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PEDIANEWS

The Official Newsletter of RxPups - Student Society of Pediatric Advocates

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OUR MISSION

The Student Society of Pediatric Advocates is a student organization affiliated with the University of Georgia College of Pharmacy. We are a student group associated with the Pediatric Pharmacy Advocacy Group. The Mission of the SSPA is to bring awareness to the proper use of medication therapy in pediatric populations through various service and education- based initiatives. Service activities center around lending our medication- based knowledge to pediatric patients and their parents in our community. Educational activities are directed toward student members in an effort to safely and effectively extend pharmacy practice to pediatric populations by building relationships with mentors and professionals in the health care community, as well as supplementing didactic coursework with lectures by specialists and our peers. Overall, SSPA advocates for the safety and happiness of young patients while learning and having fun along the way. The purpose of our newsletter is to educate pharmacy students about pediatric pharmacy and advocate for pediatric patients within the University of Georgia College of Pharmacy.

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INSIDE THIS ISSUE

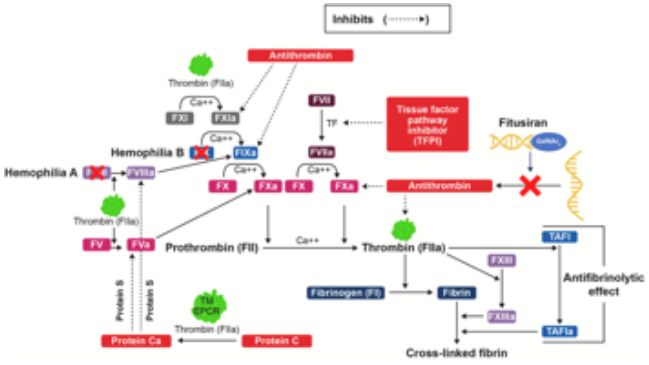
Revolutionizing Treatment of Pediatric Hemophilia: Exploring a Novel siRNA Therapeutic

Written by Sam Van Horn, PharmD Candidate 2025

The most prevalent severe congenital bleeding disorders are hemophilia A and B, which are caused by a protein shortage in factor VIII and factor IX. The etiology is almost exclusively due to a gene mutation or defect in the clotting factor gene. [1] Due to factor VIII and factor IX genes being situated on the X chromosome, males are more likely to be impacted by hemophilia as they do not possess an additional X chromosome to offset the effects of the mutated gene. All female offspring born from fathers impacted by the condition will be carriers, whereas no male offspring will be impacted. The Y chromosome is passed down from the father to the male offspring; therefore, the male offspring will not receive the X-linked hemophilia gene. If the mother is a carrier, there is a 50% chance of having an affected male and a carrier female. [1] Therefore, hemophilia primarily impacts males, but females still have the potential to be affected.

The clinical manifestations of hemophilia range from mild to severe, including spontaneous and frequent recurrent bleeding episodes seen primarily in joints, muscles, and soft tissues. In severe circumstances, these bleeding episodes may potentially become fatal or result in long-term joint damage and pain. [2] While mild or moderate hemophilia might appear later in childhood or adolescence, severe hemophilia typically presents as early as the first few months of life1. Most children are treated using intravenous clotting factor concentrates, suchas recombinant factor VIII or factor IX. [2] However, these concentrates have shown hemophilia might appear later in childhood or adolescence, severe hemophilia typically presents as early as the first few months of life. [1] Most children are treated using intravenous clotting factor concentrates, suchas recombinant factor VIII or factor IX. [2] However, these concentrates have shown development of inhibitory antibodies over time with the only real alternative being immune tolerance induction to eliminate the antibody inhibitors. Immune tolerance induction involves frequent infusions with high dose factor VIII and IX. Even this alternative is ineffective for 20 to 30% of patients with hemophilia A and 70% of patients with hemophilia B when antibodies are present. Activated prothrombin complex concentrate or recombinant activated factor VII may also be needed for prophylactic or episodic treatment in patients who qualify for immune tolerance induction in the event of bleeding episodes, which both impose a significant treatment burden when employed for prophylaxis. [3] Hence, the limited number of therapeutic alternatives exhibiting diverse degrees of efficacy and the consequently high treatment burden of the available choices renders the emergence of inhibitors a formidable challenge for individuals with hemophilia as well as healthcare providers.

