

Anticoagulation Therapies in Children



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KEYWORDS

- Anticoagulation • Children • Heparin • Low-molecular-weight heparin • Warfarin
- Argatroban • Bivalirudin • Fondaparinux

KEY POINTS

- The coagulation system in the youngest children (<1 year of age) has not fully matured, which affects the way anticoagulants exert their effect in this age group.
- The properties of anticoagulant drugs that are prescribed in children are varied and the clinician should be familiar with the pros and cons of the standard anticoagulants.
- Clinicians should understand when nonstandard anticoagulants should be considered for use in children.
- Anticoagulation in children will undergo a dramatic shift and the standard agents will largely be replaced by direct oral anticoagulants currently being evaluated.

INTRODUCTION

The incidence of venous thromboembolism (VTE) in children has been increasing steadily over the past 20 years.^{1–3} This increase is attributed primarily to the increasing use of central venous access devices and the significant advances made in the management of children with chronic and/or serious medical conditions.³ The increase in the prevalence of VTE has resulted in a corresponding increase in the use of anticoagulants.¹ Although the rationale for prescribing anticoagulation to children in many situations mirrors the use in adults (VTE, extracorporeal circulation, heart disease), anticoagulating children results in problems specific to this population. First, the coagulation system in the youngest children (<1 year of age) has not fully matured, such that the very coagulation proteins that anticoagulants exert their effect on have much lower physiologic levels in children in this age group. Somewhat paradoxically, higher weight-based doses of anticoagulants are, nevertheless, required for these children owing to the pharmacokinetic differences in drug metabolism. Second, there exist significant issues with the seemingly simple act of administering medications to children. Whereas adults can swallow tablets and tolerate subcutaneous injections

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with relative ease, children, especially younger ones, may have difficulty swallowing tablets (the only available formulation for vitamin K antagonists [VKA]) and will not likely not be cooperative with injectable drugs. This consideration is in addition to the fact that it puts parents in the uncomfortable and awkward position of inducing pain in their children. Furthermore, children who require anticoagulation often have serious medical conditions that could potentially exacerbate the risk for serious bleeding or result in serious adverse drug interactions, making the use of VKA even more challenging. Last, in comparison with adults, there are relatively few data from prospective clinical trials of anticoagulation in children, rendering decision making that much more difficult.

Regardless, there remains a need to treat children with anticoagulant medications for several indications. The clinical conditions and their corresponding duration of therapy are highly variable ranging from hours to days for the prevention of thrombosis in children on extracorporeal circulation (cardiac bypass and extracorporeal membrane oxygenation) to lifelong anticoagulation for children with recurrent deep vein thrombosis and cardiac valve replacement. In addition to therapeutic anticoagulation, there is a movement to bring the ubiquitous practice of prophylactic anticoagulation in adult patients with the proper indications to pediatric practice. Although few scenarios in pediatrics exist where there is consensus regarding the use of prophylactic anticoagulation,^{4,5} current studies evaluating newer anticoagulants, specifically, the direct oral anticoagulants (DOACs) are exploring prophylactic indications. Although there is widespread use of anticoagulation, especially in hospitalized patients, there is precious little high-level evidence on which to base decisions such as choice of anticoagulant, intensity of treatment, and duration of treatment. There are published treatment guidelines, albeit with low levels of evidence, providing recommendations for the management of thrombosis for children in general⁴ and more specifically for children with heart disease.⁶ Thus, this review focuses more specifically on the properties of the anticoagulants themselves and review the pros and cons of the standard anticoagulants (heparin, low-molecular-weight heparin [LMWH], and VKA), followed by a discussion on the alternative anticoagulants, which are not widely used in clinical practice (argatroban, bivalirudin, and fondaparinux). Finally, there will be a brief mention of the potential for treatment with DOACs⁷ in children for a variety of indications by examining the properties of these agents and presenting the very limited published data. For a historical context on the anticoagulation in children, the reader is referred to [Table 1](#).

THE FUTURE LANDSCAPE OF ANTICOAGULATION IN CHILDREN

The standard anticoagulants currently in widespread use in children include unfractionated heparin, LMWH (of which there are several available), and VKA, primarily warfarin.

| Anticoagulant | Discovery | First Clinical Use in Adults | First Use in Children | First Prospective Study in Children |
|------------------------------|-----------|------------------------------|-----------------------|-------------------------------------|
| Heparin | 1916 | 1934 | 1954 | 1994 |
| Warfarin | 1929 | 1954 | 1976 | 1994 |
| Low-molecular-weight heparin | 1970s | 1980s | 1991 | 1996 |
| Direct thrombin inhibitors | 1884 | 1997 | 1999 | 2007 |
| Fondaparinux | 1985 | 2001 | 2004 | 2010 |
| Direct oral anticoagulants | 2005 | 2010 | 2013 | 2015 |

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