



Philippine Pediatric COVID-19 Living Clinical Practice Guidelines

In cooperation with the Pediatric Infectious Disease Society of the Philippines

Funded by the Philippine Pediatric Society

EVIDENCE SUMMARY

Should anticoagulation be used in the treatment of children with COVID-19 infection?

Evidence Reviewers: Vaneza Leah A. Espino, MD, DPPS, DPAPP, Ma. Lucila M. Perez, MD, MSc, FPPS, Maria Teresa S. Tolosa, MD, FPDS, DipCE; Leonila F. Dans, MD, MS

Recommendation

We suggest against the use of anticoagulation in children with COVID-19 infection or MIS-C.

Certainty of Evidence: Very Low

Strength of Recommendation: Weak

Consensus Issues

The recommendation was based on the findings from two cohort studies done on pediatric patients with COVID-19 infection and MIS-C. There were no significant benefits noted in both studies. However for those with high risk of thrombotic events, the panel suggested to seek expert opinion.

Key Findings

There was no significant benefit for prophylactic anticoagulation over no anticoagulation in preventing thrombotic events for hospitalized children with COVID-19 or MIS-C in two cohort studies. Risk of bleeding while on prophylactic anticoagulation was inconclusive. In the second study, no deaths and thrombotic events were reported. Overall certainty of evidence was downgraded to very low due to high risk of bias, very small sample size, low event rate and wide confidence intervals.

Introduction

COVID-19 infection in adults has exhibited the predisposition to thrombotic coagulopathies speculated to be caused by an inflammatory-driven endothelial dysfunction and a hypercoagulable state. There is a reported incidence of 21-31% for venous thromboembolism in adults with COVID-19, with many patients having elevated levels of D-dimer, fibrinogen, and mild prolongation of prothrombin time. In contrast, the reported rate of thrombotic events in hospitalized children with COVID-19 and MIS-C is 2.1%, and 6.5% respectively compared to 0.7% in those who are asymptomatic. In a particular retrospective review by Whitworth et al, thrombotic events in adolescents is higher at 6.8% with a mortality rate of 28%. [1,2]

The Philippine COVID Adult Living CPG suggests the use of prophylactic anticoagulation based on a very low certainty of evidence. While a handful of other guidelines have suggested the use of anticoagulation in adults with COVID-19, there is still very limited data for thromboprophylaxis in children.



Review Methods

An electronic search for published and pre-print studies (PubMed, Cochrane Library, Herdin, MedRxiv) and ongoing trials (Clinicaltrials.gov Registry, International Clinical Trials Registry Platform) was conducted. The inclusion criteria are stated in Table 1. Free text and MeSH terms were used for the search which lasted until January 17, 2021. Appraisal of cohort studies was done using Newcastle Ottawa Scale (NOS). Subgroup analysis for COVID severity classification, age group, kind of anticoagulant, prophylactic versus therapeutic dosing and duration was planned however was not possible due to unavailability of data. (Appendices 2,3).

Table 1. PICO criteria for anticoagulation and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Anticoagulation, thromboprophylaxis
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Bleeding, thrombosis, adverse effects

Results

Two cohort studies on children were identified (Del Borello 2020, Whitworth 2021). Cases with COVID-19 infection requiring hospitalization across all severity were enrolled, including MIS-C. Primary anticoagulants used were enoxaparin and unfractionated heparin in both studies. Results could not be pooled due to differences in anticoagulation regimen and reported outcomes.