Figure 1. Fiturisan Mechanism of Action



Fiturisan is a subcutaneous, prophylactic therapeutic that works through a novel mechanism for hemophilia treatment seen in Figure 1. This investigational small interfering RNA (siRNA) therapeutic interferes with antithrombin translation leading to a reduction in antithrombin synthesis to induce thrombin production. [4]

During phase 1 of the clinical development of fiturisan, once monthly fitusiran exhibited "dose-dependent mean maximum lowering in antithrombin levels by 70% to 89% from baseline" and enhanced thrombin production in those with hemophilia A or B without inhibitors. In addition, there were fewer bleeding episodes documented each month than prior to the initiation of fitusiran. [4] Phase 2 reinforced data found in phase 1, with similar data. The ATLAS-INH study is a multicentre, open-label, randomized phase 3 trial, in which an 80 mg subcutaneous monthly dose was given to patients 12 years or older. [3] Phase 3 showed a 90% reduction in bleeding rate while on fiturisan when compared to a bypassing agent. In addition, the fiturisan prophylaxis was shown to have a decrease in bleeding events when compared to clotting factor concentrates in participants with severe hemophilia A or B without inhibitors. [3] This study's secondary endpoint included the effect of fitruisan on physical health score, which showed a significant improvement in health-related quality of life in fiturisan-treated patients. [3]

This treatment is a promising hemophilia therapeutic, but the published phase 3 trial only included 12 patients under 18 years old, with only 1 of those receiving the bypassing agent and 11 receiving fiturisan. Thus, subgroup analysis was not able to be conducted based on the small number of participants in the two treatment groups. Although this data cannot be correlated to pediatric patients, fiturisan showed sustained protection against bleeding and improved quality of life with a well-tolerated side effect profile. [3] Fiturisan has the potential to be used in pediatric patients; however, children less than a year old will not be suitable as antithrombin levels do not reach adult levels until around six months of age. Currently, Sanofi is conducting the ATLAS-PEDS study, which is a phase 3 trial to verify the proper fitusiran dosage levels for male pediatric patients 1-12 years old with severe hemophilia A or B. [4] Based on these trials, fitusiran may be the first medication to help all patients with hemophilia receive preventative treatment to satisfy their unmet medical needs. Fitusiran prophylaxis may demonstrate hemostatic efficacy in patients with hemophilia A or hemophilia B with inhibitors. With its novel mechanism, fiturisan has the potential to be transformative in hemophilia management as it impacts quality of life and reduces the overall treatment burden by decreasing the need for bypassing drugs.

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FDA Approval of Dabigatran in Pediatrics for the Treatment and Prevention of Venous Thromboembolisms

Written by Jocelyn Barnett and Abigail Millsaps, PharmD Candidates 2025

Venous thromboembolism (VTE) is a serious medical condition occurring when the body is in a hypercoagulable state and leads to clot formation and potential for vascular occlusion. This can cause pulmonary embolism, stroke, ischemia, cardiovascular arrest, obstructive shock, and death. Unfortunately, this disease state is becoming more common in children. Pediatric patients who are at a greater risk for thromboembolism include those who have a central venous catheter, cancer, congenital heart disease, lupus, inheritable thrombophilia, patients taking high dose estrogen products, and post orthopedic surgery.

Treatment options for VTE in children include low molecular weight heparin (LMWH) injected subcutaneously (SC) or the vitamin K antagonists (VKA) warfarin. Both of these treatment options present significant barriers to pediatric patients. SC administration of LMWH can be stressful to administer for both patients and parents. VKAs require frequent INR monitoring, can have significant drug interactions, and often require complex dosing schedules. However, in June 2021 the FDA approved dabigatran etexilate (Pradaxa®) an oral direct thrombin inhibitor, for pediatric use.

