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Recommendations from the ICM-VTE: Pediatric

The ICM-VTE Pediatric Delegates*

1 - Are the risk factors for VTE following orthopaedic procedures different between children and adults?

Response/Recommendation: Many risk factors for venous thromboembolism (VTE) in pediatric orthopaedic patients are similar to those in adults. These include older age (adolescents), trauma, malignancy, certain infections, clotting disorders and a personal or family history of VTE. However, certain VTE risk factors reported in adult literature (e.g., smoking) may be less prevalent in children, and vice versa (e.g., congenital thrombophilia).

Strength of Recommendation: Moderate.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: VTE is a common complication in adults undergoing orthopaedic surgery, and the risk factors for this condition are well established. In contrast, VTE is extremely rare in pediatric orthopaedic patients[1]. The incidence of VTE has been reported at 0.0515% for pediatric patients admitted following elective orthopaedic procedures[2]. The incidence rises to 0.10% when non-elective procedures are included[3], and peaks at 0.68% in trauma patients[4,5].

Epidemiologic data has demonstrated that the incidence of pediatric VTE is bimodal, with the highest incidence rates in infants and adolescents[6]. Pediatric patient populations with certain conditions are at an increased risk for VTE. These conditions include: congenital heart disease, nephrotic syndrome, prior splenectomy in patients with hemolytic anemia, colectomy in patients with inflammatory bowel disease, congenital thrombophilia and other genetic or metabolic diseases[7]. Catheter-related thrombosis is the single most common cause of pediatric VTE[8-10]. Central venous catheters (CVC) may directly damage the vessel wall, increase blood flow turbulence, introduce substances that damage endothelial cells, and contain thrombogenic materials.

Due to the complex pathophysiology of pediatric patients, pediatric orthopaedic patients have different risk factors for VTE compared to their non-orthopaedic counterparts[11,12]. Currently, literature suggests that the most common risk factors for VTE in pediatric orthopaedic patients are adolescent age, trauma, infection, cancer, clotting disorders, and a personal or family history of VTE[9,11,13].

Pediatric trauma patients are an identifiable subgroup that is at highest risk of VTE[14]. However, the risk of VTE is not uniform across age groups, with most cases occurring in children aged 10 – 15 years (0.1%). In one study, Guzman et al.[4], found that younger pediatric trauma patients (i.e., under 10 years) had a much lower risk of VTE compared to adolescents aged 13 - 15. Moreover, older adolescent patients (> 16 years) physiologically resembled adults, and had similar VTE frequencies to the adult population[4,8,11,15-18].

Another specific pediatric orthopaedic population at increased risk of VTE is children with musculoskeletal infections such as osteomyelitis or septic arthritis, especially if the infecting organism is *Staphylococcus aureus*[9,19-23]. The severity and duration of elevation in C-reactive protein (CRP) may predict the development of VTE, with every 20 mg/L increase in peak CRP associated with a 29% increase in risk of thrombosis[24].

In conclusion, there is a paucity of high-quality data on the risk factors for VTE in pediatric orthopaedic patients. Risk factors for VTE in pediatric orthopaedic patients are largely similar to those in adults when the same comorbid conditions are considered. Further studies are needed to develop risk-stratification protocols specific for pediatric orthopaedic patients in order to determine which subgroup of patients may benefit from VTE prophylaxis.

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*A list of the ICM-VTE Pediatric Delegates is included in a note at the end of the article.

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2 - Are there specific risk stratification methods for VTE in pediatric patients undergoing orthopaedic procedures?

Response/Recommendation: Adolescence, central venous catheter (CVC) placement, obesity, trauma, and oral contraceptive use are the most commonly reported risk factors for venous thromboembolism (VTE) in pediatric patients undergoing orthopaedic surgery. Currently, there are no standardized tools that are well-developed enough to captures all these factors. Due to the low incidence of VTE in the pediatric population, VTE chemoprophylaxis should not be routinely used except in high-risk individuals who can be identified with the use of simple screening questions.

Strength of Recommendation: Moderate.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Numerous studies have documented the increased risk for venous thromboembolism (VTE) in patients undergoing orthopaedic surgery. It has been widely reported that the incidence of VTE is lower among pediatric patients than adults[25-30]. Existing literature documents various patient characteristics, comorbidities, and perioperative variables that can correlate with increased VTE risk among pediatric orthopaedic patients. Based on these studies, a number of screening tools and VTE risk assessment algorithms have been proposed to guide risk stratification and inform clinical decision-making regarding the utilization of thromboprophylaxis strategies[31-33]. However, compared to existing VTE guidelines for adult patients, current information on pediatric patients has been poorly synthesized, with no clear consensus on the independent predictors of VTE risk. Previous studies have been limited by narrow clinical focus (e.g., lower extremity trauma patients only), too few VTE events for meaningful correlations, uncontrolled confounding variables, and conflicting findings with previously published reports. As a result, guidelines on VTE prophylaxis are reliant on seemingly discordant methods of risk stratification. We conducted a review of current literature on the risk factors for VTE among pediatric orthopaedic patients. This was done in an effort to gauge the reliability of recent studies, and to evaluate the most widely adopted risk stratification methods for this population.

