

医学信息速递

Medical Information Express



First
Edition

新生儿和儿童的抗栓治疗 (P1)
Antithrombotic Therapy
in Neonates and Children

|医学及事务部|2019.10|

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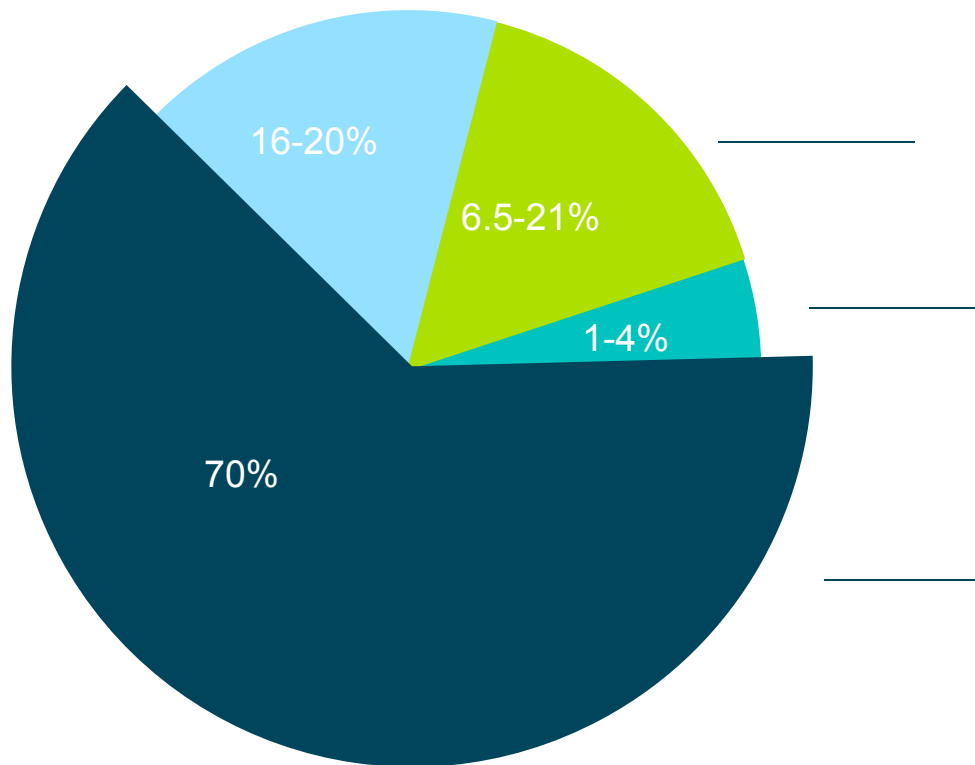
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抗凝药物的选择和抗栓方案