The prospective cohort study by Del Borrello et. al (2020) enrolled 35 pediatric patients with SARS-CoV-2 infection requiring hospitalization in a tertiary care center in Italy. Risk for thrombosis was appraised using the International Society on Thrombosis and Hemostasis (ISTH)-endorsed recommendations to determine which patients underwent prophylactic anticoagulation. Only a total of six patients (moderate – 1, severe – 1, critical – 2, MIS-C – 2) were given prophylactic anticoagulation using Enoxaparin (100 U/kg) every 24 hours or unfractionated heparin (10 U/kg/hr). All patients on anticoagulation had preexisting conditions: obesity, cystic fibrosis, leukemia, sickle cell disease. Outcomes documented were mortality, thrombotic/bleeding events. However, data on comparison was not available, only adverse events were reported. [1] (Appendix 3)

The retrospective cohort by Whitworth et al. conducted in 7 pediatric hospitals in the U.S. reviewed the rate of thrombosis in 564 pediatric patients (0 to <21 years of age) hospitalized for either COVID or MIS-C. Of these, 128 of 426 (30%) of COVID-19, and 80 of 138 (58.0%) MIS-C admissions were given thromboprophylaxis with varying regimens and dosing. The most commonly used anticoagulant was enoxaparin (89%), followed by unfractionated heparin (6.8%). Dosing regimen for prophylactic anticoagulation using enoxaparin varied depending on physician prescription either once or twice a day at approximately 0.5mg/kg. Dosing used for heparin and duration of treatment for both anticoagulants were not available. Post hoc analysis was done to determine effect on preventing thrombotic events and risk of bleeding while on prophylactic anticoagulation. [2] (Appendix 5)

Summary of Certainty of Evidence

Certainty of evidence was deemed very low for both studies due to high risk of bias, a very small sample size (Borello et al. 2020), heterogeneity in intervention, low event rate and wide confidence intervals (Whitworth et al. 2021). Assessment of outcomes was not mentioned and follow up was not defined in the study by Borello et al. (Appendix 4)



Mortality

There was no reported mortality in the six patients that received prophylactic coagulation in the study by Borello et al. On the other hand, Whitworth et al did not identify the number of deaths specific to the group that was given anticoagulation therapy.

Thrombosis

Data from Whitworth revealed no significant benefit for prophylactic anticoagulation over no anticoagulation in preventing thrombotic events for hospitalized children with COVID-19 and MIS-C. (RR 2.14, 95% CI 0.86 - 5.34, n= 564). On subgroup analysis, likewise there was no significant benefit for hospitalized children regardless of diagnosis of COVID-19 (n = 426) or MIS-C (n = 138) with RR 1.16 (95% CI 0.29 - 4.57) and RR 2.41 (95% CI 0.52 - 11.22), respectively. There was no thrombotic event in any of the six patients that received prophylactic coagulation in the study by Borello et al.

Bleeding

Post hoc analysis of data from Whitworth et. al. showed inconclusive results in terms of the risk of bleeding while on prophylactic anticoagulation, for both COVID and MIS-C pediatric patients. (RR 0.35, 95% CI 0.04 - 2.94, n = 564). Subgroup analysis for bleeding in COVID patients only and in MIS-C were also inconclusive with RR 0.47, 95% CI 0.06 - 4.00 (n = 426) and RR 0.73, 95% CI 0.01 - 36.19 (n = 138), respectively. In contrast, no bleeding events were identified by Del Borello et al. among patients given anticoagulation.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost [3] ^{a,b}	No evidence was found on the cost-effectivity of anticoagulation therapy in COVID-19 patients. <i>Enoxaparin 100 mg/ml, 0.4 mL pre-filled syringe: Php 179.89 – 398.00</i> <i>Enoxaparin 100 mg/mL, 0.6 mL pre-filled syringe: Php 195.00 – 465.00</i> <i>Heparin (as sodium) 1000 IU/mL, 5 mL vial: Php 42.23 – 134.22</i> <i>Heparin (as sodium) 5000 IU/mL, 5 mL vial: Php 140 - 180</i>
Availability	Enoxaparin and heparin are included in the Philippine National Formulary. [3]
Patient’s Values or Preferences; Social Impact	No available evidence.
Factors to Impact Acceptability or Compliance	Fernando et al. demonstrated that in critically ill, non-COVID adult patients, anticoagulation-associated bleeding led to higher mortality, prolonged hospital stay, and subsequent higher hospitalization cost. Around 15% of patients maintained on anticoagulation experienced major bleeding episodes throughout their hospital or ICU admission. [4]

^aHealth facilities may have a price variation up to 10% above DPRI to account for inflation

^bDosing regimen is dependent on the weight of the child, and duration is variable.

