Developing and Evaluating Evidence-Based Medicine in Pediatric Orthopaedic Surgery

by
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ABSTRACT

The purpose of this thesis was to review how a simple clinical pediatric orthopaedic surgeon might be able to create and use different levels of Evidence Based Medicine.

Practicing evidence-based medicine involves the assessment of current available literature for its level of evidence, validity, and significance; and subsequently applying results to clinical practice. Much of the literature in pediatric orthopaedic surgery is level IV (case series) or level V (case reports). Despite the lower level, this literature is still important for reporting adverse events and disseminating information of novel treatment techniques.

A case report of a novel adverse event is presented: permanent physeal arrest from the use of eight plate for guided growth. Following, a case series aimed to assess if the Fitbone intramedullary lengthening nail could provide successful lengthening with improved rehabilitation and minimal hospital stay, while achieving therapeutic aims of lengthening and correcting mechanical axis. Thirdly, one year of publications in 3 highly respected pediatric orthopaedic journals was reviewed. The use of "numbers needed to treat" as an adjunct to statistical analysis and level of evidence was determined for each article.

And finally, a systematic review of the literature looks at the incidence of venous thromboembolism in pediatric orthopaedics. This study began with a stringent, comprehensive

protocol that detailed the plan and search strategy. Initially, a meta-analysis was planned, but due to the level of evidence of the articles included, only descriptive statistics could be used.

The many setbacks and delays demonstrated the difficulties in producing literature. A case study, case series, review of use of the statistical analysis Number Needed to Treat, and finally, a systematic review were produced.

GENERAL SUMMARY

This thesis provides four independent papers demonstrating multiple ways a simple clinician may contribute to the medical literature, enhance their understanding of current available literature, and develop an appreciation for the time and commitment each article entails.

Firstly, a case report demonstrates a never published complication (growth arrest with use of eight-plates). A case series demonstrates successful use of a novel device (Fitbone intramedullary lengthening nail). A review of one year of select pediatric orthopaedic literature highlights the under-utilization of the statistical analysis of number needed to treat (NNT), and finally, a systematic review provides clarification of incidence of venous thromboembolism in pediatric orthopaedics.

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List of Symbols and Abbreviations

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α = alpha = p-value = probability of making Type I error (concluding significant difference when there is none)

β = beta = probability of making Type II error (concluding there was no difference when there was one)

Δ = magnitude of difference in primary outcome between two groups

AIS = Adolescent Idiopathic Scoliosis

aPDFA = Anatomic Posterior Distal Femoral Angle

ARR = Absolute Risk Reduction (ARR=CER-EER)

AVN = Avascular Necrosis

BMI = Body Mass Index

CER = control group event rate

CI = Confidence Interval

CT = Computed Tomography

CVC = Central Venous Catheter

DVT = Deep Venous Thrombosis

EBM = Evidence Based Medicine

EER = experimental group event rate

Fitbone SAA = Fitbone Slide Active Actuator

Fitbone TAA = Fitbone Telescopic Active Actuator

$\mathbf{H_o}$ = Null hypothesis

$\mathbf{H_1}$ = Alternative hypothesis

ICU = Intensive Care Unit

ISKD = Intramedullary Skeletal Kinetic Distractor

JCO = Journal of Children's Orthopaedics

JPO A = Journal of Pediatric Orthopaedics (American)

JPO B = Journal of Pediatric Orthopaedics (British)

LR = Likelihood Ratio

MAD = Mechanical Axis Deviation

MeSH = Medical Subject Headings

MINORS = Methodological Index for Non-Randomized Studies

mLDFA = Mechanical Lateral Distal Femoral Angle

mMPTA = Mechanical Medial Proximal Tibial Angle

mPDFA = Mechanical Posterior Distal Femoral Angle

mPPTA = Mechanical Posterior Proximal Tibial Angle

MRSA = Methicillin-resistant Staphylococcus aureus

MSK = Musculoskeletal

MSSA = Methicillin-sensitive Staphylococcus aureus

NNH = Number Needed to Harm

NNT = Number Needed to Treat (NNT = 1/ARR)

OCP = oral contraceptive pill

POSNA = Pediatric Orthopaedic Society of North America

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO = International Prospective Register of Systematic Reviews

PSA = Posterior Slip Angle

RCT = Randomized Controlled Trial

RR = Relative Risk (RR = EER/CER)

RRR = Relative Risk Reduction [RRR = (CER-EER)/CER]

SCFE = Slipped Capital Femoral Epiphysis

VTE = Venous Thromboembolism

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Chapter 1: Introduction and Overview

1.1 Background

In pediatric orthopaedic surgery, like all medical specialties, one must incorporate the use of evidence-based medicine into the practice of clinical application. Firstly, one must have an inherent understanding of evidence, its classification, interpretation of both validity and significance, and applicability to one's patient population. Finally, development of studies from one's own practice can contribute to evolution of treatment.