Studies on the pediatric population consistently cite older age and adolescence as the most common risk factors for VTE[26-28,34-38]. Jain et al.[35], reported that for each year of age, the incidence of VTE increased 1.37-fold ($p < 0.01$) among patients ≤ 18 years of age undergoing spinal fusion surgery. Samineni et al.[37], found that the mean age of VTE amongst orthopaedic patients was 15.2 years, compared to 9.9 years for VTE amongst non-orthopaedic patients ($p < 0.0001$). Murphy et al., and Guzman et al., reported that the mean ages of children who did and did not develop VTE were 16.9 years versus 15.1 years ($p = 0.01$) and 17 years vs. 12 years, respectively[10,39]. Van Arendonk et al., subdivided their study population and found the following risk profiles for each age subgroup: 0 - 12 years (odds ratio [OR]: 1), 13 - 15 years (OR: 1.96, $p < 0.001$), 16 - 21 years (OR: 3.77, $p < 0.001$). Only one study in our review claimed that they did not find an association between age and VTE risk. However, the authors of that study were unable to identify any risk factors at all[40]. Overall, studies reported that increased age (generally past 12 years), increased the risk of VTE.

A frequently reported perioperative variable associated with increased risk of VTE is presence of a CVC or peripherally inserted central catheter (PICC)[34,36,38,41,42]. Van Arendonk et al., found that the presence of a PICC increases the OR for the diagnosis of VTE to 1.33 ($p < 0.001$)[38]. More recently, Baker et al., suggested that the pathophysiology of this relationship may pertain to CVC-associated bloodstream infection ($p < 0.001$)[41].

Another commonly cited patient comorbidity known to increase VTE risk is obesity or metabolic syndrome[26,27,34,38]. Van Arendonk et al., reported an OR of 3.03 for VTE development among obese patients compared to patients with a normal body mass index (BMI) ($p < 0.001$)[38]. Prolonged hospital stay has also been associated with an increased risk of VTE. However, it maybe be challenging to infer causal relationships as patients may have other medical comorbidities or socioeconomic factors, that can affect this variable[26,34,38,41].

The restricted clinical focus of most articles we reviewed made it difficult to analyze the distribution of the different injury types among patients who develop VTE in this setting. Overall, we found that pediatric patients with multiple fractures, or those presenting with polytrauma, were more likely to be diagnosed with VTE during their orthopaedic care[26,28,34,38]. Furthermore, the association between Injury Severity Score (ISS) and the diagnosis of VTE was further validated by Van Arendonk et al. They found a direct relationship between the two: mild injury, ISS < 9 (OR: 1, reference); moderate injury, ISS 9 - 15 (OR: 3.95, $p < 0.001$); severe injury, ISS 16 - 24 (OR: 5.94, $p < 0.001$); very severe injury, ISS 25 - 75 (OR: 7.19, $p < 0.001$). Additionally, they also found a similar relationship between VTE risk and a worsening Glasgow coma scale (GCS) score[38].

There is also some evidence to suggest that patients with neuromuscular diseases or other syndromic conditions may be at increased risk for VTE[26,35]. Jain et al., reported that among pediatric spine patients, children with idiopathic scoliosis demonstrated the lowest incidence of VTE after corrective spine surgery (OR: 1, reference). By comparison, children with congenital and syndromic scoliosis/kyphoscoliosis were at much higher risk (OR: 4.21, $p = 0.04$ and OR: 7.14, $p < 0.01$, respectively). In addition, children with thoracolumbar fractures who underwent spine surgery were found to have the highest incidence of VTE (OR: 12.59, $p < 0.01$)[35]. Similarly, Georgopoulos et al., (2016) reported that neuromuscular and neurological disorders were significantly associated with VTE ($p = 0.0042$)[26].

A number of other factors associated with VTE were considered in this review. However, a consensus on these variables was based on limited information. Two studies suggested that a patient's intubation status was associated with development of VTE in the pediatric orthopaedic population[38,41]. Additionally, one study in our review reported on prolonged tourniquet time in adolescents undergoing knee arthroscopy[27]. Most evidence suggests that both males and females are vulnerable to VTE, and that a patient's sex is not a significant predictor of VTE risk[27,35,38,40].

We found that a limited number of screening tools for VTE were specifically being used for pediatric orthopaedic patients[31-33,39]. Risk factors commonly highlighted in the pediatric population include older age, obesity, CVC use, and a positive family or past individual history of VTE. Padhye et al., developed a screening tool that assigned one point for each of the following risk factors: age > 14 years, BMI > 30kg/m^2, limited or altered mobility > 48 hours, cardiovascular flow anomalies, metabolic syndromes, CVC use, prolonged surgery > 120 minutes, and repeat/complicated surgery. If patients had a score of 4 or more points, immediate referral to hematology is advised. Furthermore, patients should be under automatic consideration for both chemical and mechanical VTE prophylaxis[33]. In another study, Ellis et al., reported on the efficacy of a screening tool that categorized risk factors as high-risk (family or past medical history of VTE), major risk (oral contraceptives, CVC, and cancer), and minor risk (obesity and other various comorbidities). Utilizing the screening tool significantly increased sensitivity for identifying risk factors such as family history of blood clots ($p < 0.001$), history of previous blood clot ($p = 0.059$), recurrent miscarriages in the family ($p = 0.010$), and smoking exposure ($p = 0.062$)[31]. Both studies recommended the initiation of VTE prophylaxis depending on the number and/or severity of risk factors as determined by their screening tools[31,33].

A recent study by MacNevin et al., evaluated the efficacy of an existing perioperative VTE screening tool. Similar to the two previous screening tools, they classified patients by "risk levels" based on their "risk scores": Level 1 low risk (risk score 0 to 2), Level 2 moderate risk (risk score 3), and Level 3 high risk (risk score $\geq$ 4). Although specific risk factors were not reported in the study, they found a significant reduction (4.09% vs. 2.13%, $p = 0.046$) in the use of thromboprophylaxis in the surgical patient cohort after implementation of the screening tool. Moderate and high-risk patients were also more likely to be undergoing bony surgical procedures, scoliosis surgery and hip procedures[32].

