Disseminated intravascular coagulation in paediatrics

Revathi Rajagopal, Jecko Thachil, Paul Monagle

ABSTRACT
Disseminated intravascular coagulation (DIC) in paediatrics is associated with significant morbidity and mortality. Although there have been several recent advances in the pathophysiology of DIC, most of these studies were done in adults. Since the haemostatic system is very different in early life and changes dramatically with age, creating a variety of challenges for the clinician, delay in the diagnosis of DIC can happen until overt DIC is evident. In this review article, we report the aetiology, pathophysiology, clinical manifestations, diagnostic tests and a management algorithm to guide paediatricians when treating patients with DIC.

AETIOLOGICAL FACTORS FOR DIC
DIC is a secondary effect caused by various underlying clinical conditions. In paediatric population, the aetiological factors vary based on age group.

Neonates
The haemostatic system in neonates is significantly different from children and adults, yet is dynamic and balanced. Neonates are more vulnerable to DIC than older infants and children. Platelets and coagulation factors are first detectable at 5 and 10 weeks of gestation, respectively. Platelets reach normal range of 150–450 × 10^9/L at 22 weeks of gestation and most coagulation factors achieve adult values by 6 months of postnatal age, with a few notable exceptions. Platelets are found to be hyporeactive and aggregation is impaired due to deficiency of α-adrenergic receptors on platelet membrane, especially in preterm infants <30 weeks of gestation, but this dysfunction is balanced by elevated von Willebrand factor levels. Andrew et al found that the mean values of procoagulant factors and anticoagulant factors in healthy preterm infants between 30 and 36 weeks of gestation were low, with a range of 25%–70% of adult values. Given the significant differences in the value of coagulation factors, it is important for neonatologists to understand the development of haemostasis and interpret the results with caution.

The main causes of DIC in neonates are given in table 1. Dairaku et al reported that 24 neonates were histopathologically confirmed to have DIC with microthrombi involving three or more organs during autopsies, but only 1 of the neonates was diagnosed with clinical DIC. Whereas Schmidt et al found abnormal coagulation results in 57 out of 100 sick neonates diagnosed with DIC. The discrepancy in the incidence of neonatal DIC in these reports highlights the difficulty in diagnosing this condition in neonates. Also, there are no universally accepted DIC diagnostic criteria specific for neonates.

Older infants and children
Sepsis is the most common cause of DIC in older infants and children. Other factors are detailed in table 1. Oren et al documented an incidence of 1.12% for DIC in children between 1 month and 18 years. Sepsis (95%) was the most common aetiological factor followed by major trauma (5%). The incidence of DIC in this report was probably underestimated as paediatric ICU and emergency care patients were not included. The incidence of DIC in childhood acute lymphoblastic leukaemia and acute promyelocytic leukaemia (APML) were reported as 14% and 4%–8%, respectively.
Acquired inhibitors of coagulation factors such as prothrombin inhibitors in transient lupus anticoagulant following infection, factor VIII inhibitors in autoimmune disease and other inhibitors post major surgery are other miscellaneous factors in paediatric DIC.13

PATHOPHYSIOLOGY OF DIC

Understanding the pathogenesis of DIC is crucial to providing optimal treatment to reverse the underlying condition.7 Sepsis, trauma, major surgery or severe hypoxia leads to release of tissue factor (TF) from endothelial cells and mononuclear cells, which activates extrinsic pathway involving factor VIIa (FVIIa).13 TF-FVIIa complex initiates thrombin generation and further augments the haemostatic cascade by platelet activation-aggregation process, activation of factors VIII, V, XI and XIII, thrombin-activatable fibrinolysis inhibitor and promotes inflammatory effect of white blood cells. Neutrophil extracellular traps in patients with sepsis promote the apoptosis of endothelial cells, platelet aggregation and decompose tissue factor pathway inhibitor (TFPI) in order to augment thrombogenesis.3 Hence, TF pathway is the primary triggering factor of DIC. This mechanism results in the consumption of the endogenous anticoagulants AT, PC, PS and downregulation of thrombomodulin and TFPI activity to promote thrombosis.3 In addition, elevated cytokines such as interleukin-1 and tissue necrosis factor-α in bloodstream stimulate the production of plasminogen activator inhibitor type 1 and further impair the fibrinolytic process (figure 1).4 The inflammatory process that activates the coagulation system also plays a crucial role in the organ damage of DIC. More recent advances in DIC have focused on this inflammation-coagulation cross-link.14