The Philippine Drug Price Reference Index (DPRI) of the Department of Health (DOH) [3]

Recommendations from Other Groups

Locally, the Philippine Pediatric Society (PPS) and the Pediatric Infectious Disease Society of the Philippines (PIDSP) suggest the use of prophylactic anticoagulation for high risk hospitalized COVID-19 pediatric patients. Only one other society was identified to provide a statement on the



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use of anticoagulation in children with COVID-19: The Australian Living CPG (Clinical Practice Guidelines), updated last December 2021, which acknowledges the lack of available data of the intervention in the pediatric population.

The Philippine COVID Living CPG conditionally suggests the use of prophylactic anticoagulation in admitted adult patients based on a very low certainty of evidence. Recommendations from other societies and associations are detailed in the table below. Most recommend the use of thromboprophylaxis in adults with COVID-19 that require hospitalization.

Table 3. Summary of Recommendations from other Groups

Association/Institution (Date last updated)	Recommendation/s
PPS-PIDSP Interim COVID Guidelines (01/08/2022) [5]	Prophylactic anticoagulation may be started (in consultation with Hematology) for hospitalized COVID-19 patients with D-dimer levels more than 5 times the upper limit of normal values or if with presence of at least 1 clinical risk factor for VTE.
Australian Living CPG (12/2021) [6]	<ul style="list-style-type: none"> • There is insufficient evidence in children and adolescents to recommend a modified thromboprophylaxis regimen. • Consider known risk factors for initiating thromboprophylaxis in children and adolescents. <p><i>Certainty of the Evidence (CoE):</i> currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in children and adolescents with COVID-19.</p>
Philippine COVID Living CPG (10/2021) [7]	<p>Among admitted patients with COVID-19 infection, the use of prophylactic anticoagulation is suggested, unless with contraindications. (<i>Very low certainty of evidence, Conditional recommendation</i>)</p> <p>The use of prophylactic over therapeutic dose anticoagulation is recommended among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. (<i>Low certainty of evidence; Strong recommendation</i>)</p>
American Society of Hematology (7/15/2021) [8]	<p>All hospitalized patients with COVID-19:</p> <ul style="list-style-type: none"> • Prophylactic anticoagulation is recommended unless risk of bleeding outweighs risk • Standard dose prophylaxis is suggested over intermediate or therapeutic dose
National Institute of Health (NIH) (2/11/2021) [9]	<p>Non-hospitalized patients with COVID-19: Anticoagulation should not be initiated unless there are other indications or the patient is participating in a clinical trial.</p> <p>Hospitalized patients with COVID-19: All non-pregnant adults are recommended to receive prophylactic anticoagulation. There is insufficient evidence to support the use of higher than standard dose outside of clinical trials</p>
World Health Organization (WHO) (1/25/21) [10]	Hospitalized patients with COVID-19: Standard dose prophylactic anticoagulation rather than higher prophylactic dose or therapeutic dose is suggested unless there is a warranted indication. (<i>Conditional recommendation</i>)



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Research Gaps

One ongoing randomized controlled trial (RCT) in children was identified (Appendix 7). The COVID-19 Anticoagulation in Children – Thromboprophylaxis or COVAC-TP Trial is a multicenter single arm trial in children less than 18 years of age with COVID using Enoxaparin as the intervention. Outcomes expected are safety and efficacy. The trial concluded recruitment in June 2021.