Finally, in a recent survey of members of the Pediatric Orthopaedic Society of North America (POSNA), respondents reported oral contraceptive pills (OCP) use (81.2%), family history of thrombosis (72.8%), and obesity (70.7%), as the top risk factors they used to guide implementation of VTE chemical and mechanical prophylaxis in their patients[39]. Trauma-related procedures (65%), spinal fusion (64%), and hip reconstruction (60%) had the highest frequency of VTE prophylaxis use, surgery on patients with a neuromuscular diagnosis had a considerably lower frequency (34%, $p < 0.001$)[36]. Similarly, Van Arendonk et al., reported on an increased OR for VTE in trauma patients with a high ISS[38].

In summary, older age, CVC placement, obesity, trauma, and OCP use are the most commonly reported risk factors for VTE in pediatric patients undergoing orthopaedic surgery. Currently, there are no standardized tools that are well-developed enough to capture all these factors. Due to the low incidence of

VTE in the pediatric population, VTE chemoprophylaxis should not be routinely used except in high-risk individuals who can be identified with simple screening questions.

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3 - In pediatric patients undergoing orthopaedic procedures, does skeletal maturity and gender influence the choice of VTE prophylaxis?

Response/Recommendation: Gender does not influence the choice of venous thromboembolism (VTE) prophylaxis. However, high-risk pediatric patients ≥ 13-years old, may benefit from the administration of VTE prophylaxis.

Strength of Recommendation: Strong.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Several clinical practice guidelines (CPG) have repeatedly identified adolescence as an independent risk factor for the development of VTE. Conversely, patient gender has not been recognized as a risk factor for the development of VTE. Most studies refer to skeletal maturity as chronologic age. Terminology such as "puberty" and "adolescence" is also used by some authors[43-48]. Unlike in adults, there is a scarcity of evidence on the risks and benefits of VTE prophylaxis in children. In addition, most of the existing studies were carried out in pediatric patients who sustained traumatic injuries[49-52], with very few evaluating patients undergoing elective orthopaedic procedures[53-56].

Interventions to prevent VTE include early postoperative ambulation, mechanical prophylaxis, and pharmacologic prophylaxis. The VTE risk threshold for administration of prophylaxis must evaluate both the harm of a VTE event, as well as the possible adverse side effects brought-on by the prophylactic agent itself[57-66].

Most studies evaluating the incidence of VTE in pediatric patients showed no difference in risk with respect to gender[67-75]. Some isolated studies identified female gender as a contributing factor; however, the level of risk contribution was negligible compared to other risk factors[76,77].

The precise age at which pediatric patients are at highest risk of VTE remains unknown. The evidence to date currently suggests that in pediatric patients undergoing orthopaedic procedures, children ≥ 13-years old are at the highest risk of VTE development[78,79].

Due to the low incidence of VTE in the pediatric orthopaedic surgical patients, and the considerable risks associated with thromboprophylaxis administration, universal thromboprophylaxis cannot be recommended[72]. The age at which a pediatric patient is considered at significant risk for VTE development remains a contentious issue. Age cut-offs for VTE risk tend to range from 9 to 15. The ambivalence towards age and risk is best reflected in a national multidisciplinary consensus study on VTE in pediatric trauma. They found that the risk of VTE appears augment in early adolescence and continues to increase into young adulthood[72].

A survey of pediatric trauma practices indicated that 13% of trauma centers described their utilization of low-molecular-weight heparin (LMWH) prophylaxis in patients aged 11 to 15 as "often" or "always." Additionally, the incidence increased to 57% in patients aged 16 to 20[46].

In 2017 the Pediatric Trauma Society (PTS), in conjunction with the Eastern Association of Surgery for Trauma (EAST), conducted a systematic review and published CPG on prophylaxis against VTE in pediatric trauma[80]. They recommended that pharmacologic and/or mechanical thromboprophylaxis be considered in all pediatric trauma patients ≥ 15 years-old who are at low risk of bleeding. However, due to the inadequacies of available data, the significance of these CPG was limited. Additionally, there is no evidence to support routine surveillance with ultrasound screening for VTE in injured children[81].

In one study, Hanson et al.[79], concluded that despite the low incidence of VTE, emerging data indicates that critically injured adolescent patients are at significant risk of developing VTE. As the risk of bleeding with prophylactic doses of LMWH is quite low, critically injured adolescent patients is one population that stands to benefit greatly from the implementation of a protocol for VTE prophylaxis. In conjunction with mechanical prophylaxis, LMWH is appropriate for many critically injured adolescent patients who have a low risk of bleeding. CPG on early and aggressive postoperative mobilization have helped drastically reduce VTE occurrence and must continue to be part of the standard of care.

In a recent meta-analysis of studies on VTE risk factors and VTE risk-assessment models, Mahajerin et al.[80], found that in children with a low risk of bleeding who are hospitalized for a traumatic injury, pharmacologic prophylaxis should be considered for those > 15 years old and in younger post-pubertal children with injury severity score (ISS) > 25. Furthermore, we recommend against the use of routine pharmacologic prophylaxis in pre-pubertal children, even those with ISS >25. Similarly, current EAST guidelines state that pharmacologic prophylaxis should only be used in either children ≥ 15-years old, or post-pubertal children under the age of 15 with an ISS greater than 25. However, these guidelines are not definitive due to the lack of supportive data and overall low quality of evidence.