儿童DVT的发病率为5/10000万人，
呈上升趋势



其中16-20%的VTE患儿发生PE

6.5-21%的患儿发生复发性VTE

1-4%的患儿发生大血管血栓导致死亡

70%的患儿受血栓后综合征的影响

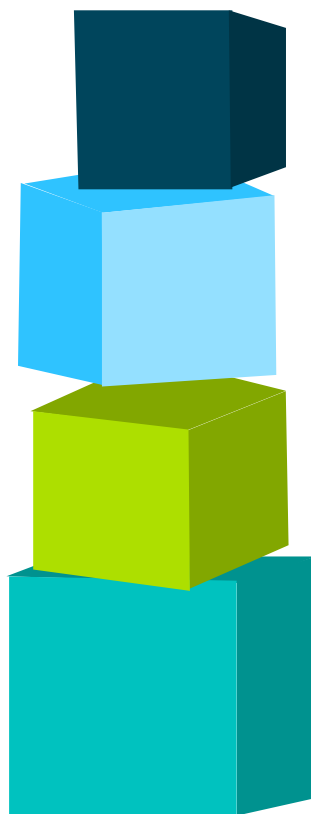


儿童DVT 发生率虽远低于成人，但是PE 发生率和VTE 复发率增高，并且血栓后综合征的发生会对儿童的生长发育与生活行动产生极大影响。



急性淋巴细胞性白血病 (ALL)
患儿血栓栓塞并发症平均发生率为5.2%

D-二聚体水平升高为静脉血栓形成的独立危险因素，
可作为体内高凝状态和血栓形成的重要指标



中心静脉置管 (CVC) 为儿童深静脉血栓的首要独立危险因素，至少85%的DVT与CVC有关

肾病综合征 (NS) 患儿血栓发病率高达6.6%

Caruso V,et al.Blood.2006;108:2216-2222.

Vidal E,et al. J Thromb Haemost. 2014;12(7) :1096-109.

Kerlin BA,et al. J Pediatr.2009;155(1):105-10.



CLINICAL GUIDELINES

 blood advances

American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism

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Recommendations

Anticoagulation in symptomatic and asymptomatic deep vein thrombosis or pulmonary embolism

Recommendation 1. The American Society of Hematology (ASH) guideline panel *recommends* using anticoagulation rather than no anticoagulation in pediatric patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) (strong recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** Although there remains limited direct evidence in children, there is very strong indirect evidence from adults that symptomatic VTE requires treatment. Further, given that the majority of VTEs occur in sick hospitalized children, in whom VTE is often life-threatening, low-quality evidence suggesting benefit justifies a strong recommendation. Hence, the panel made a strong recommendation based on extrapolation from adults, as well as potential consequences of symptomatic VTE in children, despite low certainty of evidence.

Recommendation 2. The ASH guideline panel *suggests* either using anticoagulation or no anticoagulation in pediatric patients with asymptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The adult data would suggest that treatment of most asymptomatic VTE is not required. However, there are major epidemiological, anatomical, and pathophysiological differences between VTE in adults and children that make extrapolation in this regard very difficult. The unknown benefits of anticoagulation therapy relative to the known potential risks associated with therapy do not support routine radiological screening for asymptomatic VTE. However, if detected, the decision to treat or not treat should be individualized. Research to understand the natural history of asymptomatic VTE in a variety of subgroups is a high priority.



- 症状性DVT或PE的患儿建议抗凝治疗而不是不抗凝治疗（强烈推荐）
- 建议单独抗凝治疗，反对血栓清除术或放置下腔静脉过滤器后抗凝（条件性推荐）
- 无症状性DVT或PE的患儿可以抗凝也可以不抗凝（条件性推荐），推荐根据患儿个体因素（患者栓塞并发症的风险、儿童的整体状况、抗凝治疗的风险及父母的倾向）来决定。

DVT和PE患儿是先溶栓后抗凝还是单独抗凝？

Thrombolysis, thrombectomy, and inferior vena cava filters

Recommendation 3. The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with DVT (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel considered issues such as the size and clinical impact of VTE as important in deciding the relative risk benefit ratio of thrombolysis. In most cases, the risks seem too high for the potential benefit; however, there may be individuals in whom the opposite is true. Extrapolation of adult data was difficult. There are insufficient data to address the relative risk benefit of local thrombolysis via interventional radiology compared with systemic thrombolysis, and the panel noted that the centers with access to pediatric interventional radiology were often stronger advocates of thrombolysis.

Recommendation 4. The ASH guideline panel *suggests against* using thrombolysis followed by anticoagulation; rather, anticoagulation alone should be used in pediatric patients with submassive PE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel considered submassive PE to represent children with PE who did not have hemodynamic instability. There were minimal pediatric data, and review of adult data revealed considerable uncertainty that was complicated by limitations in ability to extrapolate. The panel concluded the risks outweighed the benefits in most cases; hence, a conditional recommendation against thrombolysis.