Evidence is any observation or information presented in support of an assertion.[1] The evidence may be strong or weak, depending on the scientific method used. Unsystematic clinical experience and rationale based on anatomic and physiologic knowledge provides evidence of the lowest value. These experiences are sometimes shared as case reports and in certain instances case series. These unsystematic observations can lead to insights, but are limited by small sample size and the deficient human nature to create inferences in absence of internal validity.[1]

"Evidence-based Medicine" (EBM) involves taking the currently available best evidence to make clinical decisions about individual patients. The practice of EBM involves the five following sequential steps[2]:

1. Asking a question
2. Finding the current best evidence
3. Assessing the evidence for its validity and applicability
4. Integrating critical appraisal into practice
5. Self-evaluation

The notion of evidence based medicine and grading research articles on their "level of evidence" was first introduced by Sackett in the 1980's.[3] The Journal of Bone and Joint Surgery (American Volume) provides a level of evidence rating for its articles since January of 2003. Recently, Hanzlik *et al.*[4] found that the level of evidence in this journal had improved significantly over the past thirty years. Specifically, they reviewed a total of 1058 articles. Inclusion criteria was met for 134, 123, 120, and 174 articles for the years 1975, 1985, 1995, and 2005, respectively. In 1975, 5 articles were level I (4%), compared with 37 (21%) in 2005. They found the combined percentage of Level I, II, and III studies increased from 17% to 52%.[4]

When Cashin *et al*. reviewed pediatric orthopaedic journals (Journal of Pediatric Orthopaedics - A, Journal of Pediatric Orthopaedics-B, and Journal of Children's Orthopaedics), they found minimal change over the past ten years.[5] Conversely to what was found in the adult literature, articles from 2001 and 2002 (pre-2003) demonstrated that of the 310 articles, 2.6% (8) were graded level I, 7.1% (22) level II, 18.1% (56) level III, and 62.3% (193) were level IV. Of the 440 articles from 2007 and 2008 (post-2003), 3.0% (13) were graded as level I, 5.0% (22) as level II, 24.1% (106) as level III, and 58% (255) as level IV. There was no statistically

significant change, but a modest increase in level III articles with a corresponding decrease in level IV articles was noted.[5]

A stepwise process allows the level of evidence to easily be identified for a clinical research study. The first step is to define the primary research question, then the type of study that would be most appropriate to answer the question, followed by the level of evidence. Study type is categorized by type of study design performed (prognostic, diagnostic, economic/decision analysis, or therapeutic). Finally, the level of evidence is assigned.[6-8] (Table 1.1)

A prognostic study is one where the variable is not controlled by the researcher, such as fracture pattern on the outcome.[6-8] "Prognosis" refers to the different types of outcomes possible for a given disease and the frequency that each such outcome could be expected. "Prognostic factors" such as demographics (age), disease specific (fracture pattern), or co-morbid (diabetes) need not necessarily cause the outcome, just have a strong enough association to predict that the outcome will likely occur. Due to the unethical nature of randomizing patients based on prognostic factors, the best study to assess increased risk with an associated prognostic factor is the cohort study, such as the Framingham study used to determine prognostic importance of certain characteristics in relation to the development of cardiovascular disease. In this study, 5209 people were followed prospectively since 1948.[9] This study showed that artherosclerosis is an arterial abnormality and not simply a normal part of aging. The increased risk of cardiovascular disease in persons with elevated cholesterol levels was solidified.

