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RECOMMENDATIONS AND GUIDELINES

Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness

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Abstract

Background: Observational studies indicate that children hospitalized with COVID-19-related illness, like adults, are at increased risk for venous thromboembolism (VTE). A multicenter phase 2 clinical trial of anticoagulant thromboprophylaxis in

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children hospitalized with COVID-19-related illness has recently been initiated in the United States. To date, there remains a paucity of high-quality evidence to inform clinical practice world-wide. Therefore, the objective of this scientific statement is to provide consensus-based recommendations on the use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illnesses, and to identify priorities for future research.

Methods: We surveyed 20 pediatric hematologists and pediatric critical care physicians from several continents who were identified by Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee leadership as having experience and expertise in the use of anticoagulant thromboprophylaxis and/or the management of COVID-19-related illness in children. A comprehensive review of the literature on COVID-19 in children was also performed.

Results: Response rate was 90%. Based on consensus of expert opinions, we suggest the administration of low-dose low molecular weight heparin subcutaneously twice-daily as anticoagulant thromboprophylaxis (in the absence of contraindications, and in combination with mechanical thromboprophylaxis with sequential compression devices, where feasible) in children hospitalized for COVID-19-related illness (including the multisystem inflammatory syndrome in children [MIS-C]) who have markedly elevated D-dimer levels or superimposed clinical risk factors for hospitalassociated VTE. For children who are clinically unstable or have severe renal impairment, we suggest the use of unfractionated heparin by continuous intravenous infusion as anticoagulant thromboprophylaxis. In addition, continued efforts to characterize VTE risk and risk factors in children with COVID-19, as well as to evaluate the safety and efficacy of anticoagulant thromboprophylaxis strategies in children hospitalized with COVID-19-related illness (including MIS-C) via cooperative multicenter trials, were identified among several key priorities for future research.

Conclusion: These consensus-based recommendations on the use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illnesses and priorities for future research will be updated as high-quality evidence emerges.

KEYWORDS

children, COVID-19, SARS-CoV-2, thromboprophylaxis, venous thromboembolism

1 | INTRODUCTION

Following the initial report of the outbreak of the SARS-CoV-2 virus by the Chinese government on December 31, 2019, several institution-based analyses[1-5] described marked coagulation activation—in particular, greatly elevated D-dimer levels—in association with the systemic inflammatory response in patients hospitalized with COVID-19. Autopsy studies have identified macrovascular pulmonary artery thrombosis/embolism, microvascular pulmonary thrombosis, and deep venous thrombosis of the limbs and other sites.[6] Other studies have revealed an increased incidence of venous thromboembolism (VTE) in patients hospitalized with COVID-19 compared to those with other underlying illnesses,[3-5] and one large retrospective analysis indicated a significantly reduced mortality among hospitalized patients with COVID-19 who received anticoagulant thromboprophylaxis, predominantly with low molecular weight heparin (LMWH).[5] All of these studies were principally, if not exclusively, comprised of adult patients. The International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology (in the latter case, via a web-based "COVID-19 and VTE/Anticoagulation: Frequently Asked Questions" resource) subsequently provided independent, preliminary recommendations that anticoagulant thromboprophylaxis be administered, in the absence of contraindications, in patients hospitalized with COVID-19,[7,8] and called for cooperative clinical trials to inform future guidelines. Neither guidelines specifically addressed the pediatric population.

More recently, devoted pediatric studies have described the heterogeneity of COVID-19 manifestations and disease severity in hospitalized children.[9-15] While the classic pulmonary disease and respiratory distress syndrome predominated in early reports, several publications from April 2020 to the present have described the emergence of a multisystem inflammatory syndrome phenotype in children (MIS-C, also known as the pediatric multisystem inflammatory syndrome [PMIS]) characterized by fever; laboratory indices of systemic inflammation; skin lesions; gastritis/colitis; and in some cases, cardiac manifestations including myocarditis and/or coronary arteritis resembling Kawasaki disease.[12-15] From early June 2020 to present, a rise in hospitalization rates among pediatric patients with COVID-19 has been observed among numerous children's hospitals in the United States, with MIS-C as the predominant phenotype, with markedly elevated D-dimer levels described in one large case series from New York state in the United States.[14]