Recommendation 5. The ASH guideline panel *suggests* using thrombolysis followed by anticoagulation, rather than anticoagulation alone, in pediatric patients with PE with hemodynamic compromise (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel considered PE with hemodynamic compromise to be life-threatening with limited time to respond to standard anticoagulation and so conditionally recommended thrombolysis in addition to anticoagulation based predominantly on extrapolation of adult data.



- DVT患儿建议单独抗凝，反对溶栓后抗凝（条件性推荐），VTE面积和临床影响决定溶栓的相对风险和获益比
- 次大面积PE患儿建议单独抗凝，反对溶栓后抗凝（条件性推荐）
- 血流动力学不稳定的PE患儿建议溶栓后抗凝，而不是单独抗凝（条件性推荐）。

新生儿和儿童常见相关血栓形成的治疗推荐-中心静脉导管 (CVDA)

CVAD-related thrombosis

Recommendation 9. The ASH guideline panel suggests no removal, rather than removal, of a functioning CVAD in pediatric

patients with asymptomatic CVAD-related thrombosis who continue to require venous access (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel placed a high value on avoiding the insertion of another CVAD in children who may have limited availability of access sites and considered the thrombogenic effect of placing another line and new endothelial injury. The panel considered that treatment of symptomatic CVAD-related thrombus with anticoagulation likely leads to minimal complications.

Recommendation 10. The ASH guideline panel recommends removal, rather than no removal, of a nonfunctioning or unneeded CVAD in pediatric patients with symptomatic CVAD-related thrombosis (strong recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** In situations in which ongoing care of the primary condition can be delivered adequately without central venous access, removal of the stimulus to the thrombosis is appropriate. An overriding principle is that any central access device should be removed as soon as feasible within the confines of the overall treatment of the child. The panel made a strong recommendation despite very low certainty of evidence for benefits based on high evidence of harm or high cost.

Recommendation 11. The ASH guideline panel suggests delayed removal of a CVAD until after initiation of anticoagulation (days), rather than immediate removal in pediatric patients with symptomatic central venous line-related thrombosis who no longer require venous access or in whom the CVAD is nonfunctioning (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel placed high value on avoiding potential risk of emboli leading to PE or paradoxical stroke, and this was thought to be achieved by a few days of anticoagulation. The risk of infection and bleeding with anticoagulation before removing the CVAD was considered to be small. The panel recognized that surgical availability was often a pragmatic determinant of timing of CVAD removal.

Recommendation 12. The ASH guideline panel suggests either removal or no removal of a functioning CVAD in pediatric patients who have symptomatic CVAD-related thrombosis with worsening signs or symptoms, despite anticoagulation and who continue to require venous access (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel considered the variability in value placed by families and clinicians on maintaining line access compared with potential risk of infection and further thrombus progression, which will vary for individual patients. If alternative venous access is readily available, then removal of CVAD in the setting of worsening VTE symptoms, despite anticoagulation, is appropriate. However, in some children, venous access is paramount.



- 对持续性需要静脉通道的症状性CAVD相关性血栓形成的患儿建议无需移除功能症状的CAVD (条件性推荐)
- 无功能或者不再需要的CAVD，建议移除导管 (条件性推荐)，并且建议抗凝数天后移除CAVD,而不是立即移除 (条件性推荐)
- 尽管进行了抗凝治疗但血栓症状持续恶化和持续需要静脉通路的患儿，可以移除也可以不移除功能正常的CAVD (条件性推荐)。

Right atrial thrombosis

Recommendation 17. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in pediatric patients with right atrial thrombosis (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Renal vein thrombosis

Recommendation 19. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in neonates with renal vein thrombosis (RVT) (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel considers the intervention to have a potential beneficial effect if the long-term benefits of avoiding hypertension and/or renal damage are considered. Anticoagulation is likely more important with bilateral compared with unilateral involvement or with progression to the inferior vena cava. Severity of disease, age, gestational age, and degree of thrombocytopenia will impact bleeding risk with treatment.