In a recent study, Binkley *et al.* retrospectively reviewed ankle radiographs at their institution taken from 2001-2010. Skeletally immature fracture patterns were classified according to the Dias-Tachdjian classification system. Premature physeal closure with angular deformity was more likely if the initial injury was pronation-external rotation. The odds ratio of having an angular deformity with pronation-external rotation injury versus supination-external rotation and supination plantar flexion is 25, meaning that an angular deformity due to premature physeal closure is 25 times more likely to have had a pronation-external rotation injury. This prognostic level III study is important indication of need for follow up with these injuries.[10]

Diagnostic studies evaluate the ability of a modality to detect the condition of interest.[6-8] A test or modality can be used to help increase the certainty about the presence or absence of a disease. A physician starts the diagnostic process by assessing a patient that presents with a set of signs and symptoms. A diagnostic test helps increase or decrease the probability that a patient has a certain diagnosis. A "likelihood ratio" (LR) indicates by how much a diagnostic test will raise or lower the pre-test probability that a disease exists.

$$LR = \frac{\text{PROBABILITY OF CLINICAL FINDING/POSITIVE TEST IN PATIENT WITH DISEASE}}{\text{PROBABILITY OF CLINICAL FINDING/POSITIVE TEST IN PATIENT WITHOUT DISEASE}}$$

A likelihood ratio of 1 means the pre-test and post-test probability are the same. A likelihood ratio greater than one increases the probability that the disease exists, and less than one decreases

the probability that the disease is present. Likelihood ratios greater than ten or less than 0.1 generate large changes from pre-test to post-test probability.[11]

Diagnostic studies also evaluate sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity purports to tell how well a test can detect true positives, whilst specificity describes how well the test detects true negatives. Positive predictive value is the ratio of patients truly diagnosed as positive to all those who had positive test results. Negative predictive value is the ratio of those truly diagnosed as negative to all subjects having negative test results.[2]

Schematically this can be represented as follows:

		TARGET DISORDER	
		PRESENT	ABSENT
DIAGNOSTIC TEST RESULT	POSITIVE	a	B
	NEGATIVE	c	D

Sensitivity: a/(a+c)

Specificity: d/(b+d)

Positive Predictive Value: a/(a+b)

Negative Predictive Value: d/(c+d)

In 2003, Levine *et al*.[12] assessed the test characteristics of C-Reactive Protein for septic arthritis in children. Currently, there is no single diagnostic test for septic arthritis. This group reviewed stratum specific likelihood ratios, sensitivities, specificities, positive predictive values, and negative predictive values. The study showed that C-Reactive Protein was a better negative predictor of septic arthritis. If C-reactive protein was <1.0 mg/dL, the probability that the patient did not have septic arthritis was 87%. [12]

Economic studies compare costs of care while Decision Analysis compare outcomes of care.[6-8] These studies can help facilities decide on formulary guidelines by comparing economics of health care strategies while ensuring outcomes of care are compared.[13] Recently, Shivji *et al*. studied the implementation of telehealth for pediatric surgical consultations. 94% of the patients indicated that it made access to health care services easier and telehealth was found to reduce travel time and expenses for patients. 48% reported a cost saving in excess of $500.[14]

Therapeutic studies evaluate the effect of a controllable treatment on the outcome of a condition. These are the most common type of study in the orthopaedic literature. Therapeutic studies can be divided into five different categories based on the level of evidence they provide (Table 1.1). Level 5 studies are case reports of expert opinion. Level four are case series. Both these types of studies do not have a control group to compare the effect of treatment versus no treatment.[6] Level 3 therapeutic studies are case control studies or retrospective comparative studies. Level 2 therapeutic studies are randomized controlled trials of lesser quality. This would be in cases where there is less than 80% follow-up or poorly performed randomization. A prospective

comparative (cohort) study can also be a level 2.[6] High quality randomized controlled trials (RCT) are considered level one evidence.[6] Systematic reviews are classified by the types of articles entered into the review.[6]

Table 1.1: Levels of Evidence[6] Reprinted with permission DeVries, J.G. and G.C. Berlet, *Understanding levels of evidence for scientific communication.* Foot Ankle Spec, 2010. **3**(4): p. 205-9 DOI: 10.1177/1938640010375184.