In a recently published analysis of a national multicenter registry of MIS-C/PMIS in children and adolescents in the United States, the rate of symptomatic VTE (ie, imaging confirmation prompted by signs and symptoms or underlying clinical suspicion) was 7% (3/45) among patients 13 to <21 years of age and 1.3% (1/75) in children 5 to <13 years old.[15] Routine clinical use of LMWH thromboprophylaxis in children hospitalized with COVID-19 at centers with a high volume of pediatric cases was recently anecdotally reported in an ISTH-sponsored webinar on prevention and treatment of thromboembolism in COVID-19 in special populations.[16] While a multicenter phase 2 trial on the safety, dose requirements, and preliminary efficacy of enoxaparin thromboprophylaxis in children hospitalized with COVID-19-related illnesses (including MIS-C) was launched in June 2020,[17] no prospective studies on the efficacy and safety of anticoagulant thromboprophylaxis in either adults or children hospitalized with COVID-19 have been published to date.

In response to the need for expert pediatric guidance pending suitable evidence, the objective of this scientific statement is to provide consensus-based recommendations on the use of anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illnesses and identify priorities for future research.

2 | METHODS

We surveyed the co-chair pediatric hematologists of the Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee of the ISTH Scientific and Standardization Committee (SSC), along with the chair, 1 to 2 Subcommittee member pediatric hematologists, and 1 to 3 pediatric critical care physicians from each of several continents, regarding their expert opinions on the use of anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illness, including the primary respiratory phenotype and the MIS-C phenotype. The survey questions are provided in the Appendix in supporting information. All physicians surveyed were identified by the chair/co-chairs as having experience and expertise in the use of anticoagulant thromboprophylaxis and/or the management of COVID-19–related illness in children. All survey respondents were mutually blinded.

Twenty surveys were sent, and there were 18 respondents (response rate, 90%), consisting of 11 pediatric hematologists (North America, n = 6; South America n = 1; Europe, n = 1; Asia/Middle East, n = 2; Australia/New Zealand, n = 1) and seven pediatric intensivists (North America, n = 2; South America, n = 1; Europe, n = 3; Asia and Australia/New Zealand, n = 1). Specific management approaches serving as the basis for consensus recommendations reported here (see Results) had received affirmative votes by 61% to 89% of respondents; agreement of >80% was designated as "strong consensus" while agreement of 60 to <80% was designated as "weak consensus," Priorities for future research were evaluated for themes, which were then ranked in order of frequency of mention across the respondents. The four most frequently cited themes (ranging from 39% to 78% of respondents) were used to inform consensus-based recommendations reported here on priorities for future research. In addition, to inform the background for this work and the discussion of our survey findings and recommendations, the first author performed a comprehensive review of the English- and French-language literature on pediatric COVID-19 on 08 August 2020, using the search term strategy ["pediatric" OR "children"] AND ["COVID-19" OR "SARS-CoV-2"].

3 | RESULTS

3.1 | Clinical recommendations

Based on a consensus of expert opinions (see survey Methods, above), we *suggest* that (see also Table 1):

1. Anticoagulant thromboprophylaxis (in combination with mechanical thromboprophylaxis with sequential compression devices, where feasible) be administered in children hospitalized with COVID-19–related illness (including MIS-C) who have superimposed clinical risk factors for hospital-associated VTE (examples provided in Table 2[18,19]) or markedly elevated plasma D-dimer levels (eg, ≥5 times the upper limit of normal values), in the absence of contraindications *[expert opinion, with strong consensus (83%, 15/18)]*;
2. Low-dose LMWH subcutaneously twice daily, targeted to achieve a 4-hour post-dose anti-Xa activity level of 0.2 to <0.5 U/mL, is a preferable option for anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illnesses (including MIS-C) who are clinically stable without severe renal impairment, in the absence of contraindications (for the latter circumstances, we suggest unfractionated heparin by continuous intravenous infusion, targeting an anti-Xa activity of 0.1 to <0.35 U/mL) *[expert opinion, with weak consensus (78%, 14/18)]*;