Recommendation 20a. The ASH guideline panel recommends against using thrombolysis followed by standard anticoagulation; rather, anticoagulation alone should be used in neonates with non-life-threatening RVT (strong recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** All evidence comes from observational studies in which patients who are treated with thrombolytics are typically more unwell and have bilateral RVT, as well as inferior vena cava involvement; studies did not adjust for severity of disease.

Portal vein thrombosis

Recommendation 21a. The ASH guideline panel suggests using anticoagulation, rather than no anticoagulation, in pediatric patients with portal vein thrombosis (PVT) with occlusive thrombus, postliver transplant, and idiopathic PVT (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○).

Recommendation 21b. The ASH guideline panel suggests using no anticoagulation, rather than anticoagulation, in pediatric patients with PVT with nonocclusive thrombus or portal hypertension (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks for recommendations 21a and 21b:** In children who will not be anticoagulated, follow-up monitoring is important, because extension of thrombus or organ dysfunction may require reconsideration of treatment options.



- 右心房血栓形成的患儿建议单独抗凝治疗，反对溶栓或手术血栓切除术后抗凝（条件性推荐）
- 非危及生命的新生儿肾静脉血栓形成，建议单独抗凝，反对溶栓后抗凝（强烈推荐）
- 对于闭塞性血栓、肝移植后门静脉血栓形成和先天性、特发性门静脉血栓形成的患儿建议抗凝治疗（条件推荐），非闭塞性血栓或门静脉高压的门静脉血栓形成患儿则不建议抗凝治疗（条件推荐）。

Low-molecular-weight heparin vs vitamin K antagonists

Recommendation 13. The ASH guideline panel suggests using either low-molecular-weight heparin or vitamin K antagonists in pediatric patients with symptomatic DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The decision should depend on patient values and preferences, health services resources, infrastructure and support, and underlying condition, comorbidities, and other medications.

Provoked DVT or PE

Recommendation 14. The ASH guideline panel suggests using anticoagulation for ≤ 3 months rather than anticoagulation for > 3 months in pediatric patients with provoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** The panel noted that the exact duration for optimal anticoagulation was unknown, and there are ongoing studies comparing durations within this time frame. In cases in which the provoking factor is resolved, treatment for > 3 months is unjustified. However, for patients who have persistence of the causative risk factor for provoked DVT/PE, longer anticoagulation could be considered.

Unprovoked DVT or PE

Recommendation 15. The ASH guideline panel suggests using anticoagulation for 6 to 12 months rather than anticoagulation for > 6 to 12 months in pediatric patients with unprovoked DVT or PE (conditional recommendation based on very low certainty in the evidence of effects ⊕○○○). **Remarks:** There were little pediatric data. Extrapolation of adult data might favor prolonged treatment periods in terms of VTE recurrence. However, the bleeding risk and impact on quality of life of prolonged therapy were judged to be significantly higher in children compared with adults. Patient values and preferences should be considered.



- 症状性DVT或PE的患儿建议使用低分子肝素或者维生素K拮抗剂（条件性推荐）
- 对诱发性的DVT或PE的患儿建议抗凝 ≤ 3 个月（条件性推荐），对于持续存在引起DVT或PE的致病风险因素患者应该考虑更长期的抗凝。
- 对非诱发性的DVT或PE的患儿建议抗凝3-6个月（条件性推荐）。

■ 根据现有的数据，低分子量肝素是一种有效和安全的替代普通肝素和口服抗凝剂用于治疗和预防不同年龄和基础疾病的儿童血栓栓塞事件的药物。

Albisetti M, al. Eur J Pediatr. 2002;161(2):71-7.



传递最有价值的医学信息

结束语

新生儿和儿童抗栓治疗方案和治疗药物的现有研究非常有限，目前儿童血栓栓塞性疾病的治疗主要是根据成人的数据推断而来，所以治疗中需要权衡风险和获益依据患者的个体来决策治疗。

谢谢关注!

thanks for your attention.