Despite the paucity of evidence supporting reliable treatment algorithms, CPG on the management of VTE in pediatrics have been established. In general, they have all identified adolescence and older age as independent risk factors and identified particular age cut-offs for the administration of specific VTE prophylactic agents[82,83]. While the overall incidence of VTE in pediatric patients remains low, the identification of a prophylactic agent that is both safe and effective remains a challenge. Currently, a reliable treatment algorithm for the management of VTE in pediatric patient is non-existent, further clinical trials with innovative study designs are required to aid in its development.

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4 - Is routine VTE prophylaxis necessary in children with chronic neuromuscular conditions?

Response/Recommendation: The overall risk of venous thromboembolism (VTE) in children with chronic neuromuscular conditions is very low. Routine VTE prophylaxis in children with chronic neuromuscular conditions is not necessary, unless additional VTE risk factors are identified.

Strength of Recommendation: Moderate.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: In comparison to adults, the incidence of VTE in children is significantly lower[84-86]. Large multicenter investigations of pediatric VTE have reported an incidence of 5.3 per 10,000 hospital admission and 0.7 per 100,000 children[86,87]. More than 80% of pediatric VTE events occur in children with 1 or more risk factors[88]. Furthermore, the incidence of 'idiopathic' VTE is only 5% in children, compared to 40% in adults[89-94]. Pediatric incidence of VTE has a bimodal distribution, with the highest proportions reported in infants aged 1 to 23 months and adolescent females[90,95]. The incidence peaks in adolescents due to contraception use, smoking, and obesity. Additionally, the composition of the hemostatic system in adolescents is simultaneously transitioning to the comparable adult system[96,97]. Despite the significant differences in the epidemiology and pathophysiology between pediatric and adult VTE, most clinical management guidelines for pediatric patients are extrapolated from adult literature without targeted evidence[97,98].

In 2000, Feudtner et al.[99], developed the definition for children with complex chronic conditions (CCC), of which there are 12 categories. Neuromuscular complex chronic conditions (NCCC) was defined to encompass a host of conditions including cerebral palsy, spina bifida, brain malformations, muscular dystrophy and seizure disorder[100]. VTE events occurs much less frequently in disabled children than in their adult counterparts[101]. Children with NCCC frequently require hip and spine surgery that is resource expensive[102]. Additionally, spine and lower-extremity orthopaedic surgery can be associated with a substantial increase in VTE risk, attributed to immobility, and inconsistent use of thromboprophylaxis[103]. However, in children with NCCC, due to their chronic immobility, the general consensus is that the risk of VTE is rare, yet little research exists to support this assertion.

Adults with neuromuscular disease undergoing orthopaedic total joint arthroplasty (TJA) have been shown to experience an increased risk for perioperative complications[104-107]. Specifically, abnormalities in muscle tone associated with cerebral palsy, among others, are associated with a high rate of complications of the vascular system, especially deep venous thrombosis (DVT)[108]. In an adult study of 28 patients with severe motor and intellectual disabilities, the authors found that the rate of asymptomatic DVT was high. Additionally, thrombosis was absent in the soleal veins but present in the femoral and common femoral veins[108]. Conversely, similar findings in children have not been noted. Over a 4-year period at one rehabilitation institution, 532 children's (< 18 years old) charts were reviewed, 9 of whom were diagnosed with a DVT. The authors found that the majority of these children had suffered a spinal cord injury leading to an acute change in their baseline mobility[101]. In this study, the majority of patients diagnosed with DVT were over 13 years of age, leading the authors to conclude that VTE chemoprophylaxis in the disabled pediatric population, especially prepubertal patients, should be questioned.

Previous research has demonstrated that overall complication rates are considerably higher amongst patients undergoing surgical correction for neuromuscular scoliosis, vs. those undergoing surgical correction for idiopathic scoliosis[109-111]. VTE is a known complication after pediatric spinal fusion[112]. However, a detailed review of the neuromuscular complications from the Scoliosis Research Society Morbidity and Mortality (SRSMM) database showed that the reported annual rate of VTE was low, varying between 0 to 0.31%.

Shore et al.[100], utilized the Pediatric Health Information System Plus (PHIS+) database to assess the incidence of VTE after elective hip and spine surgery in children with NCCC. They found that of 4,583 pediatric patients undergoing orthopaedic surgery, only four experienced a VTE event, all of whom had a prior diagnosis of cerebral palsy. However, 2 of the 4 children experienced their VTE episode prior to surgery, resulting in a corrected VTE rate of 0.04%. It is also important to note that in both cases of VTE, patients had a preoperative diagnosis of a coagulation disorder, leading the authors to conclude that based on their findings, no prophylaxis is required in children with NCCC undergoing elective hip and spine surgery, unless other known risk factors are also present.

VTE in pediatric orthopaedic patients is a rare occurrence. Furthermore, limited data is currently available to guide decision making and practice management. The presence of a neuromuscular disorder has been shown to increase the risk of VTE in adults undergoing TJA by 30%[107]. Despite this, a similar association has not been demonstrated in the limited literature on orthopaedic procedures in pediatric patients. In summary, based on the limited evidence available to date, VTE prophylaxis for children with NCCC undergoing orthopaedic surgery is not recommended, unless additional identified risk factors for thrombosis exist.

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5 - Do pediatric patients placed in a lower extremity cast immobilization require routine VTE prophylaxis?

Response/Recommendation: Routine thromboprophylaxis is not recommended in pediatric patients with cast immobilization. Furthermore, young age is protective against deep venous thrombosis (DVT) in children. Unlike the adult population, the association between lower extremity cast immobilization

and venous thromboembolism (VTE) risk has not been established in children. As development of acute DVT is unusual in children, routine prophylaxis is not recommended. However, there are also no clear recommendations for children with more than 3 risk factors for the development of VTE.

