A multicenter, randomized, blind comparison of amrinone with milrinone after elective cardiac surgery. *Anesth Analg*, 86(4): 683-90., 1998, *[B]* ☜

Saal, J. P., R. Habbal, et al.: Effects of piroximone on the right ventricular function in severe heart failure patients. *Intensive Care Med*, 20(5): 341-7., 1994, *[C]* ☜

Werner, H. A., M. J. Herbertson, et al.: Amrinone increases ventricular contractility and diastolic compliance in endotoxemia. *Am J Respir Crit Care Med*, 152(2): 496-503., 1995, *[F]* ☜