Dabigatran is available as capsules for patients eight years and older and as pellets that can be sprinkled on food for patients ages three months and older who are unable to swallow capsules. Dosing in this population is based on age and actual body weight and can be started after a completing five days of treatment with an injectable product such as LMWH or unfractionated heparin (UF).

The FDA approved dabigatran in pediatric patients after the “DIVERSITY” trial showed that it was non-inferior to the standard of care in both safety and efficacy. “DIVERSITY” was an open label randomized trial that included 203 patients. Ninety patients were assigned to the standard of care treatment while 177 patients were assigned to dabigatran. Of the patients in the standard of care group, 20% experienced a serious adverse event, while only 12.3% experienced these in the dabigatran group. Within the dabigatran group, none of the serious adverse events lead to death, and only two were considered to be potentially life-threatening. Additionally, only two of 203 children experienced recurrent VTE, one child within three months of treatment and the other within six months of treatment. Adverse events were reported by 152 of 203 children. The most common adverse events were nasopharyngitis, headache, and abdominal pain.
Overall, a low frequency of recurrent VTEs and major bleeding events occurred during this trial. The frequency of any bleeding event while on dabigatran was 19.7% in this trial and the incidence of major bleeding events was 1.5%. The dabigatran pharmacokinetic and pharmacodynamic relationships observed in the pediatric population were similar to that of the response to dabigatran in adult populations.

This trial has proven that dabigatran is both safe and effective in the pediatric population, as well as comparable to the standard of care. However, dabigatran may prove to be a better option due to its ease of administration as an

oral option compared to the highly variable warfarin option or injectable LMWH options.

Table 1. Occurrence of Major Clotting Event on Dabigatran at 12 Months

	12 to < 18 yo (n = 153)	2 to < 12 yo (n = 42)	0 to < 2 yo (n = 8)	Total, N = 203
Recurrent VTE event	2	0	0	2
Bleeding event	37	2	1	40
All-cause death	0	0	0	0

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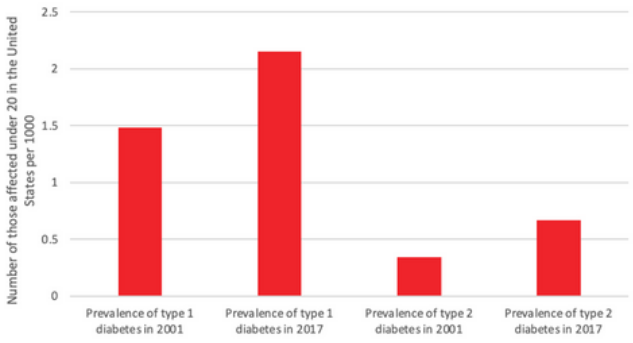
FDA Approval of SGLT2 Inhibitors for Type 2 Diabetes in Pediatric Patients

Written by Brooke Bobo, PharmD Candidate 2026

Type 2 diabetes in children is an ongoing issue around the world. Although type 1 diabetes is much more common in pediatric patients, type 2 diabetes is associated with worse patient outcomes.[1] Because of the significant difference in incidence of type 1 diabetes versus type 2 diabetes in pediatric patients, there is a significant knowledge gap in the management of the two diseases. Type one diabetes is more commonly seen in children due to an autoimmune reaction in which the body stops producing insulin. Type two diabetes develops over time, when the body develops an insulin resistance and cannot maintain blood sugar at a normal level between 70 to 150 mg/dL. [2] The SEARCH For Diabetes in Youth Study was conducted in six areas over three different years and showed almost a two times increase in prevalence of type 2 diabetes in youths from 2001 to 2017, as shown in Figure 1. [3]

Figure 1. Prevalence of Diabetes in Patients Under the Age of 20 in the United States (per 1000)



According to the International Society of Pediatric and Adolescent Diabetes, type 2 diabetes in children is typically treated with lifestyle changes, metformin, and insulin either alone or in combination. [4] In 2000, metformin was the first and only drug approved for treatment of type 2 diabetes in children. [5]