Strength of recommendation: Weak.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: The presence of specific thromboembolic risk factors such as older age, along with the nature of extremity injury, are the main determinants when deciding whether to administer thromboprophylaxis in patients with lower leg trauma immobilized in a cast or a splint[113-115].

Amongst pediatric trauma inpatients, those aged 16 to 21 years had a 4-fold increase in risk of VTE development, compared to patients 12 years or younger. Additionally, patients aged 16 to 21 years also had significantly higher odds of VTE development compared to those aged 13 to 15 years. Furthermore, no association of significance was identified between patients' age and injury severity. Clinical screening for risk of VTE may be applied to older age groups (≥ 13 years). In addition, a VTE prophylaxis protocol must be implemented in patients > 16 years old, as the risk of VTE increases most dramatically at 16 years, after a smaller increase at 13 years[116].

The association between VTE and altered mobility has been demonstrated in adult patients. However, there is paucity of data on VTE following cast immobilization in children. Decreased mobility, even without the use of a cast, is known to increase the risk of DVT. Similarly, immobilization for longer than 3 days ($p < 0.0001$) and hospitalization for ≥ 7 days ($p < 0.0001$), are potential risk factors for VTE development in admitted pediatric patients (< 20 years old)[117]. The definition of 'immobilization' is challenging in children as younger infants may not necessarily be ambulatory. Further evidence based on prospective studies is necessary to validate these findings.

Oral contraceptive (OCP) use is a common risk factor for VTE in adolescent females. Long travel, immobilization, plaster cast, and/or trauma are all transient risk factors that can trigger VTE events in OCP users[118].

Common risk factors for VTE in adults with inherited thrombophilia do not seem to increase the thrombotic risk in children who are carriers of their parents' mutated gene. Screening for thrombophilia in otherwise healthy children (< 15 years old) with have a family history of coagulation disorders seems unjustified[119].

The 2017 Polish Consensus Statement (PCS) does not recommend routine thromboprophylaxis in patients with lower limb trauma immobilized by the use of a plaster cast (class C recommendation)[120]. Their findings have since been validated by several studies[121-124]. On the other hand, the PCS does recommend VTE prophylaxis in moderate to high VTE risk patients immobilized following lower limb trauma. Additionally, they recommend the administration of low-molecular-weight heparin (LMWH) in this patient population. Furthermore, prophylactic LMWH is recommended for the duration of immobilization, and for 5 – 7 days afterwards. However, all the above recommendations are based on studies in adult populations. Currently, no studies suggest the above in the pediatric age group.

Testroote et al., recommended that all adult patients treated with cast immobilization be considered to receive VTE prophyalxis[113,125-127]. However, based on the limited available literature, the incidence of VTE in patients receiving cast immobilization is not large enough to justify pharmacological prophylaxis in all these patients, as the additional costs and bleeding risks associated with pharmacotherapy must also be considered (0.3% major bleeding)[128].

Haque et al., developed a patient questionnaire based on the National Institute for Health and Care Excellence (NICE) in-patient guidelines as well as the UK College of Emergency Medicine (CEM) outpatient guidelines. Ambulatory outpatients being managed with cast immobilization for foot and ankle fractures were the primary target of this questionnaire. Risk factors included: age > 65 years, above-knee plaster cast, long travel in cast, hormone replacement therapy or estrogen-containing contraceptive, varicose veins, active (heart, lung, bowel, or joint) disease, body mass index (BMI) > 30 kg/m^2, personal history of blood clot, first degree family history of blood clot, known thrombophilia, pregnant or within 6 weeks of child birth, hospital admission within the last six weeks, active cancer or receiving cancer treatment (including tamoxifen and raloxifene), and achilles tendon rupture. Patients were classified as high- or low-risk for VTE and administered LMWH accordingly[129]. Additionally, the Leiden–Thrombosis Risk Prediction score (L-TRiP cast) was developed for adult patients with cast immobilization and has a cutoff of 10 points to stratify individuals into high- vs. low-risk categories[128]. This score was developed with data from the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis and includes patients 18 to 70 years old. Further studies are required to develop similar risk prediction models in children. The difference in pathophysiology of coagulation in children, compared to their adult counterparts, seems to confer protection against VTE in younger patients.

Given the low incidence of VTE in the pediatric population, the risks associated with routine VTE prophylaxis administration, and lack of available evidence to recommend regular screening, routine VTE prophylaxis cannot be recommended in pediatric patients treated with cast immobilization. As has been done in the past for the adult population, research efforts should focus on the development of evidence-based risk-stratification models that include a recommendation for the type and duration of VTE prophylactic agent in pediatric patients receiving cast immobilization.

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6 - Is early ambulation and/or mechanical intermittent devices sufficient for VTE prophylaxis in otherwise healthy pediatric patients undergoing orthopaedic procedures?

Response/Recommendation: Considering the rarity of venous thromboembolism (VTE) events in healthy pediatric and adolescent patients undergoing elective orthopaedic procedures, early ambulation and/or mechanical intermittent devices are sufficient for the prevention of VTE. However, pediatric orthopaedic patient undergoing surgery following major trauma, as well as patients undergoing major reconstruction resulting in prolonged immobilization, require critical care. Additionally, they exhibit other risk factors for VTE and prophylaxis with a supplementary pharmacologic agent should be considered.