CLINICAL ASPECTS OF DIC

DIC is classically described as a thrombo-haemorrhagic disorder. Although mixed thrombotic-haemorrhagic picture is characteristic of DIC, very often either bleeding or thrombotic manifestations predominate at one particular time (box 1).3 It is unfortunate in this context to note that most paediatricians tend to entertain the possibility of DIC only when there is extensive and uncontrollable bleeding from multiple sites. Thrombi in the microvasculature leading to MODS may represent the onset of DIC. Occasionally, the thrombotic process can be dramatic as in the case of meningococcal sepsis-related DIC with the development of Waterhouse-Friderichsen syndrome, which is associated with high mortality.15

The haemostatic derangement in children with DIC results from cumulative effects of hypercoagulation and hyperfibrinolysis. When hypercoagulation is dominant, organ failure is the main clinical manifestation and this is frequently seen in infection and trauma.3 16 If hyperfibrinolysis is the predominant mechanism, bleeding will be the primary presentation, for example, in APML.7 Consumptive coagulopathy with massive bleeding is observed when both hypercoagulation and hyperfibrinolysis are simultaneously activated.3 Oren et al17 found that the frequency of bleeding and thrombosis were 48.8% and 4.8%, respectively in the setting of DIC.

One of the key clinical features to note is the contribution of the liver to the DIC process. The consequences of liver disease that may develop due to the underlying cause of DIC or secondary to microvascular ischaemia are manifold. These include consumption of platelets and clotting factors due to endothelial damage, impaired production of vitamin K-dependent coagulation factors, activation of platelet-coagulation-fibrinolytic system, hypersplenism and sequestration of clotting factors in ascitic fluid.13 17

DIAGNOSIS OF DIC

Laboratory tests for DIC

DIC is a clinico-laboratory diagnosis.4 The diagnosis is considered only in patients with an underlying disorder, which is known to be associated with DIC in conjunction with several laboratory features. The laboratory tests commonly used are platelet count, coagulation screen, serum fibrinogen and D-dimer or fibrin degradation products (FDP). These tests are easily available in most laboratories and can identify the procoagulant and fibrinolytic processes activated in DIC. Prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count and fibrinogen provide important information on the procoagulant system, whereas D-dimer or FDP measures fibrin formation and fibrinolysis.2 These parameters should never be considered in isolation and also a single set of these values should be deemed diagnostic. A reduction in platelet count, prolongation of the clotting screen, decrease in fibrinogen level and an increase in the D-dimer values all point towards extreme coagulation activation and uncontrolled thrombin generation.3 Table 2 outlines the most frequently used investigations in DIC. In conjunction with the clinical picture, monitoring of the results over time helps to determine the transition from non-overt to overt DIC.

Additional investigations such as haemoglobin level, white blood cell count, blood film (looking for red cell fragmentation or schistocytes), liver and renal function tests, lactic dehydrogenase level, arterial blood gas, blood culture and appropriate imaging (eg, chest X-ray, brain MRI) may provide clues on precipitating factors and extent of organ involvement.

Some of the practical issues faced in the laboratory diagnosis of DIC are (a) difficult venous or arterial access in sick children to obtain adequate blood volume for repeated tests, especially in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Aetiological factors associated with DIC in neonates, older infants and children</th>
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<tbody>
<tr>
<td>neonates</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Group B streptococcus, neonatal cytomegalovirus and enterovirus, necrotising enterocolitis, systemic candidiasis</td>
</tr>
<tr>
<td>Perinatal</td>
<td>Birth asphyxia, respiratory distress syndrome, meconium aspiration syndrome</td>
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<tr>
<td>Others</td>
<td>Single-true demise, hyperthermia, acidosis</td>
</tr>
<tr>
<td>Older infants and children</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Bacteria: Gram-positive (group B streptococcus) and Gram-negative (Neisseria meningitidis, Haemophilus influenzae) bacterial infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Drowning: hypoxia with profound shock</td>
</tr>
<tr>
<td>Injury</td>
<td>Accidents: neuro-trauma, crush injury, electrocution, massive burns</td>
</tr>
<tr>
<td>Toxin</td>
<td>Snake bites, recreational drugs</td>
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<tr>
<td>Gastrointestinal tract disorder</td>
<td>Acute and chronic liver disease</td>
</tr>
<tr>
<td>Immunological insults</td>
<td>Acute haemolytic transfusion reaction, transplant rejection</td>
</tr>
<tr>
<td>Others</td>
<td>Giant haemangiomata, autoimmune disease</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation.