	Types of Studies			
	Therapeutic Studies—Investigating the Results of Treatment	**Prognostic Studies—Investigating the Effect of a Patient Characteristic on the Outcome of Disease**	**Diagnostic Studies—Investigating a Diagnostic Test**	**Economic and Decision Analyses—Developing an Economic or Decision Model**
Level I	• High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review[b] of level I randomized controlled trials (and study results were homogeneous[c])	• High-quality prospective study[d] (all patients were enrolled at the same point in their disease with ³80% follow-up of enrolled patients) • Systematic review[b] of level I studies	• Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference gold standard) • Systematic review[b] of level I studies	• Sensible costs and alternatives; values obtained from many studies; multiway sensitivity analyses • Systematic review[b] of level I studies
Level II	• Lesser quality randomized controlled trial (eg, <80% follow-up, no blinding, or improper randomization) • Prospective[d] comparative study[e] • Systematic review[b] of level II studies or level I studies with inconsistent results	• Retrospective[f] study • Untreated controls from a randomized controlled trial • Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% follow-up) • Systematic review[b] of level II studies	• Development of diagnostic criteria on the basis of consecutive patients (with universally applied reference gold standard) • Systematic review[b] of level II studies	• Sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analyses • Systematic review[b] of level II studies
Level III	• Case control study[g] • Retrospective[f] comparative study[e] • Systematic review[b] of level III studies	• Case control study[g]	• Study of nonconsecutive patients (without consistently applied reference gold standard) • Systematic review[b] of level III studies	• Analyses based on limited alternatives and costs; poor estimates • Systematic review[b] of level III studies
Level IV	• Case series[h]	• Case series	• Case control study • Poor reference standard	• No sensitivity analyses
Level V	• Expert opinion	• Expert opinion	• Expert opinion	• Expert opinion

This chart was adapted from material published by the Centre for Evidence-Based Medicine, Oxford, United Kingdom. For more information, please see www.cebm.net.

[a]A complete assessment of the quality of individual studies requires critical appraisal of all aspects of the study design.

[b]A combination of results from 2 or more prior studies.

[c]Studies provided consistent results.

[d]Study was started before the first patient enrolled.

[e]Patients treated one way (eg, with cemented hip arthroplasty) compared with patients treated another way (eg, with cementless hip arthroplasty) at the same institution.

[f]Study was started after the first patient enrolled.

[g]Patients identified for the study on the basis of their outcome (eg, failed total hip arthroplasty), called "cases," are compared with those who did not have the outcome (eg, had a successful total hip arthroplasty), called "controls."

[h]Patients treated one way with no comparison group of patients treated another way.

Application in Clinical Practice

It is important to consider all types of evidence when answering questions on therapy. Randomized controlled trials have the highest level of evidence, but are not feasible to answer all questions for technical and ethical reasons.[15] Much of the lower quality research tends to be undervalued. Even case reports, level 5 evidence, can be extremely valuable in areas such as reporting adverse events, new diseases, and innovative therapies.[16]

Level 4 evidence, the case series, cannot be used to make causal inference, but describes a group of patients undergoing a similar therapy or surgical intervention. This descriptive study differs from cohort and case control studies in many ways, including that there is no comparison group. There is no hypothesis tested, but the study can be used to generate a hypothesis that can subsequently be tested. There are many strengths exhibited by a case series. Case series tend to have high external validity due to a wide range of patients.[15] . Cross-sectional and cohort studies are also called observational studies, and the investigators do not control the treatment decision process. As with case series, investigators do not control treatment decision process. These observational studies, in comparison to randomized controlled trials, tend to be relatively inexpensive and do not take a lot of time. However, limitations of case series include the fact that there is no comparison group, and studies are susceptible to selection bias and measurement bias. Selection bias occurs when data is less likely to be collected from patients with a certain outcome. Prospectively designing the case series can help eliminate this type of bias. Measurement bias occurs when differing types of outcome measures are used in a study. This

tends to occur more often with case control and cohort studies where different measures are used in treatment and control group.[15]

Following are a few examples of different biases in the pediatric orthopaedic literature.

In a 2015 review of newborn extrophy closure, Inouye *et al*. found no difference in the rates of failure in patients having undergone pelvic osteotomy or not. This retrospective study is limited by selection bias. The osteotomy group known to have larger diastasis and operated at later age than the non-osteotomy group. As well, the follow up time for the non-osteotomy group was less, leading to possibility of failure to diagnose late failures.[17]

Attrition bias can be considered a form of selection bias. It can create a difference in study groups in the number and way participants are lost from a study. In a 2014 review of the literature, Akilapa studied the medial open reduction for developmental dysplasia of the hip. He included five retrospective observational studies, with several indicating attrition rates of 20%-35%, introducing attrition bias and compromising cumulative methodological rigour.[18]