TABLE 1 Summary of consensus-based clinical recommendations on use/non-use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness and children hospitalized with asymptomatic SARS-CoV-2 infection

Scenario	D-dimer >5 times upper limit of normal values	Non-COVID-19 clinical risk factors for HA-VTE (see Table 2)	Anticoagulant thromboprophylaxis suggested
Hospitalized for COVID-19–related illness (includes MIS-C)	Yes	N/A	Yes
	No	One or more[a]	Yes
		None	No
Hospitalized with asymptomatic SARS-CoV-2 infection	N/A	Multiple[b]	Yes
		Few or none	No

Abbreviations: HA-VTE, hospital-associated venous thromboembolism; N/A, not applicable.

[a]While there was consensus among experts surveyed for the stated recommendations, specific risk factors endorsed by survey respondents varied. Please see also Table 2 for risk factor examples.

[b]Several studies in critically ill and non–critically ill children without COVID-19 (analyzed in Mahajerin et al.18 or published subsequently) have suggested a clinically meaningful increase in the risk of hospital-associated VTE in association with the co-existence of multiple (eg, ≥3) specific risk factors. We presume that these findings also apply to hospitalized children with asymptomatic SARS-CoV-2 infection, until data may emerge that indicate otherwise.

TABLE 2 Examples of risk factors for hospital-associated VTE in children, informed by meta-analysis findings,[18] previously published recommendations from the Subcommittee,[19] and/or endorsed by experts surveyed

- Central venous catheter[18,19]
- Mechanical ventilation[18,19]
- Prolonged length of stay (eg, anticipated >3 days)[18,19]
- Complete immobility (eg, Braden Q Mobility Score = 1)[19]
- Obesity (ie, BMI >95th percentile)[19]
- Active malignancy, nephrotic syndrome[a], cystic fibrosis exacerbation[a], sickle cell disease vaso-occlusive crisis[a], or flare of underlying inflammatory disease (eg, lupus, juvenile idiopathic arthritis, inflammatory bowel disease)[19]
- Congenital or acquired cardiac disease with venous stasis or impaired venous return,
- Previous history of VTE[19]
- First-degree family history of VTE before age 40 years or unprovoked VTE[19]
- Known thrombophilia (eg: protein S, protein C, or antithrombin deficiency; factor V Leiden; factor II G20210A; persistent antiphospholipid antibodies)[19]
- Pubertal, post-pubertal, or age >12 years[15]
- Receiving estrogen-containing oral contraceptive pill
- Status-post splenectomy for underlying hemoglobinopathy[a]

Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

[a]Not Included in survey, but endorsed by all co-authors post hoc.

3. Marked thrombocytopenia (eg, platelet count <20 000–50 000/μL), hypofibrinogenemia (eg, fibrinogen activity <100 mg/dL by Clauss method), recent ISTH-defined major bleeding,[20] and concomitant aspirin administration at doses >5 mg/kg/d *likely* confer a heightened bleeding risk in association with anticoagulant thromboprophylaxis (however, in the absence of other risk factors for bleeding, the use of low-dose anticoagulant thromboprophylaxis is not believed to confer a high risk of clinically significant bleeding in MIS-C patients who are receiving aspirin at doses ≤5 mg/kg/d due to the presence of cardiac abnormalities or features of Kawasaki-like illness) *[expert opinion, with strong consensus (89%, 16/18)]*;
4. Continued anticoagulant thromboprophylaxis post-discharge from hospital be *considered* in children with COVID-19–related illness (including MIS-C) who have markedly elevated plasma D-dimer levels at hospital discharge and superimposed clinical risk factors for VTE (as above)—with a planned duration of, for example, the sooner of clinical risk factor resolution or 30 days post-discharge—using low-dose LMWH subcutaneously twice daily (as above) or therapeutic-intensity LMWH (eg, targeted anti-Xa activity of 0.5–1.0 U/mL) once daily, in the absence of contraindications or heightened bleeding risk *[expert opinion, with weak consensus (61%, 11/18)]*; and
5. Anticoagulant thromboprophylaxis *not* be routinely prescribed in hospitalized children who have asymptomatic SARS-CoV-2 infection in the absence of an indwelling central venous catheter or multiple clinical risk factors for hospital-associated VTE, nor in asymptomatic outpatients in the absence of indwelling central venous catheters, as the potential benefit of VTE prevention in most asymptomatic children is likely outweighed by the risk of clinically relevant bleeding *[expert opinion, with strong consensus (89%, 16/18)]*.