neonates, (b) standardisation of reference range is hard for variables like fibrinogen and D-dimer and (c) low levels of normal physiological coagulation factors in neonates may be misinterpreted as abnormal results.

**Diagnostic scores for DIC**

Three separate guidelines for diagnosis of DIC have been published by the British Committee for Standards in Haematology, Japanese Society for Thrombosis and Haemostasis and Italian Society for Haemostasis and Thrombosis. These are broadly similar but some variations in the recommendations were noted. Hence, the ISTH Subcommittee harmonised these differences and published a standardised DIC scoring system.23

The ISTH criteria recommended five-step diagnostic algorithm to calculate the DIC score by using four laboratory tests (table 3).2 The criteria have 91% sensitivity with 97% specificity among adults and demonstrated strong correlation between DIC score with incidence of mortality.18 Unfortunately, data on validation of ISTH DIC criteria in children are limited, even though it has been used universally in paediatric patients.19 Furthermore, to our knowledge no studies have evaluated the sensitivity and specificity of ISTH DIC criteria in neonates.

**Data on the use of diagnostic scores in paediatrics**

Kutny et al19 evaluated the predictive value of ISTH DIC score in newly diagnosed paediatric patients with APML treated on Children’s Oncology Group study AAML0631. In this study, DIC score of ≥6 was used to assess the correlation of ISTH DIC score with haemorrhagic death. This cut-off score of ≥6 was based on the previous study by Mitrovic et al.20 DIC score ≥6 was significantly associated with a high incidence of fatal bleeding compared with score of <6 (13% vs 0%, p=0.025) and also an increased rate of coagulopathy (32% vs 9%, p=0.015). However, the sensitivity and specificity of the DIC score in predicting at least one coagulopathy event during induction was low with the rate of 66.7% and 65.6%, respectively.19 The authors concluded that other investigations are essential to improve the predictive value, but did not address the reason for using the diagnostic score of ≥6 instead of ≥5 as per the ISTH DIC recommendation.

Soundar et al retrospectively compared the Texas Children’s Hospital (TCH) DIC modified criteria and the ISTH DIC scoring system. TCH criteria used serial platelets and fibrinogen levels in DIC diagnosis. The sensitivity of this scoring system was significantly higher than the ISTH DIC score (82% vs 63%),

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**Figure 1** Pathophysiology of disseminated intravascular coagulation (DIC). AT, antithrombin; F, factor; FVIIa, activated factor VII; PAI-1, plasminogen activator inhibitor-1; PARs, protease-activated receptors; PC, protein C; PS, protein S; TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

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p≤0.05), whereas the specificity was lower (29% vs 43%, p≤0.05). This suggests that ISTH score is only able to identify overt DIC and not evolving DIC in paediatric population. Platelets, PT and D-dimer are important parameters in predicting DIC in both scoring systems but fibrinogen did not show significant impact in the diagnosis of DIC. Fibrinogen is an insensitive indicator of DIC as it acts as an acute-phase reactant. Therefore, serial fibrinogen measurement is more useful in predicting an overt DIC.4

Khemani et al analysed the association between ISTH DIC score and the risk of mortality in children admitted with shock. Paediatric index of mortality (PIM 2) and 12-hour paediatric risk mortality III (PRISM III) score were used along with ISTH DIC score. The analysis demonstrated that a unit increase in DIC score was strongly associated with 1.3-fold increase in mortality rate. Most of the children achieved peak ISTH DIC score within 2 hours and 75% within 6 hours of paediatric ICU admission. Mortality in patients with DIC score ≥5 was 50% compared with 20% in patients with DIC score <5 (p=0.0003). The ISTH DIC score predicted mortality better than other validated paediatric mortality scores such as PIM 2 and PRISM III.21