Measurement bias was assessed in the 2018 article by Nowicki *et al.*: "Measurement of Intraoperative Blood Loss in Pediatric Orthopaedic Patients: Evaluation of a New Method". They prospectively collected surgical sponges from patients undergoing various pediatric orthopaedic procedures where expected blood loss was greater than 200mL. They evaluated the

Triton sponge scanning system, visual method, gravimetric method, and measured assay (reference) method. The most common method used, the visual estimate, was found to have very little correlation with the reference method. It tended to overestimate blood loss at lower measured values and underestimate blood loss at high measured values. These inaccuracies lead to measurement bias when used as outcome measure for estimated blood loss.[19]

Case-control studies or retrospective cohort studies are classified as level 3. Case-control studies identify subjects by the outcome of interest (undergone a surgery, developed a complication, or diagnosed with a disease). The subjects with the outcome of interest are "cases" and are matched with "controls" or persons from same population but without outcome of interest.[6-8] Data is then collected retrospectively to identify exposure to risk factors. These studies are important to study rare outcomes or outcomes that occur over a long period of time. Although these studies are inexpensive and fast to perform, they are subject to many biases such as recall bias (i.e. subjects who have disease more likely to recall exposure than controls not affected) or information bias (where information is collected or recorded differently for cases and controls).[20]

Recall bias is inevitable in intra-observer studies. This was the main weakness of a study used to evaluate smartphone based instant messaging application in pediatric orthopaedic trauma by Stahl *et al.* They used WhatsApp instant messaging to have orthopaedic surgeons initially evaluate an image, diagnose, classify, and determine course of treatment. After a four-week interval, the same surgeons were asked to evaluate the same images using PACS. The time lapse

was felt to help decrease recall bias for this intra-observer comparison, albeit memory of the images may persist.[21]

Prospective cohort studies provide level 2 evidence. The design of the cohort study is to compare two groups, one exposed to a substance or intervention, and the second group, similar in every way to the first albeit exposure to substance.[6-8] These two groups are followed over time to determine if a difference in disease frequency exists.[22] Cohort studies are useful for investigating rare exposures and multiple outcomes can be examined simultaneously. However, these studies are susceptible to many biases including attrition bias (sicker patients more likely to be lost to follow up) and may require long follow-up.[20]

The best research design, level 1, is the randomized controlled trial which assigns subjects to a treatment or control group at random. The strongest methodology includes blinding of clinicians and patients as to which group they are allocated, albeit this is not always feasible.[22] For the study to attain level 1 status, follow-up must be at least 80%.[6-8]

To address a focused clinical question, a systematic review of the current literature may summarize the results and the confidence we have in those results. These reviews use explicit strategies to identify and appraise the current literature. An important component of the systematic review is to begin with a stringent protocol defining which studies will be included and which ones excluded as well as the outcomes to be analyzed.[23] When the systematic review

uses statistical techniques to pool results, it is described as a meta-analysis.[24] The level of evidence of these articles is that of the primary articles being reviewed.[6-8] The review should address a clinical question with a detailed search of current studies. The data from included studies is then abstracted and analysed, with results pooled, if appropriate.[24]

Prospective therapeutic trials are typically set to determine if there is a difference in outcome between two groups given two different interventions, leaving all other variables the same. A clinical trial involves human subjects, and a randomized controlled trial (RCT) involves assigning treatment intervention by chance mechanism (i.e. tossing a coin). The principles of RCT that make it high quality include randomization, placebos, double-blinding, and statistical power.[25]

A well-designed RCT will have a clear objective with a well-defined primary end point. Subjects are selected based on inclusion and exclusion criteria. They are then randomized to either treatment or control group to ensure the two groups are the same apart from intervention proposed. In a double blind study, neither the patient nor clinician will know into which group the subject has been placed to prevent bias.[25]

To ensure the trial gives a definitive outcome (positive or negative), a mathematical assessment must be performed at the outset that incorporates the following[25]:

1. primary end point
2. hypothesis to be tested
3. amount of difference that is medically important
4. acceptable magnitude of error
5. calculation of sample size necessary

