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RECOMMENDATIONS AND GUIDELINES

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Official communication of the SSC: Recommendations for future research in catheter-related arterial thrombosis in children

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Abstract

Catheter-related arterial thrombosis (CAT) are increasingly recognized in infants and children. Insufficient data are available on the incidence, risk factors, treatment and outcome of these thrombotic events. This work provides consensus recommendations for future research on catheter-related arterial thrombosis in the paediatric population. In particular, future studies should distinguish between CAT due to indwelling arterial catheters or cardiac catheterization in two different subpopulations (neonates and older children). Further studies should investigate sensitivity and specificity of clinical signs and symptoms for early screening of CAT and the most appropriate imaging modality, focusing on ultrasound due to better feasibility in the very young pediatric population. Adequately powered, well-designed clinical trials should investigate efficacy and safety of different treatment and prevention strategies as well as the risk for and the optimal management of short- and long-term complications.

KEYWORDS
arterial thrombosis, catheter, child, pediatric

Essentials

- Arterial clots in children mostly develop from indwelling or cardiac catheters.
- Catheter-related arterial clots can cause severe immediate and long-term complications.
- Only sparse data from clinical trials and no guidelines on optimal diagnostic and treatment modalities are available.
- The present work provides recommendations for dedicated future research on catheter-related arterial clots in children.

1 | BACKGROUND AND RATIONALE

Catheter-related arterial thrombosis (CAT) is increasingly recognized in children requiring monitoring in intensive care units or during surgery, and in children with congenital heart disease undergoing cardiac catheterization. CAT can cause serious acute signs and symptoms but also long-term complications such as leg length difference, claudication, and loss of arterial access for future diagnostic and therapeutic interventions.[1-3] However, there remains a paucity of data from well-designed studies on the incidence, risk factors, optimal diagnosis and treatment modalities, outcomes, and prognostic factors of pediatric CAT.

In order to advance knowledge on CAT in children, the Pediatric and Neonatal Thrombosis and Haemostasis Subcommittee of the International Society on Thrombosis and Hemostasis (ISTH) established a pediatric CAT Working Group in 2013. Specific tasks of the group were to: systematically review the existing literature on pediatric CAT; identify instances of heterogeneity in definitions employed across studies; assess gaps in knowledge; and make recommendations for standardization of definitions and key objectives for future research. The Working Group and collaborators have recently completed a systematic review of pediatric CAT including studies from 1945 to 2014,[4] whose key findings informed the present work, and are summarized below:

- Two types of pediatric CAT were distinguished: (A) CAT from indwelling arterial catheters (IC-CAT, principally affecting neonates) and (B) CAT from cardiac catheterization (CC-CAT, principally affecting neonates with known/suspected cardiac disease).
- The cumulative incidence of CAT among patients with indwelling arterial catheters (IC-CAT) was 24%, and that among for CC-CAT was 11%. However, incidence rates varied widely among studies depending on whether CAT was diagnosed based on surveillance imaging (including both symptomatic and asymptomatic CAT) or only in the presence of clinical signs or symptoms (symptomatic CAT).
- Prematurity (70%), respiratory distress syndrome (56%), asphyxia (35%), infection (32%), and cardiac disease (33%) were commonly identified factors/co-morbidities associated with IC-CAT. Risk factors for CC-CAT included younger age and body weight less than 10 kg.
- While CAT was frequently diagnosed by Doppler ultrasound, and less commonly by conventional angiography, studies comparing diagnostic performance among these and other imaging modalities are lacking.
- Antithrombotic treatment approaches varied widely between no antithrombotic therapy, the use of anticoagulant and/or antiplatelet therapy, and acute thrombolysis or thrombectomy. Use of thrombolysis (71%) or thrombectomy (31%) was highly prevalent among published studies, also potentially reflecting some reporting bias.
- With regard to outcomes, studies have mainly focused on acute mortality (3% among prospective studies, including mortality attributed to underlying disease) and on thrombus resolution; data on long-term outcomes and predictors of outcome (by which to optimally design future interventional trials) were sparse, even among prospective studies.

2 | METHODS

The recommendations provided here are based upon presentations made at the Pediatric and Neonatal Thrombosis and Haemostasis Subcommittee meetings held during the 2014, 2015, and 2016 meetings of the ISTH. The pediatric CAT Working Group was comprised of M. Albisetti (Working Group lead), N. Goldenberg (SSC subcommittee co-chair representative), M. Rizzi, M. Bonduel, and S. Revel-Vilk.

3 | RECOMMENDATIONS

1. Future studies should better distinguish patients with IC-CAT and patients with CC-CAT, in order to achieve greater standardization in disease/subpopulation definitions. This will limit heterogeneity across studies, permitting more robust meta-analyses in the future.
2. Given the substantive mortality and potential morbidities associated with pediatric CAT—yet the significant limitations in current knowledge of risk factors, optimal diagnosis and treatment strategies, treatment-outcomes relationships and other prognostic factors—a high priority should be placed on the design and conduct of cooperative prospective cohort and interventional studies in pediatric CAT. Specific study aims/investigations should evaluate:
   a. The sensitivity and specificity of early screening for CAT by means of clinical signs and symptoms compared with Doppler ultrasonography.
   b. The most appropriate imaging modality, in terms of sensitivity, specificity and acceptability in neonates and children. Studies should focus on ultrasound, which is noninvasive and more feasible in the very young population rather than magnetic resonance angiography or conventional angiography, and avoids the radiation exposure of computed tomography with angiography.
   c. Risk factors for CAT including, for example, duration of catheter insertion, catheter type, and thrombophilia laboratory testing findings. Studies should focus on establishing predictors of poor outcome and the role of targeted prophylaxis.
   d. Short-term outcome (including limb ischemia, amputation, skin necrosis) in neonates and children with IC-CAT and CC-CAT as such acute symptoms may require aggressive therapeutic intervention and greatly impact morbidity and mortality.
   e. Long-term outcomes (including functional outcomes and quality of life) as well as predictors of outcome in neonates

and children with IC-CAT and CC-CAT. As children grow and mature through the developmental stages, it will be useful to develop, adapt, and validate specific instruments/measures relevant to the sequelae of CAT for different pediatric age groups. In turn, findings on outcomes and prognostic stratification from such studies will be critical to the optimal design of future interventional trials in IC-CAT and CC-CAT.