3.2 | Research priorities

Based on a consensus of expert opinions (see survey Methods, above), we identify the following priorities for future research:

1. Characterization of VTE risk and identification of VTE risk factors in children (particularly those hospitalized) with COVID-19–related illness (including MIS-C), via multi-institutional cohort studies, registries, and retrospective studies;
2. Determination of the safety and efficacy of anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illness (including MIS-C), via cooperative multicenter clinical trials;

3. Investigation of hypothesized pathophysiological mechanisms underlying the prothrombotic state (eg, coagulation activation, endothelial dysfunction) and their putative associations with SARS-CoV-2 pathogenesis and immune response in children with COVID-19–related illness; and
4. Elucidation of pathophysiological mechanisms distinguishing the MIS-C phenotype from the primary respiratory phenotype of COVID-19–related illness in children.

4 | DISCUSSION

In this scientific statement, we provide consensus-based recommendations on the use of anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illness and priorities for future research. These recommendations are based on responses to a survey conducted among 20 pediatric hematologists and pediatric critical care medicine physicians around the world who were identified by the leadership of the Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee of the ISTH SSC for their expertise and experience in the use of anticoagulant thromboprophylaxis and/or the management of COVID-19–related illness in hospitalized children, with 90% response (n = 18). We identify efforts to characterize VTE risk and to evaluate safety and efficacy of anticoagulant thromboprophylaxis as being key priorities for future research in children hospitalized for COVID-19. In addition, among other recommendations, we suggest the use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness who have either markedly elevated plasma D-dimer levels or *one or more* superimposed clinical risk factors for hospital-associated VTE (Table 2). This recommendation should be considered in the context of several prior studies on hospital-associated VTE risk in critically ill and non–critically ill children without COVID-19 (analyzed in Mahajerin et al.18), which have suggested a clinically meaningful increase in the risk of hospital-associated VTE in association with the co-existence of *multiple* (eg, ≥3) specific risk factors. These recommendations also share commonalities with institutionally derived recommendations reported by Loi et al[21] in a recent Letter to the Editor in the journal *Pediatric Blood and Cancer*. Notably, our recommendations go beyond those of the American College of Rheumatology MIS-C and COVID-19-Related Hyperinflammation Task Force, which has recommended consideration of anticoagulant thromboprophylaxis in patients with left ventricular ejection fraction <35%, and antithrombotic management otherwise based on Kawasaki disease criteria (ie, therapeutic anticoagulation for giant coronary artery aneurysms, else aspirin for other Kawasaki disease features).[22]

While the present consensus-based recommendations suggested LMWH subcutaneously twice daily, targeting a 4-hour post-dose anti-Xa activity level of 0.2 to <0.5 U/mL, as the preferred regimen of anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness, it should be recognized that at many pediatric centers, monitoring of anti-Xa (or activated partial thromboplastin time [aPTT]) is not routinely being performed in hospitalized children receiving prophylactic dosing of LMWH in the absence of renal insufficiency, and at some centers, a once-daily LMWH regimen is prescribed for pediatric in-hospital thromboprophylaxis. In pediatric patients who are clinically unstable or have severe renal impairment, low-dose unfractionated heparin (eg, 10–12 U/kg/h) is often employed for anticoagulant thromboprophylaxis. Our preferences for a twice-daily low-dose approach and for monitoring anti-Xa activity (at least to inform initial dosing of LMWH) may reflect concerns regarding limited experience in an underlying illness (COVID-19) for which data on bleeding risk in hospitalized children are still limited, and for a medication regimen (LMWH thromboprophylaxis) for which pediatric dose-finding data are also limited.