To assess if there is a difference, researchers develop a null hypothesis (H_0) that there is no difference between the groups, and an alternative hypothesis (H_1) that the two groups are different.[22] The study attempts to refute the null hypothesis by gathering sufficient evidence. One needs to discern the magnitude of difference in primary outcome between the two groups (Δ) that is necessary to say there is a medically important difference. The p-value for the study is the result of the statistical test and is a probability. It reflects the measure of evidence against the null hypothesis. Small p-values indicate strong evidence. When the p-value is below a pre-determined limit (typically 0.05), the results are statistically significant.[26] The p-value gives one the likelihood of making a Type I (α) error where one concludes there is a significant difference when in fact there isn't. The opposite, a Type II or β error is the probability of concluding there was no difference when in fact there was one.[22, 25] For comparison studies, p-value (α-level) is typically and arbitrarily set at $p<0.05$ and the β level 0.20. The power level ($1-\beta$) is thus arbitrarily set at 80%. Using the information of α, β, and Δ, statistical calculations can estimate the sample size necessary for the trial to acquire enough statistical power to detect the statistically important difference. This should be reported as a "power statement" at the beginning of the RCT.[25]

If a randomized controlled trial is poorly randomized, or if it has less than 80% follow up, or if it has insufficient blinding of evaluators, it becomes a level 2. As well, if a post hoc power analysis shows a power of less than 80%, the study drops to level 2. [6-8, 25] Although the study may provide statistically significant results, it will be increased in risk of bias.

When appraising articles about therapy, one must look at the validity, treatment effect, and whether the results can be applied to the physician's own patient population.

Validity refers to whether the study is scientifically able to answer the question it intended to answer. In order to assess the strength of the validity, there are a series of questions that need to be asked.[2, 27]

1. Was the assignment of patients to treatment randomized? Was the randomize list concealed?
2. Was follow up of patients sufficiently long and complete?
3. Were all patients analyzed in the group to which they were randomized?
4. Were the patients and clinicians kept blind to treatment?
5. Were groups equally treated, apart from experimental therapy?
6. Were the groups similar at the start of the trial?

Generally, follow-up should be >80%. To preserve the value of randomization (that the two groups are initially the same), patients should be analyzed in the groups to which they were

assigned, regardless of whether they received the assigned therapy (intention to treat analysis). Comparative tests should be done to analyze if the two groups were similar at the baseline of the RCT. These tests eliminate any difference in prognostic factors which could account for differences in outcomes between the two groups, or allow for adjustment of these differences in statistical analysis.[2, 27]

Once the study is purported to be valid, it is important to assess if the valid results are important. The following questions should be asked:[2, 28]

1. How large was the treatment effect?
2. How precise was the estimate of the treatment effect?

In studies with dichotomous outcomes (i.e. death), the difference between the two groups can be described as an absolute risk reduction (ARR). This is calculated by finding the difference in proportion of patients that died in control (CER= control event rate) and treatment (experimental) groups (EER=experimental event rate): [28]

ARR= CER-EER

Another way to express treatment effect is relative risk (RR). That is the risk of the adverse event (death) in patients receiving treatment (EER) compared to risk in control group patients (CER), described as a proportion:[28]

Relative Risk = EER/CER

Relative risk reduction (RRR) is the most common method used to report treatment effects that have dichotomous outcomes. It expresses the reduction of death by treatment as a percentage:[28]

RRR= [1-(EER/CER)] x 100%

The greater the RRR, the more effective the therapy, statistically speaking.

When looking at the estimate of treatment effect, it is important to determine how much of the difference is the result of treatment, and how much of the difference is due to chance alone. In other words, how precise is the estimate of treatment effect.

The precision of the estimate of treatment effect can be expressed using a confidence interval (CI). This displays the range of estimates in which the true difference will lie 95% of the time.

The 95% confidence interval is arbitrarily chosen and closely relates to the p-value of $P<0.05$ which indicates statistical significance. If the 95% confidence interval for relative risk reduction falls completely on the positive side of 0, then there is a difference with significance of $P<0.05$. If the lower end of the confidence interval falls below 0, then the p-value is said to be >0.05, or not significant. Thus a study that has found no significant difference, but has an upper level of confidence interval well above 0, has truly failed to exclude an important treatment effect.[28]

An example of calculation for confidence interval of absolute risk reduction follows:[2]

ARR+/-95% CI= ARR +/-1.96 x Standard Error

When appropriate statistical analysis for assessing a difference between the groups is performed, a p-value, which indicates a probability, is used to determine if the difference is due to a true difference between groups, or chance alone.[22] The Null hypothesis is typically accepted or rejected based on the p-value found and reflects the measure of evidence against the null hypothesis. Small p-values (<0.05) indicate strong evidence and that the probability is small that the difference can purely be assigned to chance. A p-value of less than 0.05 is typically accepted as indicating a significant result, due to the fact that the probability that the difference is due to chance alone is less than 5%. Thus, the null hypothesis (no difference between groups) would be rejected and alternative hypothesis (there is a difference) accepted. P-values do not comment about the size of difference.[26]

Articles about therapy need also to be assessed for their applicability to care for your patients. One should ask the following questions : [28]

1. Can the results be applied to my patient care?
2. Were all clinically important results considered?
3. Are the likely treatment benefits worth the potential harms and costs?