Strength of Recommendation: Moderate.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Studies of national databases have found that the incidence of VTE following pediatric orthopaedic procedures is generally quite low. The lowest incidence rates of VTE have been reported in pediatric patients undergoing elective orthopaedic procedures, with estimates as low as 0.0515%[130], and 0.04%[131]. Additionally, the incidence of VTE rose to 0.10% when including patients undergoing any orthopedics procedure, including patients where the indication was trauma or infection[132]. The highest rates have been reported in studies of pediatric orthopaedic patients undergoing surgery following trauma (up to 0.68%)[133,134].

Current literature is also considerably limited when examining the rates of VTE occurrence in specific pediatric orthopaedic conditions or procedures. In one study of adolescents undergoing knee arthroscopy, 0.25% of patients experienced a symptomatic VTE event[135]. Additionally, Jain et al., found that in a review of the National Inpatient sample (NIS), 0.21% of pediatric patients undergoing spinal fusion surgery experienced a VTE event[136]. The remainder of studies were surveys of current members of the Pediatric Orthopaedic Society of North America (POSNA)[137-139].

Clinical practice guidelines (CPG) by the American Academy of Pediatrics (AAP) recommend that the decision of whether to use mechanical or chemical prophylaxis be determined based on the level of an individual patient's VTE risk[140]. Unfortunately, the only specific elective orthopaedic risk factor was for hip and knee reconstruction. Additionally, the only orthopaedic reference came from the American College of Chest Physicians (ACCP) guidelines, which focus on adult reconstruction[141]. Nevertheless, the AAP guidelines found that early ambulation and mechanical prophylaxis were adequate for the prevention of VTE following most pediatric orthopaedic operations. However, they do list certain high-risk scenarios where chemical prophylaxis must be considered. These include patients with a history of prior VTE, obesity, immobility, and trauma. Similarly, recommendations on effective risk-stratification models have been provided by the Association of Pediatric Anesthetists of Great Britain and Ireland[142].

In conclusion, the utilization of existing risk stratification tools and prediction algorithms may help delineate which patients are at an increased risk of VTE following orthopaedic procedures[143-145].

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7 - Concerning VTE risk, which surgeries can be considered major, and which surgeries can be considered non-major in pediatric orthopaedics?

Response/Recommendation: The overall risk of venous thromboembolism (VTE) in pediatric patients undergoing orthopaedic surgery is low. Pediatric orthopaedic patients undergoing surgery for the management of certain severe musculoskeletal infections (Methicillin-resistant *Staphylococcus aureus* [MRSA] with Panton-Valentine Leukocidin [PVL] +) are an increased risk of VTE. Additionally, hip, spine, and sports surgery have been identified as risk factors of VTE. Furthermore, the risk of VTE after pediatric orthopaedic surgery appears to be greatest in adolescents. Moreover, coagulation disorders (such as familial thrombophilia), as well as the presence of indwelling central venous catheters (CVC), were found to increase VTE risk substantially more than any specific orthopaedic surgical procedure. In conclusion, adolescents with identifiable confounding VTE risk factors in this setting would benefit greatly from the utilization of perioperative VTE screening tools and risk stratification models.

Strength of Recommendation: Moderate.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: VTE, a disease process that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE), is a rare occurrence in pediatric patients. Estimates have placed the occurrence of VTE in pediatric patients to be between 0.07 to 0.49 per 10,000. However, it is the second most common cause of hospital-acquired morbidity for pediatric patients in the United States, with a reported incidence of 5.3 per 10,000 pediatric hospital admissions[146-150]. Previous literature has demonstrated that the incidence of VTE in pediatric patients has a bimodal distribution, with the highest proportions reported in infants aged 1 to 23 months and in adolescent females[150,151]. In hospitalized pediatric patients, the risk factors for VTE development include venous catheterization/central line, malignancy, infection/sepsis, congenital heart disease, trauma/surgery, and inherited thrombophilia. From the aforementioned list, the presence of a central venous catheter/center line demonstrated the greatest risk of VTE development[152-154]. Despite this, there is a paucity of pediatric-specific literature aimed at determining the risk of VTE risk after orthopaedic surgery.

Recent studies have demonstrated that the incidence of VTE in pediatric patients has been rising over the last two decades[146,155-157]. It is hypothesized that this rise may be attributed to a combination of factors. These include: increasing awareness of pediatric VTE, increasing medical complexity of pediatric patients, and increased frequency of application of central venous access[158]. In adults, certain orthopaedic procedures are associated with an increased risk of VTE. Despite this, the same association has not been demonstrated in pediatric patients. Conversely, in pediatric patients, individual patient attributes are more predictive of VTE risk than the procedure being performed. Georgopoulous et al.[159], first reported on the incidence of pediatric VTE after elective orthopaedic surgery. In a study evaluating the Pediatric Health Information System (PHIS) database, the authors found that the incidence of pediatric VTE after elective orthopaedic surgery was 0.0515%. Increased age, a diagnosis of a metabolic condition (such as fluid-electrolyte imbalance), obesity, and complications associated with implanted devices and/or surgical procedures were independently identified as significant risk factors for VTE development.

Central catheter related thrombosis has been reported to have the greatest risk for VTE development in pediatric patients[160]. In a retrospective study of 78 patients, Sandoval et al.[146], found that in patients with a CVC, 45% experienced a DVT episode, 50% of which occurred in the femoral vein. To summarize, recognition of increased VTE risk in pediatric patients undergoing orthopaedic surgery with a CVC in place is critical. Furthermore, immediate removal of the catheter as soon as it is no longer needed is paramount.