References

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- [4] Fernando S, Mok G, Castellucci L, Dowlatshahi D, Rochweg B, Mclsaac D et al. Impact of Anticoagulation on Mortality and Resource Utilization Among Critically Ill Patients With Major Bleeding. *Crit Care Med.* 2020;48(4):515-524.
- [5] PPS-PIDSP. Interim guidelines on the screening, classification, and management of pediatric patients with suspected or confirmed coronavirus disease 2019 (COVID-19). 2022.
- [6] MAGICapp - Making GRADE the Irresistible Choice - Guidelines and Evidence summaries [Internet]. App.magicapp.org. 2022 [cited 5 January 2022]. Available from: <https://app.magicapp.org/#/guideline/L4Q5An/section/L0Or0j>
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- [9] National Institute of Health. Antithrombotic Therapy | COVID-19 Treatment Guidelines [Internet]. [cited 2022 Jan 05]. Available from: <https://www.covid19treatmentguidelines.nih.gov/therapies/antithrombotic-therapy/>
- [10] World Health Organization. Therapeutics and COVID-19: living guideline [Internet]. [cited 2022 Jan 05]. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.3>



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Appendix 1. Search Yield and Results

Search terms:

#1 COVID-19 OR SARS-COV2

#2 anti-coagulation OR thrombolysis OR thromboprophylaxis

#3 children OR pediatric age group

#4 - #1 AND #2

#5 - #3 AND #4

<p>Search: #1 AND #2 (“covid 19”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19 vaccines”[All Fields] OR “covid 19 vaccines”[MeSH Terms] OR “covid 19 serotherapy”[All Fields] OR “covid 19 serotherapy”[Supplementary Concept] OR “covid 19 nucleic acid testing”[All Fields] OR “covid 19 nucleic acid testing”[MeSH Terms] OR “covid 19 serological testing”[All Fields] OR “covid 19 serological testing”[MeSH Terms] OR “covid 19 testing”[All Fields] OR “covid 19 testing”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[MeSH Terms] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication]) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[All Fields])) AND (“anti-coagulation”[All Fields] OR “thrombolysis”[All Fields] OR “thromboprophylaxis”[All Fields])</p> <p>Translations COVID-19: (“COVID-19” OR “COVID-19”[MeSH Terms] OR “COVID-19 Vaccines” OR “COVID-19 Vaccines”[MeSH Terms] OR “COVID-19 serotherapy” OR “COVID-19 serotherapy”[Supplementary Concept] OR “COVID-19 Nucleic Acid Testing” OR “covid-19 nucleic acid testing”[MeSH Terms] OR “COVID-19 Serological Testing” OR “covid-19 serological testing”[MeSH Terms] OR “COVID-19 Testing” OR “covid-19 testing”[MeSH Terms] OR “SARS-CoV-2” OR “sars-cov-2”[MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2” OR “NCOV” OR “2019 NCOV” OR (“coronavirus”[MeSH Terms] OR “coronavirus” OR “COV”) AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))</p> <p>SARS-COV 2: “sars-cov-2”[MeSH Terms] OR “sars-cov-2”[All Fields] OR “sars cov 2”[All Fields]</p>	791
<p>Search: #3 AND #4 (“child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields] OR “child s”[All Fields] OR “children s”[All Fields] OR “childrens”[All Fields] OR “childs”[All Fields] OR (“paediatrics”[All Fields] OR “pediatrics”[MeSH Terms] OR “pediatrics”[All Fields] OR “paediatric”[All Fields] OR “pediatric”[All Fields]) AND (“age groups”[MeSH Terms] OR (“age”[All Fields] AND “groups”[All Fields]) OR “age groups”[All Fields] OR (“age”[All Fields] AND “group”[All Fields]) OR “age group”[All Fields])) AND (“covid 19”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19 vaccines”[All Fields] OR “covid 19 vaccines”[MeSH Terms] OR “covid 19 serotherapy”[All Fields] OR “covid 19 serotherapy”[Supplementary Concept] OR “covid 19 nucleic acid testing”[All Fields] OR “covid 19 nucleic acid testing”[MeSH Terms] OR “covid 19 serological testing”[All Fields] OR “covid 19 serological testing”[MeSH Terms] OR “covid 19 testing”[All Fields] OR “covid 19 testing”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[MeSH Terms] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication]) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[All Fields])) AND (“anti-coagulation”[All Fields] OR “thrombolysis”[All Fields] OR “thromboprophylaxis”[All Fields]))</p>	43



