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# Central venous line-related thrombosis in children with congenital heart disease: Diagnosis, prevalence, outcomes and prevention

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**Abstract**

Thrombosis is a newly emerging clinical entity in children who are surviving previously lethal underlying disorders such as congenital heart disease. Children with congenital heart disease are the largest identifiable pediatric patient group with thrombosis accounting for 1/3 of children with thrombosis. In children, the most important risk factor for venous thromboembolic events is the use of central venous lines. Therefore, the authors reviewed the literature in what is known about the diagnosis, prevalence, outcomes and prevention of central venous line-related thrombosis in children with congenital heart disease.

Ultrasound and venography must be performed to diagnose or exclude the presence of venous thrombosis in venous system in the upper body. In the studies to date in children with congenital heart disease, only echocardiograms, linograms and ultrasounds have been performed to assess thrombosis. Therefore, the prevalences of thrombosis are an underestimate. Also, both prevalences of thrombosis and prevalences of outcomes are influenced by the study design with retrospective reviews being the weakest study design as compared to prospective studies. The prevalences of thrombosis where as low as 1.1% in retrospective studies. In the two prospective studies, the prevalences were 20% and 42.5%. The reported mortality in children with thrombosis was substantial, between 40% and 50% in two retrospective reviews. In a majority of the deaths, the thrombotic event contributed or was causal to mortality. In 20% of the surviving children, there was varying relatively mild to severe debilitating sequela directly related to the thrombotic event.

There is mounting evidence that children with congenital heart disease are at an increased for thrombotic events that result in significant mortality and morbidity. However, the true prevalence of thrombosis and the associated mortality and morbidity related to thrombosis needs to be determined in adequately powered prospective studies using sensitive radiographic tests.


*Keywords:* Central venous line; Thrombosis; Children; Congenital heart disease

## 1. Introduction

Congenital heart disease (CHD) is the most common congenital abnormality accounting for 30% of total congenital abnormalities. The prevalence of severe CHD requiring surgical intervention is 6/1000 live births [1]. Therefore, in North America, 26,000 new cases of CHD requiring surgical intervention occur per year. In the last two decades, advances in cardiological diagnosis, surgical techniques, anaesthesia, cardiopulmonary bypass and intensive care medicine have resulted in major decreases in mortality in children with CHD. Population-based data from the USA have shown that in the last 20 years mortality from CHD has decreased 40% from 2.54 to 1.54 per 100,000 with most of the gains being in children under 5 years of age [2]. Therefore, a majority of these patients survive until adulthood creating a "new" patient population of adults with CHD [3].

Children born with CHD are surviving to adulthood and are living with the secondary complications related to their interventional procedures. One of the most serious complications is thrombosis. Thrombosis is a newly emerging clinical entity in children who are surviving previously lethal underlying disorders such as CHD. Children with

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CHD are the largest identifiable pediatric patient group accounting for 1/3 of children with thrombosis [4].

The decrease in mortality in CHD is partially attributable to the use of central venous catheters (CVL) in the post-operative period. Most children have multiple exogenous risk factors of venous thromboembolism (VTE) related to their primary disease or its treatment. In the general pediatric patient population, the most important risk factor for VTE is the use of CVL, which are present in 30–70% of children with VTE [5–9]. Central venous lines appear to be casual risk factors for VTE, based on the close anatomical relationship found between catheters and thrombi [10] Pathogenic mechanisms of CVL-related VTE include vessel wall trauma at insertion site, obstruction of venous flow, endothelial damage by CVL adhering to the venous wall, and the intravascular presence of a foreign surface [11,12]. About two thirds of VTE in children occur in the upper venous system reflecting the most common location of CVL placement [6].

The following paper will describe what is known about the diagnosis, prevalence, outcomes and prevention of CVL-related VTE in children with CHD.

## 2. Diagnosis of central venous line-related thrombosis in children with CHD

Diagnosis of VTE in children represents a challenging area of clinical medicine. However, a clear understanding of this aspect of VTE in children is essential in order to critically appraise the literature and determine the designs of future studies. The following section reviews what is known about the accuracy of clinical diagnosis of VTE and the appropriate radiological tests for diagnosis of VTE.

### *2.1. Clinical diagnosis of venous thrombosis*

Diagnosis of VTE is usually based on clinical suspicion of presence of VTE based on symptoms like swelling, erythema, skin discoloration, increased warmth, pain, tenderness, venous distension, presence of subcutaneous collateral veins, or loss of CVL patency [13]. The fact that the clinical diagnosis of thrombosis is both insensitive and non-specific is well recognised [14,15]. In children, clinically significant VTE in children are not associated with the classic symptoms of thrombosis in adults such as edema, pain and skin discoloration. Factors that likely influence whether there is clinical manifestation of thrombosis are the location, the acuteness of thrombosis development and underlying disease which may masks symptoms of thrombosis. Central line-related VTE are mostly located in the central venous system where obstruction may not result in obvious swelling of a limb. Development of CVL-related thrombosis is usually gradual, permitting collaterals to form. The development of significant collaterals minimizes the acute symptoms of arm, neck or facial swelling while the upper deep venous system is gradually and silently being destroyed. Finally, as these are extremely complicated patients, symptoms of thrombosis are frequently not recognized or may be attributed to underlying disease in children. Therefore, in children with asymptomatic thrombosis, major destruction of the venous system may occur which results in loss of venous access, risk of sepsis and a life-long increased risk for recurrence. In addition, a real risk for pulmonary embolism occurs in the presence of asymptomatic thrombosis. Therefore, objective testing by radiographic tests is necessary to establish or rule out the presence of VTE.

### *2.2. Radiographic tests for diagnosis of venous thrombosis*

#### *2.2.1. Venography*

Venography is recognized as the reference standard for diagnosis of VTE in the lower and upper extremities [16,17]. Diagnosis of VTE is based on visualization of intraluminal filling defects or non-visualization in combination with a sudden cut-off of a deep vein present or limited or no flow in the deep venous system in combination with collateral vessels [16]. Venography allows quantification of venous occlusion and identification of collateral veins. Although venography is the gold standard, it is not ideal because of its invasive nature, technical demands, costs, adverse effects associated with contrast media, and radiation exposure [18–20].

#### *2.2.2. Ultrasound*

Several studies in adults have demonstrated that ultrasound has excellent sensitivity and specificity compared to venography for diagnosis of proximal VTE in the lower extremities [21,22]. In children, ultrasound has been shown to be insensitive for detection of VTE in the upper system [23]. The most reliable criteria of ultrasound for the presence of VTE are non-compressibility of the venous lumen while compressibility excludes presence of VTE. Other ultrasound criteria such as visualization of echogenic thrombus or alteration of Doppler flow were found to be less sensitive and specific for VTE [21]. Ultrasound has advantages compared to venography in that ultrasound is relatively easy to perform, universally available, and non-invasive. However, ultrasound can mistake large collateral veins for the normal venous anatomy [24].

#### *2.2.3. Echocardiography*

Echocardiography uses the same technical principles as peripheral vascular ultrasound for detection of VTE except that venous compression is not performed. However, different views of the central venous system are used in echocardiography, and therefore, it is reasonable to review the diagnostic utility of echocardiography as separate from peripheral ultrasound.

Several studies have used echocardiography to screen for CVL-related VTE in the central venous system and right heart reporting prevalences of 2–16% [25–30]. Trans-esophageal echocardiography was demonstrated to be more