Infection is a known risk factor for the development of VTE as inflammatory mediators contribute to the activated blood coagulation cascade[161]. This risk is compounded in patients with immobility associated with musculoskeletal infections such as osteomyelitis or septic arthritis of the lower extremity[162]. In particular, children suffering from disseminated musculoskeletal infection with *Staphylococcus aureus* appear to be at greatest risk of VTE development[162]. Specifically, infection with MRSA possessing the PVL gene has been implicated[163]. In one study, Crary et al.[162], retrospectively reviewed 35 patients with confirmed osteomyelitis. They found that 29% of patients with an active MRSA infection developed DVT during the acute infection phase, of which eight occurred adjacent to an infection, and two secondary to CVC use. Additionally, Hollmig et al.[164], found that patients > 8 years old presenting with MRSA and a C-reactive protein > 6 mg/dL are at an increased risk for the development of VTE. Clinicians must be wary of the increased risk of VTE associated with pediatric patients undergoing orthopaedic surgery for the management of disseminated musculoskeletal infection. Moreover, chemical VTE prophylaxis in this population must be considered.

Age is an important factor when considering the risk of VTE in pediatric patients undergoing orthopaedic surgery. When stratified by age, the incidence ranges from 0.02% for patients < 5 years to 0.13% in those aged 10 - 15 years. A 10 year survey of a single trauma center reported zero cases of VTE in patients < 13 years of age[165]. Additionally, recent date from the American National Trauma Bank suggests that the incidence of VTE is 0.1% in patients < 12 years, 0.3% in those 13 - 15 years, and 0.8% in patients > 16 years[166]. In conclusion, pediatric patients > 13 years old are at an increased risk for developing VTE after orthopaedic surgery. Furthermore, chemical prophylaxis should be initiated in this patient population if additional risk factors are identified preoperatively.

Although the rates of VTE in patients < 15 years-old are a 100-fold less compared to VTE rates in an 80 years-old patient, adolescents are known to have significantly increased risk of VTE after trauma than their younger counterparts[166,167]. In a study of the PHIS database, Murphy et al.[168], found the incidence of VTE to be 0.058% after lower extremity trauma. Additionally, Allen et al.[169], found that at a single institution, the incidence of VTE after orthopaedic trauma was 1.1%. Interestingly, in this cohort, 86% of children who developed VTE were receiving thromboprophylaxis. Moreover, motor vehicle injuries and orthopaedic surgery were found to be synergistic predictors for the development of VTE after orthopaedic trauma. Careful consideration of the mechanism of injury, age of the patient, and identification of additional comorbid risk is paramount in these patients. Due to the high risk of VTE occurrence, the use of chemoprophylaxis in trauma patients is warranted.

The incidence of anterior cruciate ligament (ACL) reconstruction in patients aged 15 - 18 has nearly doubled in the last 10 years[170]. Although major complications after knee arthroscopy are rare, pediatric VTE has been reported after elective knee arthroscopy[171]. In one study, Murphy et al.[171], reported a VTE incidence of 0.25% at a single institution. Similarly, in a study of the National Health Service (NHS) database, Nogaro et al.[172], found the incidence of VTE in patients undergoing ACL reconstruction to be approximately 0.37%. Additionally, in a more recent study, Ellis et al.[173], found that risk factors for VTE development were present in 32.5% of adolescent undergoing elective arthroscopic procedures. In conclusion, the findings of the aforementioned studies suggest that adolescents undergoing knee arthroscopy may benefit from the utilization of a preoperative VTE screening tool.

Adolescent idiopathic scoliosis (AIS) is the most common cause of structural spinal deformity in patients between the ages of 10 and 18[174]. Although surgical correction provides good outcomes for most patients, it carries significant risk of medical complications, including VTE[175]. In one study of the National Inpatient Sample (NIS) database, the overall complication rate of AIS surgery was 7.6%, with 0.2% of patients experiencing a VTE event[176]. Jain et al.[177], found that using the same database the incidence of VTE in pediatric patients over a 10 year period was low. Additionally, univariate analysis identified increasing age and the presence of congenital or syndromic scoliosis as independent risk factors for the development of VTE. Fatal VTE is a rare occurrence after pediatric spine surgery. However, the risk of bleeding following administration of VTE chemoprophylaxis is well-established. Therefore, expert opinion has recommended against the routine use of chemical prophylaxis in this patient population[178]. Despite this, VTE chemoprophylaxis should always be considered in pediatric spine surgery patients immobilized for prolonged periods of time[176,178].

Although recent literature has demonstrated an increase in incidence of pediatric VTE, the overall rate of VTE occurrence in pediatric orthopaedic patients remains quite low. Furthermore, particular risk factors specific to individual patients, rather than type of orthopaedic procedure, are more predictive of the risk of VTE development in this patient population. In conclusion, chemical prophylaxis should be considered in both pediatric patients with disseminated musculoskeletal infection (especially MRSA PVL +) and in adolescents undergoing orthopaedic procedures who have additional risk factors for the development of VTE.

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8 - What pediatric procedures require routine administration of VTE prophylaxis?

Response/Recommendation: In the absence of other identifiable risk factors of venous thromboembolism (VTE), chemoprophylaxis for VTE should not be routinely prescribed in patients younger than thirteen undergoing orthopaedic procedures.

Strength of Recommendation: Weak.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: VTE, a disease process that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE), is well-studied in the adult population. However, in the pediatric orthopaedic population, VTE occurrence is still rare. Recent estimates have placed the incidence of post-operative VTE in this setting to be between 0.05 – 0.1%[179]. Due to a paucity of evidence recommending routine pharmacologic prophylaxis for pediatric orthopaedic patients, we attempted to identify the reported incidence of VTE in certain "high-risk" orthopaedic procedures in the pediatric population.

