



Evidence-Based Care Guideline
**Prevention of Thromboembolism
 after Cavopulmonary Anastomosis
 (Bidirectional Glenn and Fontan operations)**
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Introduction

Children undergoing staged surgical palliation for single ventricle are at increased risk of intravascular and/or intracardiac thrombus formation and thromboembolic complications. The bidirectional Glenn operation (partial cavopulmonary anastomosis) is a vascular anastomosis in which pulmonary blood flow is supplied directly by systemic venous return from the superior vena cava. The modified Fontan operation (total cavopulmonary anastomosis) results in pulmonary blood flow supplied from direct anastomosis of the superior *and* inferior vena cava to the pulmonary arteries. These patients may develop significant sequelae from thromboembolism in the pulmonary or systemic circulation (Coon 2001 [D]).

Unfortunately, although the problem of thromboembolism has been recognized, clinicians have not systematically evaluated the use of antithrombotic therapy (Monagle 1998 [S]). A controversy exists with respect to the most appropriate choice of pharmacologic regimen (Coon 2001 [D]). To date, no prospective, randomized controlled trials have addressed this question. Monotherapy with either aspirin or warfarin is most commonly implemented. In developing this guideline, we recognize the paucity of large-scale studies with direct bearing on this particular pediatric 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.

Etiology

Incidence

Since the bidirectional Glenn procedure is a relatively short-term, intermediate step en route to the final Fontan operation, data regarding incidence of thromboembolic complications is limited by fewer patient years of follow-up. Review of the literature reveals several case reports of these complications following the bidirectional Glenn (Bradley 1996 [D], Imanaka 1999 [O]). The incidence of symptomatic thromboembolism following the Fontan operation and its modifications is between 3-5%, while asymptomatic thrombus found by transesophageal echocardiograms can occur in as many as 33% of such patients (Cheung 2005 [D], Balling 2000 [D], Day 1995 [D], Rosenthal 1995 [D], Jahangiri 1994 [D], Fyfe 1991 [D], Stumper 1991 [D]).

Risk Factors

Risk factors for thrombus formation include hematologic, anatomic and hemodynamic factors in this patient population with single ventricle anomalies (Mahnke 2005 [D], Seipelt 2002 [D]). Coagulopathies have been documented in individuals with cyanotic heart disease (Ferencz 1984 [S]). Abnormalities have been noted in vitamin K dependent factors such as prothrombin, factor VII and factor IX. Deficiencies in protein C, protein S, and factor VII have been reported following Fontan-type repairs (Jahangiri 1997 [O]). Additionally, abnormalities in factor V Leiden and antiphospholipid antibodies have been noted in populations with cyanotic heart disease (Kohlhase 1996 [D]). Finally, polycythemia is often seen in cyanotic individuals, potentiating thrombus formation.

Anatomic and hemodynamic features such as synthetic conduits or patches and non-pulsatile, low velocity flow may predispose patients to thrombus formation. During the postoperative period, these patients often have central venous lines, arrhythmias and/or low cardiac output which further predispose them to thrombus (Shirai 1998 [D], Fogel 1996 [D], Petaja 1996 [D], Wilson 1995 [O]). "Paradoxical" emboli may occur in the setting of an intracardiac right-to-left shunt.

Target Population

Inclusions: These guidelines are intended for use in infants and children who have undergone the bidirectional Glenn or modified Fontan operation.

Exclusions: The guidelines do not address all considerations needed to manage those with the following:

- coagulopathy
- salicylate allergy

Guideline Recommendations

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

Assessment

1. Preoperative history and physical exam
 - patient or family history of coagulopathy, salicylate allergy or viral exposures
 - physical findings suggestive of the coagulopathy, e.g. petichiae, purpura
2. Laboratory assessment
 - preoperative CBC with platelets
 - coagulation studies if history or physical suggests abnormalities and prior to initiation of warfarin.

Note: Available evidence does not support routine screening for coagulopathies.

Treatment Recommendations

1. It is recommended that patients begin antithrombotic aspirin therapy upon resuming oral intake following the bidirectional Glenn or Fontan operation (*Jacobs 2002 [C/D], Barker 2005 [D], Local Expert Consensus [E]*).
Note: Both aspirin and warfarin reduce the risk of thromboembolism. Although the choice of pharmacologic regimen remains controversial, the risk of hemorrhagic complications in children, compounded by the difficulties of monitoring and maintaining appropriate anticoagulation on warfarin, favors the use of aspirin for antithrombotic therapy (*Barker 2005 [D]*). The two appear equivalent in the prevention of myocardial infarction and stroke in the setting of atherosclerosis (*Anand 1999 [M]*) however in pediatric and adult populations, the risk of hemorrhagic complications is higher with warfarin

therapy (*Anand 1999 [M], Hart 1999 [M], Rao 1989 [D], Bradley 1985 [D]*).

2. It is recommended that warfarin therapy be considered in patients at higher risk due to the following factors:
 - previous thromboembolic complications (*Kaulitz 2005 [D]*)
 - poor ventricular function (*Kaulitz 2005 [D], Al-Khadra 1998 [D]*)
 - extracardiac Fontan connections (*Shirai 1998 [D], Petrossian 1999 [E], Laschinger 1996 [E]*)
 - pulmonary stump (*Oski 1996 [D]*)
 - atrial tachyarrhythmias (*Cheung 2005 [D], Kaulitz 2005 [D]*)

Note: Children with Fontan operations require a lower warfarin dosage than children receiving warfarin after other types of congenital heart surgery for a similar degree of anticoagulation (*Streif 1999 [C]*). The recommended starting dose is 0.1 mg/kg to maintain a target INR range of 2.0 to 3.0.

3. It is recommended that alternative antithrombotic therapy be considered during periods when aspirin therapy is temporarily contraindicated (reference See note).
Note: Examples of aspirin contraindications may include exposure to influenza or varicella, receipt of varicella vaccine (*AAP 2003 [O]*) and elective surgical or dental procedures associated with bleeding. Risks of discontinuation of aspirin versus the risk of Reye's syndrome or bleeding associated with dental or surgical procedures must be considered by the clinician and family on an individual basis.

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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 to the January, 2006 were reviewed to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to prevention of thromboembolism or anticoagulation following cavopulmonary anastomosis 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, 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. December, 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	O	Other evidence
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
S	Review article	X	No evidence

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 by clinical experts not involved in the development process, senior management, and other individuals as appropriate to their intended purposes. The guideline is based, in part, on three independent reviews performed by members of Evidence-Based Care Group of Health Policy & Clinical Effectiveness at Cincinnati Children's Hospital and Medical Center (CCHMC) using AGREE criteria (Appraisal of Guidelines for Research and Evaluation). 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;
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- 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 guideline 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 recommendations to meet the specific and unique requirements of individual patients. Adherence to this guideline 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 these guidelines and their supporting evidences contact the Heart Center, Division of Cardiothoracic Surgery at 513-636-4770 or thc@cchmc.org.

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