In contrast, a recent retrospective study by Jhang et al on evaluation of DIC scores in 191 critically ill patients showed that the ISTH and the Japanese Association of Acute Medicine scoring systems correlate well with other severity scores including PRISM III, modified sequential organ failure assessment and paediatric multiple organ dysfunction syndrome. Among them, 15.7% and 29.8% of the patients were diagnosed with DIC by ISTH and the Japanese Association of Acute Medicine scoring systems, respectively. In addition, ISTH and Japanese Association of Acute Medicine scoring systems showed higher mortality rate in patients with DIC than patients without DIC, suggesting that these scores could be promising prognostic factors.22

The contradicting recommendations from several analyses in paediatric population warrant further validation of ISTH DIC scoring system in this age group. However, the data to date suggest that a single time point analysis of laboratory test is of no value and should not be relied on to make the diagnosis of DIC.

TREATMENT OF DIC IN PAEDIATRICS
The basic principles of DIC treatment are outlined in box 2.
Box 2 Management of DIC

Basic principles of DIC management
1. Management of the underlying condition that predisposes to DIC
2. Supportive care with blood products and related measures
3. Inhibition of the effects of excess thrombin
4. Regular clinical and laboratory surveillance
5. Always bearing in mind that the abnormal laboratory markers may be due to several factors and not just DIC
6. Seeking treatment assistance from the relevant specialists early

DIC, disseminated intravascular coagulation.

Treatment of underlying disease
Diagnosis of DIC should be made based on the combination of clinical condition and laboratory information. The key to DIC treatment is vigorous management of the underlying condition with optimal care.2,3

Blood products transfusion
There are lots of different practices and controversies related to blood product management in DIC. Transfusion should be reserved for bleeding patients with DIC and not to transfuse primarily based on laboratory results. The Serious Hazards of Transfusion Haemovigilance scheme has highlighted the increased risk of adverse effects in transfused children as compared with adults.13 These observational data are supported by Khemani et al.,21 where higher mortality rate was found in patients who received more blood products. Platelets, fresh frozen plasma (FFP) and cryoprecipitate are commonly used blood components in patients with DIC. In general, platelets are transfused in patients with bleeding or high risk of bleeding requiring invasive procedures with platelet count of <50×10^9/L. In non-bleeding patients and patients with chronic DIC, prophylactic platelet transfusion is not recommended and close monitoring of clinical status is advisable. Thrombocytopenia is a common finding in sick preterm neonates and there is no clear correlation between severity of thrombocytopenia and risk of major bleeding. Thus, the threshold for platelet transfusion, volume and appropriate indication for transfusion in paediatric populations with DIC are still unclear. Most of the guidelines are based on expert opinion.

FFP is mainly indicated in bleeding patients with prolonged PT and aPTT >1.5 times of upper limit of normal range. However, PT and aPTT normal values in neonates vary according to the gestational age. In this situation, serial monitoring is indicated along with clinical observation to determine the severity of DIC. Generally, 10–20 mL/kg of FFP is recommended, but strict haemodynamic status must be evaluated to prevent fluid overload as these patients may require multiple blood components. Risk of cardiomyopathy secondary to sepsis may complicate the clinical condition.1 16 Occasionally, prothrombin complex (PCC) can be considered if volume overload is an issue. There are case reports on use of PCC in paediatrics,23 but one should bear in mind that PCC should be used judiciously as they may cause thrombosis and also lack certain coagulation factors, especially factor V.16 In addition, the amount of anticoagulants like AT, PC and PS in PCC may not be adequate for replacement in patients with DIC, where these proteins are markedly reduced.

Cryoprecipitate is used in bleeding patients when fibrinogen level is <1.5 g/L.1 16 Some paediatric oncology centres practice prophylactic transfusion of cryoprecipitate in non-bleeding patients with APML when fibrinogen level is <1.5 g/dL in the anticipation of coagulopathy, although this is not evidence-based. Fibrinogen concentrates have been used instead of cryoprecipitate, but are currently licensed only for congenital fibrinogenemia. However, there are several studies documenting their efficacy in acquired hypofibrinogenemic conditions such as in dilutional coagulopathy, trauma, cardiac and thoracic surgery and liver failure in adults. It is difficult to make a strong recommendation in paediatrics based on anecdotal reports and small case series. More clinical trials are needed focusing on DIC management in children and on the dosing, efficacy and safety of this blood component.