There are currently four SGLT2 inhibitors approved for adults with type 2 diabetes. In June of 2023 empagliflozin (Jardiance®), as well as the combination empagliflozin and metformin hydrochloride (Synjardy®), were approved as adjuncts to diet and exercise to manage blood sugar for children 10 years and older. [5] In adults, SGLT2 inhibitors are approved for both blood sugar regulation in type 2 diabetes and for reduction of major adverse cardiovascular effects in adults who have been diagnosed with both type 2 diabetes and cardiovascular disease.

SGLT2 inhibitors work by decreasing reabsorption of filtered glucose in the kidneys and as a result promote its excretion. [6] Medications in this class can exert positive effects on blood glucose management, cardiovascular health, and weight loss. The dosing for empagliflozin is the same in children and adults, with an initial dose of 10 mg taken by mouth once daily in the morning, and then increasing to 25 mg once well tolerated. [7] The empagliflozin and metformin hydrochloride combination pill has a similar dosing regimen and is started based on the patient's current medications, then increased to 25 mg per day of empagliflozin and 2,000 mg a day of metformin hydrochloride. [8] The FDA approval of empagliflozin was based off of the DINAMO study, which evaluated the safety and efficacy of empagliflozin in pediatric patients with type 2 diabetes over 10 years old. This study showed an almost 1%

decrease in hemoglobin A1c when comparing empagliflozin to placebo. [9] The most common side effects in children and adults taking empagliflozin are urinary tract infections and female genital mycotic infections. [8]

The approval of empagliflozin and the empagliflozin/metformin combination are a breakthrough in the treatment of pediatric type 2 diabetes. Although significant research is needed in pediatric type 2 diabetes treatment, the emergence of more treatment options is a critical step forward.

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Use of Aminophylline to Reverse Acute Kidney Injury in Pediatric Critical Care Patients

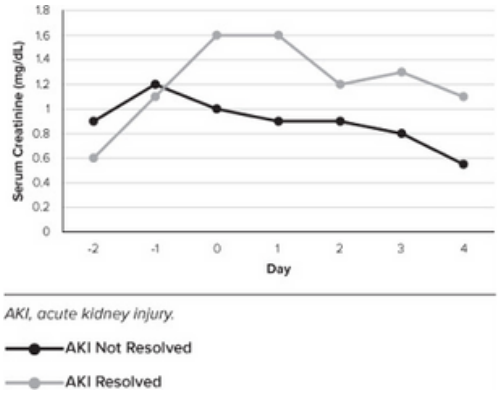
Written by Martavius Cladd, PharmD Candidate 2026

Acute kidney injury (AKI), also known as acute renal failure, is a condition in which the kidneys suddenly are unable to filter waste from the blood. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define an AKI by utilizing both serum creatinine and urine output criteria. [1] In critically ill intensive care unit (ICU) patients, vital organ dysfunction and decreased perfusion is expected. Additionally, an AKI leads to an increase in the patient's length of hospital stay, morbidity, and mortality. [2] This has created a need to investigate for potential proactive treatment options to prevent AKI in ICU patients to improve patient outcomes.

In most vessels, adenosine causes vasodilation and contributes to metabolic control of organ perfusion. However, renally it acts as a vasoconstrictor of the renal afferent arterioles, which increases reduction in renal blood flow, decreases glomerular filtration, impairs renal function, and leads to diuretic resistance. [3] Aminophylline, the prodrug of theophylline, is a bronchodilator commonly used to relieve coughing, wheezing, and shortness-of-breath (SOB) caused by asthma. It also acts as a non-selective adenosine receptor antagonist. Therefore, theoretically it should work as a reno-protective agent. [3] In one study, researchers at Le Bonheur Children's Hospital performed a single-institution retrospective chart review, using cases between January 2016 and December 2018, of AKI diagnosed pediatric ICU patients who were treated with non-continuous dose aminophylline. [3] For a patient to be diagnosed with an AKI, they must meet one of the following criteria: an increase in serum creatinine (sCr) by ≥ 0.3 mg/dL within 48 hours compared to baseline creatinine, an increase in sCr to ≥1.5 times baseline creatinine, or urinary output (UOP) volume of < 0.5 mL/kg/hr for 6 or more consecutive hours. The patient's baseline sCr was taken 1 to 2 days prior to administering the first dose of aminophylline. All patients received a standard course of 5 mg/kg/day (with a maximum dose of 300 mg/day) administered via IV either once daily over 20 to 30 minutes or divided twice daily for 5 consecutive days. [3]