It should also be noted that, while several respondents indicated a preference for higher-intensity dosing (ie, therapeutic-type LMWH regimen, targeted to achieve a 4-hour post-dose anti-Xa activity level of 0.5–1.0 U/mL) in critically ill children with persistently markedly elevated D-dimer levels (eg, ≥5 times the upper limit of normal values), this represented a minority of experts surveyed. Our recommendation for lower-intensity dosing as described above, which are consistent with COVID-19 anticoagulant thromboprophylaxis recommendations published by other groups,[7,8,23] likely reflects the as-yet ill-defined risk estimates for VTE and clinically relevant bleeding in children hospitalized with COVID-19–related illness, and our preference that evidence of safety of low-dose thromboprophylaxis be established before higher-intensity anticoagulant thromboprophylaxis is evaluated or recommended. This preference also applies in regard to MIS-C, irrespective of the fact that many of the experts believed that VTE risk may be higher in MIS-C patients than in children with the respiratory phenotype of COVID-19 group, due to the substantially upregulated systemic inflammatory response and associated marked coagulation activation in MIS-C. Nevertheless, issues of anticoagulant intensity and anticoagulant "contraindications" are further complicated by the distinct possibility that some of the same putative risk factors for bleeding (eg, hypofibrinogenemia) may also be associated with increased VTE risk.[4]

Strengths of the present work include the use of survey methodology with mutual blinding to determine and measure consensus as well as inform consensus-based recommendations. The high survey response rate achieved, at 90%, is also a strength. While the distribution of survey recipients and respondents represented six continents, the lack of African representation among the respondents is a weakness that should be addressed in future consensus-based recommendations. To that end, the Subcommittee leadership has made efforts over the past year to actively engage Working Group participants from Asia and Africa in order to expand its present expertise. An additional limitation to our recommendations stems from the heterogeneity in severity of illness among children hospitalized for COVID-19–related illness (apart from those who are critically ill with respiratory failure, disseminated intravascular coagulation, and/or receiving extracorporeal life support); indeed, based on the survey responses, a consensus was lacking regarding other illness severity criteria (if any) that should inform clinical decision making regarding use of anticoagulant thromboprophylaxis. Nevertheless, there was consensus that hospitalized children who have asymptomatic SARS-CoV-2 infection should

not generally receive anticoagulant thromboprophylaxis on the basis of SARS-CoV-2 infection alone, and that underlying clinical risk factors for VTE (and D-dimer levels) in children hospitalized for COVID-19–related illness (ie, symptomatic SARS-CoV-2 infection) may be at least as important as illness severity in informing clinical decision-making regarding use of anticoagulant thromboprophylaxis. Most important, in regard to limitations of the present work, is that our consensus-based recommendation (and indeed, the survey responses from experts themselves) are informed by a paucity of evidence from published pediatric experience and research; therefore, it will be critical that these consensus-based recommendations are updated as more evidence emerges on anticoagulant thromboprophylaxis in children hospitalized with COVID-19–related illness.

Notwithstanding the aforementioned limitations, we hope that these consensus-based recommendations will help to guide future research and aid in clinical decision making on anticoagulant thromboprophylaxis in children hospitalized for COVID-19–related illness. Although not mentioned among these recommendations, the treatment of underlying disease also deserves emphasis in any discussion of optimal thromboprophylaxis. Because the systemic proinflammatory response elicited by SARS-CoV-2 mediates marked hypercoagulability, and because SARS-CoV-2 angio-invasion appears to induce endothelial damage, evidence-based immunomodulatory and antiviral strategies—particularly in MIS-C—may provide important adjunctive therapies to reduce the risk and extent of thromboembolic complications in children hospitalized for COVID-19–related illnesses.

CONFLICTS OF INTEREST

None of the authors has relevant conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

N Goldenberg: designed the survey study, collected the data, analyzed the data, interpreted the findings, drafted the manuscript, revised the manuscript, approved submission of the final draft of the manuscript. All other authors: gave input to the survey design, interpreted the data, gave critical input to the manuscript, approved submission of the final draft of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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