Anticoagulants—heparins
In patients with DIC with predominant thrombosis, therapeutic dose of heparin should be considered.2 This approach was clearly discussed by Fox in 13 patients with widespread DIC and Waterhouse-Friderichsen syndrome following meningococcal septicaemia.15 Continuous infusion of unfractionated heparin (UFH) is a better option in paediatric population due to its short half-life and reversibility with protamine sulfate.16 In one study by Göbel et al., treatment of 40 newborns with DIC and respiratory distress syndrome were randomised between heparin infusion and placebo. The heparin group required significantly shorter duration of mechanical ventilation and faster normalisation of coagulation parameters even though mortality rate was equal in both groups.3 24 Use of UFH is contraindicated in patients with evidence of bleeding. In non-bleeding critically ill patients with DIC, prophylaxis use of heparin is recommended.7 Low molecular weight heparin (LMWH) is frequently administered in adults due its predictive pharmacokinetics, lesser bleeding risks and lower incidence of heparin-induced thrombocytopenia. LMWH usage in paediatrics in acute DIC with thrombosis is still limited and not commonly accepted practice due to lack of evidence. When using UFH in DIC, monitoring with aPTT may not be straightforward, since the excess of thrombin generation may lead to shortening of the aPTT. In the case of LMWH, abnormal renal function in children with DIC further complicates the treatment because LMWH accumulates in renal impairment.

Anticoagulants factor concentrates—AT
AT is depleted during excessive thrombin generation in DIC, and AT levels are a predictor of outcome in septic DIC patients and an independent predictor of 28-day mortality.16 Several randomised controlled trials (RCT) assessing the effect of AT treatment on mortality rate in adults have demonstrated statistically significant reduction in mortality.3 There are no RCTs available in the paediatric population, but several retrospective analyses have been reported. Nowak-Gött et al.25 reported that administration of AT in 21 preterm infants and 18 children has resulted in the normalisation of platelets, PT, aPTT, fibrinogen, thrombin time, AT within 24–48 hours and recovery from DIC without adverse effects.3 However, this result has to be interpreted with caution because all of the patients received blood components simultaneously during the treatment. AT replacement is not widely recommended in paediatric DIC.
**Anticoagulants factor concentrates—recombinant activated PC**

PC is markedly low in patients with sepsis and it has been suggested that restoration of PC may help to reduce the severity of DIC.\(^1\)\(^2\)\(^3\) Laterre\(^2\) has reviewed several clinical trials with recombinant activated protein C (rAPC) in adults and paediatrics. In Protein C Worldwide Evaluation in Severe Sepsis trial, usage of rAPC at a dose of 24 μg/kg/hour for 96 hours in among 1960 adult patients showed absolute and relative reductions in the risk of death of 6.1% and 19.4%, respectively. Mortality rate was only 24.7% in rAPC group as compared with 30.8% in placebo group (p=0.005). In addition, rAPC-treated adults demonstrated faster cardiovascular and respiratory recovery. However, the incidence of major bleeding was noted to be higher in rAPC group compared with placebo group (3.5% vs 2.0%; p=0.06), which resulted in premature interruption of the study. Subsequent adult trials of rAPC in Extended Evaluation of Recombinant Human Activated Protein C and Administration of Drotrecogin alfa (activated) in early stage Severe Sepsis revealed higher incidence of bleeding-related adverse events with no significant reduction in 28-day mortality, especially in the latter trial.\(^4\) In children, a phase III randomised, double-blind, placebo-controlled trial called Researching severe Sepsis and Organ dysfunction in children: a global perspective was conducted in 477 patients with sepsis (age >38 weeks of gestation until <18 years) to evaluate the efficacy and safety of rAPC. This study demonstrated that there was no significant difference in 28-day mortality between rAPC and placebo groups (17.2% vs 17.5%). Bleeding events were similar in both groups, but higher incidence of intracranial bleeding occurred in rAPC group (4.6%) than in placebo group (2.1%). This phenomenon was observed predominantly in children younger than 60 days.\(^5\)\(^6\)\(^7\)\(^8\)\(^9\) Hence, rAPC usage is not recommended in children.