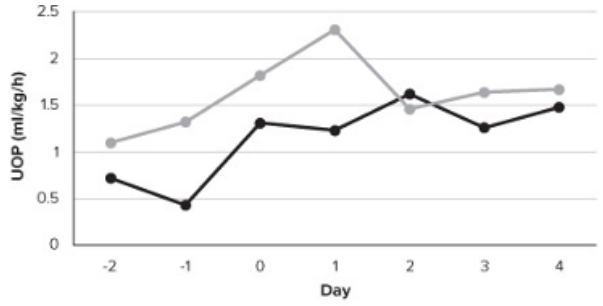
The trial was conducted using 19 individuals receiving the aminophylline therapy. Of those, 12 patients AKI resolved and 7 did not. Although the sample size was small, there was a notable difference in gender percentage of resolved versus unresolved patients. Of these 19 individuals, the female to male ratio was 14 to 5. While the male population had a roughly even split of resolved versus unresolved AKIs, the female population showed roughly double the amount of resolved AKIs versus unresolved. As shown in the figures below, the patients who were treated with aminophylline showed a decrease in median sCr (Figure 1), an increase in median UOP only after day 1 (Figure 2), and a gradual decrease in median VISCa (Figure 3). [3]

Figure 1. Median Serum Creatinine by Day



Median sCR decreased for both groups, but the AKI resolved group remained consistently higher than the not resolved group (Figure 1).

Figure 2. Median UOP by Day



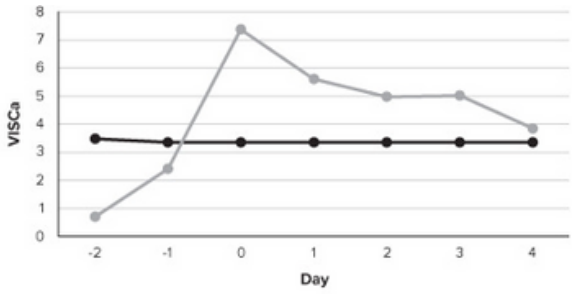
AKI, acute kidney injury; UOP, urine output.

AKI Not Resolved

AKI Resolved

Median UOP increased 19% during the first 24 hours after giving aminophylline before returning to normal (Figure 2).

Figure 3. Median Vasoactive Inotrope Score + CaCl (VISCa) by Day



AKI, acute kidney injury; CaCl, calcium chloride; VISCa = dopamine dose (µg/kg/min) + dobutamine dose (µg/kg/min) + 100 × epinephrine dose (µg/kg/min) + 10 × milrinone dose (µg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (µg/kg/min) + calcium chloride dose (mg/kg/h).

AKI Not Resolved

AKI Resolved

A gradual decrease in median VISCa is shown for patients with resolved AKI (Figure 3).

Ultimately, this trial shows a glimmer of hope that aminophylline treatment can help with improvement in renal function; however, the sample size is too small for data to be seen as clinically significant or reliable for therapy recommendations. Additionally, there is currently no clear consensus on the definition of AKI in the pediatric population is, aside from RIFLE (Risk, Injury, Failure, Loss, End Stage). [4] Therefore, the criteria for a patient that has AKI that is used in trials may impact the final results. Larger trials encompassing additional variables may yield a greater understanding of the effect that aminophylline truly has in pediatric patients appearing to have AKI and may even assist in determining a clearer definition for AKI.

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