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Translations

children: “child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields] OR “child’s”[All Fields] OR “children’s”[All Fields] OR “childrens”[All Fields] OR “childs”[All Fields]

pediatric: “paediatrics”[All Fields] OR “pediatrics”[MeSH Terms] OR “pediatrics”[All Fields] OR “paediatric”[All Fields] OR “pediatric”[All Fields]

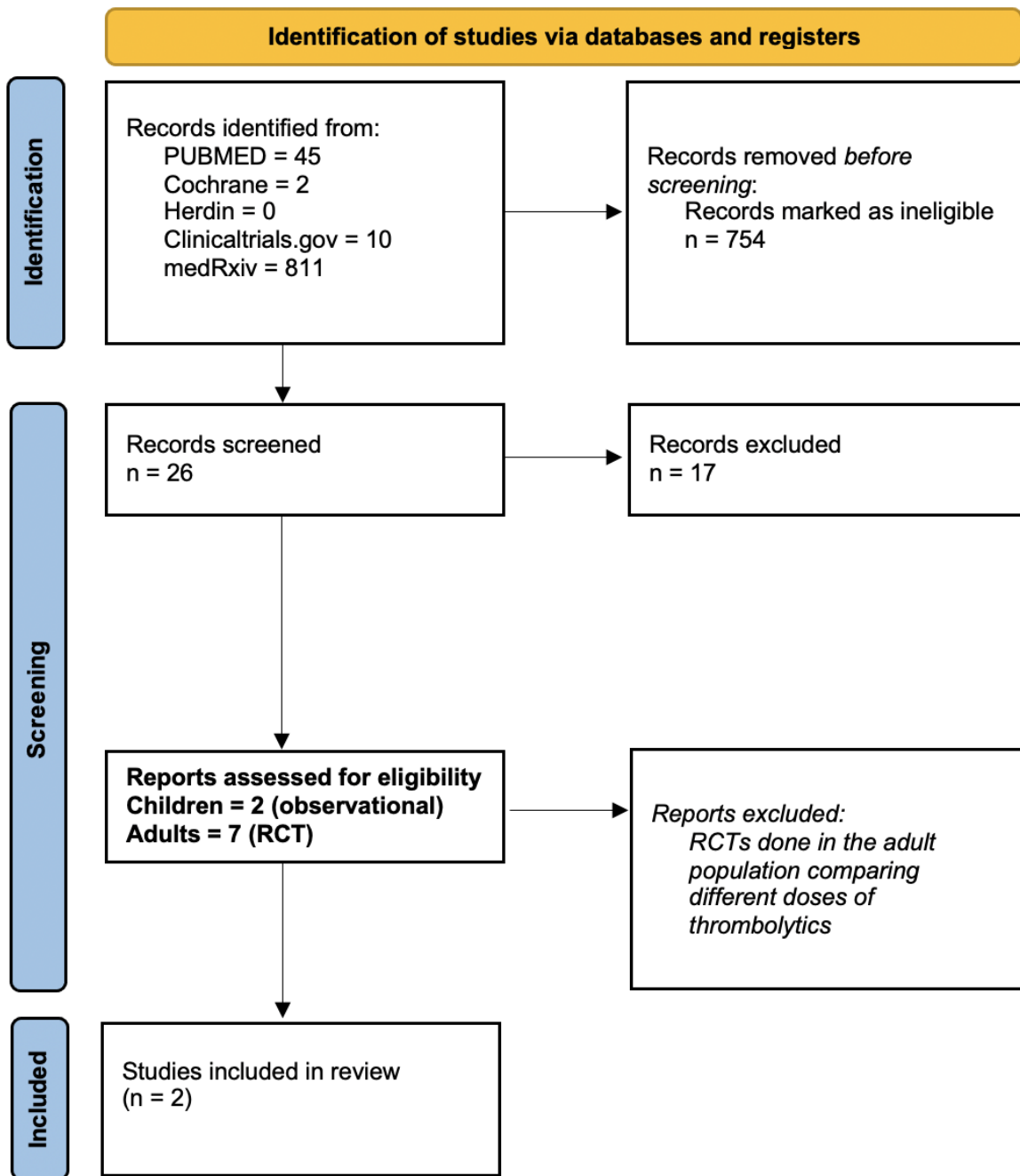
age group: “age groups”[MeSH Terms] OR (“age”[All Fields] AND “groups”[All Fields]) OR “age groups”[All Fields] OR (“age”[All Fields] AND “group”[All Fields]) OR “age group”[All Fields]