**Anticoagulants factor concentrates—thrombomodulin**

Thrombomodulin is a vascular endothelial glycoprotein, which binds to thrombin and enhances PC activation. Activated PC with PS inhibits activated factors V and VIII to prevent further thrombin generation. Recombinant soluble human thrombomodulin (rTM) has similar pharmacological mechanism as rAPC.\(^10\)

In Japan, a randomised double-blinded control trial in adults comparing rTM with low-dose heparin showed a significant improvement in DIC symptoms in rTM group as compared with heparin group (66.1% vs 49.9%) and lower incidence of bleeding-related adverse events (43.1% vs 56.5%).\(^11\) Even though this study failed to demonstrate superior outcome in the survival rate, its usage has been approved in Japanese population since 2008. In the paediatric population, Yagasaki et al reported their first experience of rTM in 25 patients (23=infants/children; 2=neonates) with sepsis and haematological malignancy. A dosage of 380 U/kg/day of rTM was recommended and dose was reduced to 130 U/kg/day in patients with impaired renal function. In this small cohort, 80% (20/25) of patients recovered from DIC by day 7 and 88% (22/25) were alive on day 28 of treatment. Laboratory results, especially PT, FDP and AT improved on day 4 and further improvement was documented on day 7 of post-rTM treatment. The result was encouraging but all the patients received FFP and platelet transfusion to maintain fibrinogen >4.4 μmol/L and platelet >20×10↑9/L. Two neonates in this study died with intracranial bleeding. The authors were uncertain whether the bleeding was associated with rTM or as a sequelae of DIC as these newborns received suboptimal treatment at initial presentation. Hence, it was concluded that rTM must be used carefully in newborns. Furthermore, low levels of PC in neonates pose a question regarding the effectiveness of rTM in this age group.\(^12\) Subsequently, Shirahata et al investigated the effectiveness of rTM in 60 neonates. This study demonstrated greater survival rates in neonates as compared with children and adults, but failed to show good DIC resolution rate. Only 31.7% neonates received rTM as monotherapy and remaining 68.3% had another anticoagulant concomitantly. The incidence of bleeding-related adverse events in neonates (6.7%) was similar to children (5.2%) and adults (7.0%). However, the result of this trial has to be interpreted carefully because the clinical assessment of DIC was made by the treating physicians. Sixteen out of 60 neonates had DIC secondary to birth asphyxia but with favourable outcome, onset of bleeding preceded the manifestation of DIC and blood products and other anticoagulants were used concomitantly. Adult criteria of Japanese Ministry of Health and Welfare was used to calculate the resolution rate in this study.\(^13\) Even though rTM seems to be safe and more effective than other anticoagulants in paediatric population, further trials are needed to confirm its efficacy as PC is required for optimal action.

**Others**

Antifibrinolytic agents and recombinant FVIIa are not recommended in the treatment of DIC. There are significant concerns about the risk of thromboembolic events following administration of these components.

**CONCLUSION**

DIC in children is associated with high mortality. Clinical manifestations in children and neonates vary and management strategies should be individualised. Early involvement of multidisciplinary teams is crucial to initiate appropriate treatments adequately. In paediatrics, the challenge is in implementing evidence-based diagnostic criteria according to the clinical and laboratory results for each patient. The diagnosis of DIC should not be interpreted based on a single result and careful observation on the patterns of clinical signs and serial results are mandatory. However, difficulty in obtaining blood samples from critically ill children is a major challenge. Treating the underlying condition and supportive treatment with blood components in bleeding patients are the mainstay of treatment. UFH is generally recommended in non-bleeding patients. Administration of other pharmaceutical agents is not routinely recommended, but requires advice from a haematologist in specific situations. Most of the treatment strategies in DIC are extrapolated from adult studies. Hence, further trials are needed to validate the ISTH DIC diagnostic criteria and management approach in paediatrics.

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