f. The optimal intensity, duration, and modality of antithrombotic therapy, including thrombolysis and thrombectomy, for IC-CAT and CC-CAT in children. Rather than extrapolation from adult practice, this will require the conduct of well-designed, pediatric clinical trials that are adequately powered to determine differences in efficacy and safety, including both short- and long-term outcomes.

g. Optimal prevention strategies against IC-CAT and CC-CAT in children. This too, will require devoted pediatric clinical trials powered to demonstrate comparative efficacy and safety.

3. Definitions of primary and secondary outcome measures to be employed in future studies investigating diagnostic, treatment, and long-term complications of CAT should be standardized. This approach will require interdisciplinary cooperation in order to cover all specific needs and features of newborns, and will permit comparisons across studies. Following the model of the previously published communication of the SSC on efficacy and safety endpoints for clinical trials in deep vein thrombosis in children,[5] the Working Group recommends adopting the outcome definitions in pediatric CAT clinical research listed in Table 1.

4 | DISCUSSION

The present recommendations represent an effort to provide evidence-based guidelines for CAT in children as an emerging complication of pediatric tertiary care associated with significant morbidity and mortality. Three major key points from these recommendations warrant emphasis and discussion.

CAT mostly affects neonates and very young infants with severe medical conditions—a very particular vulnerable population. Trial designs and standardization of definitions in CAT will have to address the specific features and needs of this very young and often medically complex population. In particular, trials assessing optimal intensity, duration, and modality of antithrombotic therapy and optimal prevention strategies may warrant adaptation of primary and secondary outcome measures.

The recommended future research strategy will investigate two type of CAT, involving two different subpopulations. While IC-CAT occurs in neonates and young infants with several underlying diseases treated in intensive care units, CC-CAT will involve neonates and young infants undergoing cardiac catheterization for congenital heart disease. It is anticipated that recommended studies may warrant inclusion of different/additional objectives. In specific regard to IC-CAT, additional partnership with the ISTH should be sought between pediatric intensivists, especially neonatology societies. For CC-CAT, partnership with the ISTH should be sought from pediatric cardiology and cardiothoracic surgery societies.

The recruitment of very young children in interventional trials is more challenging than for adults or older children because of the even greater perceived vulnerability of infants, and hence an understandable

TABLE 1 Definitions of primary and secondary outcome measures in pediatric CAT

Endpoints	Primary outcome	Secondary outcome
Efficacy	• Contiguous progression or recurrence	• Degree of radiological resolution over time • CAT-specific and all-cause mortalities • Sequelae of arterial insufficiency (limb shortening/atrophy, claudication, amputation) over the pediatric age span • Functional outcomes (QoL)
Safety	• Major bleeding: – fatal bleeding – bleeding with decrease in Hgb ≥ 20 g L^{-1} in a 24-h period – retroperitoneal bleeding – intracerebral bleeding – bleeding requiring surgical intervention in operating rooms	• CRNM bleeding: – overt bleed requiring blood product transfusion, not directly attributable to the patient's underlying condition – bleeding requiring medical or surgical intervention to restore hemostasis, other than in operating rooms – Other bleeding for which medical attention has been sought (e.g., emergency department, urgent care, or non-routine outpatient clinic visit) • Minor bleeding: – any overt macroscopic evidence of bleeding not fulfilling above criteria for major or clinical relevant bleeding

CAT, catheter-related arterial thrombosis; CRNM, clinically relevant, non-major; Hgb, hemoglobin; QoL, quality of life.

reticence of parents and clinicians to enroll infants on trials that are deemed to pose more than minimal risk. Collaborative multinational groups and/or pediatric clinical trials networks that pool quality data and resources are therefore an essential strategy to overcome the problem of underpowered trials due to low accrual in young children. In addition, a prioritization strategy of recommended studies starting from rigorously designed and executed multicenter pediatric cohort studies that deeply characterize pediatric CAT (patient demographics and comorbidities, diagnostic features of thrombosis, treatments and durations administered, short- and long-term outcomes, and prognostic factors) will inform the design and conduct of risk-stratified randomized trials on treatment and prophylaxis of CAT.[6]

In conclusion, this article provides consensus recommendations for future research in pediatric CAT. These recommendations will need to be updated as evidence accrues and interdisciplinary collaborations ensue.

RELATIONSHIP DISCLOSURE

The authors report nothing to disclose.

AUTHOR CONTRIBUTIONS

M. Albisetti was co-chair of the pediatric CAT Working Group. She was substantially involved in the concept, design, writing, and final approval of the manuscript. M. Rizzi was an active member of the pediatric CAT Working Group. He was substantially involved in the concept, design, review and final approval of the manuscript. M. Bonduel was an active member of the pediatric CAT Working Group. She was substantially involved in the concept, design, review, and final approval of the manuscript. S. Revel-Vilk was an active member of the pediatric CAT Working Group. She was substantially involved in the concept, design, review, and final approval of the manuscript. N. Goldenberg was co-chair of the pediatric CAT Working Group. He was substantially involved in the concept, design, writing, and final approval of the manuscript.

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