COVID-19: (“COVID-19” OR “COVID-19”[MeSH Terms] OR “COVID-19 Vaccines” OR “COVID-19 Vaccines”[MeSH Terms] OR “COVID-19 serotherapy” OR “COVID-19 serotherapy”[Supplementary Concept] OR “COVID-19 Nucleic Acid Testing” OR “covid-19 nucleic acid testing”[MeSH Terms] OR “COVID-19 Serological Testing” OR “covid-19 serological testing”[MeSH Terms] OR “COVID-19 Testing” OR “covid-19 testing”[MeSH Terms] OR “SARS-CoV-2” OR “sars-cov-2”[MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2” OR “NCOV” OR “2019 NCOV” OR (“coronavirus”[MeSH Terms] OR “coronavirus” OR “COV”) AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))

SARS-COV 2: “sars-cov-2”[MeSH Terms] OR “sars-cov-2”[All Fields] OR “sars cov 2”[All Fields]



Appendix 2. PRISMA Flow Chart





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Appendix 3. Characteristics of Included Studies

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Del Borello 2020	Prospective cohort	Italy	35	0 to 21 years of age Mild to critical cases MISC	Prophylactic anticoagulation : Enoxaparin or Unfractionated Heparin	No data available for comparator group	Mortality Thrombotic events Bleeding
Whitworth 2021	Retrospective cohort	USA	564	0 to <21 years of age Hospitalized children with COVID or MIS-C	Prophylactic anticoagulation : Enoxaparin or Unfractionated Heparin	No anticoagulation	Bleeding events



Appendix 4. Risk of Bias Assessment using Newcastle Ottawa Scale (NOS)

Selection	Del Borello (2020)	Whitworth (2021)
Representativeness of the exposed cohort	Selected group	Representative
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort *	Drawn from the same community as the exposed cohort *
Ascertainment of exposure	Secured record *	Secured record *
Demonstration of outcome of interest was not present at start of study	Yes *	No
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	Cohorts are not comparable	The study controls age and sex
Outcome		
Assessment of outcome	No description	Record linkage
Was follow-up long enough for outcomes to occur	Not mentioned	Not mentioned
Adequacy of follow-up of cohorts	No statement	No statement

ASSESSMENT: Poor quality*

***0 or 1 star (*) in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/ exposure domain**



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Appendix 5A. GRADE Evidence Profile: Anticoagulation in Children with COVID (Del Borello, 2020)

Author/s: Vaneza Leah A. Espino, MD; Ma. Lucila M. Perez, MD
 Question: Should anticoagulation be used in the treatment of children with COVID-19?
 Setting: Italy
 Bibliography: Del Borrello G, et al 2020

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there was no reported mortality. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical
Thrombotic event/s									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there were no reported thrombotic events. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical
Bleeding event/s									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there were no reported bleeding complications. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical

Explanations

^a high risk of bias: no description of assessment of outcome, follow up time not mentioned
^b very small sample size

Appendix 5B. GRADE Evidence Profile: Anticoagulation in Childrne with COVID (Whitworth, 2021)

Author/s: Vaneza Leah A. Espino, MD; Ma. Lucila M. Perez, MD
 Question: Should anticoagulation be used in the treatment of children with COVID-19?
 Setting: USA
 Bibliography: Whitworth H, et al.; 2021

Certainty assessment							No. of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulation	Without anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Bleeding (COVID + MIS-C)												
1 n = 564	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	1/208 (0.5%)	5/356 (1.4%)	RR 0.35 (0.04 to 2.94)	9 fewer per 1,000 (from 13 fewer to 27 more)	⊕○○○ Very low	Critical
Bleeding (COVID)												



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Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulation	Without anticoagulation	Relative (95% CI)	Absolute (95% CI)		
1 n = 426	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	1/128 (0.8%)	5/298 (1.7%)	RR 0.47 (0.06 to 4.00)	9 fewer per 1,000 (from 16 fewer to 50 more)	⊕○○○ Very low	Critical
Bleeding (MIS-C)												
1 n = 138	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	0/80 (0.0%)	0/58 (0.0%)	RR 0.73 (0.01 to 36.19)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	Critical
Thrombotic Events (COVID + MIS-C)												
1 n = 564	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	10/208 (4.8%)	8/356 (2.2%)	RR 2.14 (0.86 to 5.34)	26 more per 1,000 (from 3 fewer to 98 more)	⊕○○○ Very low	Critical
Thrombotic Events: COVID												
1 n = 426	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	3/128 (2.3%)	6/298 (2.0%)	RR 1.16 (0.29 to 4.57)	3 more per 1,000 (from 14 fewer to 72 more)	⊕○○○ Very low	Critical
Thrombotic Events: MIS-C												
1 n = 138	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	7/80 (8.8%)	2/58 (3.4%)	RR 2.41 (0.52 to 11.22)	49 more per 1,000 (from 17 fewer to 352 more)	⊕○○○ Very low	Critical

CI: confidence interval; RR: risk ratio

Explanations

^aDowngraded due to high risk of bias

^bDowngraded due to substantial heterogeneity in intervention used among different patients in the study

^cWide confidence interval and low event rate



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Appendix 6. Characteristics of Ongoing Studies

Title Identifier Expected completion date	Intervention	Comparator	Patients/population recruited	Outcome
COVID-19 Anticoagulation in Children – Thromboprophylaxis (COVAC-TP) Trial NCT04354155 June 4 2021 (no pre-print, no published results yet)	Enoxaparin Twice-daily low-dose	Single arm	Children (birth until 17 years of age)	Safety Efficacy



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Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (9)		Varies		Uncertain	
Benefits	Large (1)	Moderate	Small	Trivial (2)	Varies (1)	Uncertain (5)	
Harm	Large	Moderate	Small (1)	Trivial (1)	Varies (1)	Uncertain (6)	
Certainty of evidence	High	Moderate		Low		Very low (9)	
Balance of effects	Favors drug	Probably favors drug (1)	Does not favor drug or no drug (4)	Probably favors no drug (1)	Favors no drug	Varies	Uncertain (3)
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (4)		No important uncertainty or variability	
Resources required	Uncertain (1)	Varies	Large costs	Moderate costs (8)	Negligible costs or savings	Moderate savings	Large savings
Certainty of evidence of resources required	No included studies (8)		Very low	Low (1)	Moderate	High	
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention
Equity	Uncertain (8)	Varies	Reduced	Probably reduced	Probably no impact (1)	Probably increased	Increased
Acceptability	Uncertain (8)	Varies	No	Probably no (1)	Probably yes	Yes	
Feasibility	Uncertain (6)	Varies (1)	No	Probably no (1)	Probably yes (1)	Yes	