In a study of the Pediatric Health Information System (PHIS) database, Georgopoulos et al.[180], reported a VTE incidence of 0.063% in pediatric patients undergoing elective orthopaedic procedures. However, this database can result in a gross underestimation of the true incidence of VTE. Furthermore, after conducting a multivariate analysis, no single elective procedure was identified as significantly increasing the risk of VTE. In another study of the National Surgical Quality Improvement Program (NSQIP) database, the incidence of VTE, DVT, and PE in pediatric orthopaedic patients was 0.1%, 0.09%, and 0.01%, respectively. Additionally, the highest prevalence of VTE was reported in patients undergoing infection-related procedures[181].

In two separate studies, VTE rates in pediatric patients undergoing knee arthroscopy were reported to be between 0.25% to 0.27%. Additionally, they found that the majority of VTE events occurred in patients with known predisposing risk factors[182,183]. In a another study, Allahabadi et al.[184], reported that the incidence of VTE was 0.61% in adolescents who underwent a pelvic osteotomy. Surprisingly, of the nine patients that developed VTE, nearly half (4/9 patients) had received pharmacologic prophylaxis postoperatively.

In a study of the PHIS database, Shore et al.[185], found that the incidence of VTE after elective spine and hip surgery in children with neuromuscular disorders was 0.04%. Furthermore, both patients who experienced a VTE event had a prior diagnosis of a coagulation disorder. Therefore, in the absence of known risk factors, the administration of VTE chemoprophylaxis in this setting may be unnecessary.

In a survey of Scandinavian scoliosis centers between 1963 and 1976, the reported incidence of DVT was 0.65%[186]. In another study, follow-up doppler ultrasonography was performed on 40 consecutive post pubertal adolescents undergoing posterior spinal instrumentation. Of the 40 patients, two cases of transient thromboses were identified, both of which resolved spontaneously[187]. Additionally, in a study of 1,471 pediatric patients undergoing scoliosis surgery, Erkilinc et al.[188], reported that the incidence of DVT was 0.13%. Therefore, the authors concluded that mechanical prophylaxis was sufficient in this setting. Furthermore, in a study of the National Inpatient Sample (NIS) database, Jain et al.[189], found that in pediatric patients undergoing spine surgery, the incidence of DVT was 0.21%. In addition, when compared to children with idiopathic scoliosis, those with congenital, syndromic or traumatic etiology experienced a higher incidence of VTE[190].

Several studies have evaluated the incidence of VTE in pediatric trauma patients. In a study of the PHIS database, Murphy et al.[191], found that the incidence of VTE in patients with lower-extremity trauma was 0.058%. Conversely, in another study utilizing the Kid's Inpatient Database (KID), the incidence of VTE in pediatric orthopaedic trauma patients was 0.68%. However, incidence of VTE in pediatric patients with isolated fractures of the lower-limbs was 0.25%, compared to 0.32% in patients with pelvic injuries[192]. In another study, Greenwald et al.[12], found that over a 20-year period the incidence of DVT in patients with pelvic and femoral fractures was 0.17%. Additionally, there were no reported cases of PE or mortality secondary to VTE. Moreover, Internal fixation of lower limb fractures is commonly quoted as a risk factor for VTE development[193]. Despite this, we did not find any data to support this claim.

Current data suggests that the incidence of VTE in pediatric patients is highest during adolescence[181]. Similarly, a recent follow-up survey of the Pediatric Orthopaedic Society of North America (POSNA) for 46 VTE cases found that the average age at diagnosis was 14.3 years[194]. In addition, Murphy et al.[183], found that patients that experienced a VTE event were 15 to 18 years old and had at least one other identifiable risk factor for VTE. These included: oral contraceptive (OCP) use, smoking, obesity, an arthroscopically assisted open procedure, or tourniquet time > 60 minutes. Furthermore, two separate studies with large cohorts identified age as a statistically significant independent risk factor for the development of VTE. O'Brien et al.[195], identified 14 years of age as the threshold for increased VTE risk. Additionally, Vavilala et al.[193], found that there was a 5-fold increase in risk of DVT between the ages of 10 and 15. Moreover, Meier et al.[196], recently established the Best Evidence Statement (BESt) clinical practice guidelines (CPG) for VTE prophylaxis in children. They found that age > 10 years and altered mobility were the two most important factors when considering initiating VTE prophylaxis.

Several studies have shown that the presence of a CVC carries the single greatest risk for DVT development in the pediatric population. Furthermore, some studies have estimated that 33% to 80% of all pediatric DVT can be attributed to the presence of a CVC[188,197-200].

In a retrospective case control study, Stokes et al.[201], demonstrated a correlation between obesity and DVT. They found that obese pediatric patients were 2.1-times more likely to experience a VTE event, compared to non-obese patients. Similarly, a recent large database study demonstrated an increased risk of DVT in obese patients compared to nonobese patients[202].

Infection a common and well-established risk factor for the development of VTE[181,203,204]. Extensive septic thrombosis is associated with infections caused by microorganisms producing necrotizing toxins such as Panton-Valentine leucocidin (PVL). In conclusion, infection with methicillin-resistant *Staphylococcus aureus* infection justifies the use of VTE thromboprophylaxis[203].

The low incidence of DVT, heterogeneity of available clinical studies, multiplicity of risk factors, and age-related variability in risk levels has made it difficult to establish evidence-based guidelines for chemoprophylaxis in pediatric patients undergoing orthopaedic procedures. In conclusion, thromboprophylaxis should be considered in adolescents with additional identifiable risk factors. Specifically, thromboprophylaxis should be considered in pediatric patients with osteomyelitis or disseminated infection and in pediatric patients with a central line.

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Appendix

Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G867).

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