In applying the results to patients in one's own practice, it is important to note if your patient would fulfill the inclusion and exclusion criteria. If the patient would not have been eligible for the study, judgement is required. One needs to ensure there is no co-morbid condition that would prohibit treatment.

In looking at all clinically important results, it is important to determine if the effect of therapy, though able to provide benefit in one domain, causes harm in another. For instance, chemotherapy may be able to prolong life, but can have a deleterious effect on the quality of life.[28]

Looking at potential benefits compared to possible harms and costs, one needs to assess if the possible benefits are worth the impact of treatment on the physician and patient. This can be assessed using the calculation of "Number Needed to Treat" (NNT). The "Number Needed to

Treat" is the number of patients that need to be treated to prevent one adverse event. Mathematically, it is the reciprocal of the absolute risk reduction:[9, 29]

NNT=1/ARR

The advantage of NNT over relative risk reduction and odds ratio is that it incorporates baseline risk without therapy and risk reduction with therapy to give a measure of treatment efficacy. It expresses in simple terms how much effort (by both physician and patient) it takes to prevent one adverse event.[28, 29]

Table 1.2 shows the effect of base-line risk and relative risk reduction on number needed to treat.[29] It illustrates that is the base-line risk of an event is high, even a small relative risk reduction will lead to a low number needed to treat. If the disease has a base-line risk of 60% and the relative risk reduction by therapy is 15%, the number needed to treat will be 11. Thus, 11 patients would need to be treated to prevent an adverse event in one patient.[29]

TABLE 1.2 The Effect of the Base-Line Risk and Relative Risk Reduction on the Number Needed to be Treated[29]

BASE-LINE RISK*	RELATIVE RISK REDUCTION BY A NEW THERAPY (%)						
	50	40	30	25	20	15	10
	number needed to be treated						
0.9	2	3	4	4	6	7	11†
0.6	3	4	6	7	8	11	17
0.3	7	8	11†	13	17	22	33
0.2	10	13	17	20	25	33	50
0.1	20	25	33	40	50	67	100
0.05	40	50	67	80	100	133	200
0.01	200	250	333	400	500	667	1,000
0.005	400	500	667	800	1000	1333	2,000
0.001	2000	2500	3333	4000	5000	6667	10,000

*Risk of an adverse event in control patients. †Numbers used as examples in the text.

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The gold standard and highest quality clinical trial is the randomized controlled trial. However, this does not mean we should not pay attention to literature of lesser quality. Randomized controlled clinical trials are difficult to perform for surgical scenarios due to difficulty with blinding both surgeon and patient. When research involves children, the issue of informed consent and parental consent to enroll their child into a prospective study increases the difficulty.

All these factors contribute to difficulties in performing the highest level of evidence in pediatric orthopaedic surgery and many other fields of medicine.

1.2 Purpose of Thesis

The purpose of this thesis is to look at the current state of evidence-based medicine to enable responses to a particular set of questions in Pediatric Orthopaedic Surgery. First, two original works are presented: a case report followed by a case series exploring treatment of growth deformities. The case study helped highlight a complication risk whilst the case series showed successful lengthening with deformity correction using a novel internal device instead of a frame. An assessment of the use of Number Needed to Treat (NNT) and the current level of evidence presented in one year of pediatric orthopaedic journal articles is performed. Finally, a systematic review of venous thromoboembolism in the pediatric orthopaedic literature searches for knowledge of the incidences of VTE in different subtypes of pediatric orthopaedics.[30]

The case study presents a patient who presented with a complication of guided growth deformity correction using an eight plate. This is a unique contribution to the literature in that this complication has not been previously described when using this device. Thus, the results of this study disseminate important information about this complication to the profession as well as provide a review of literature of similar complications.

Limb lengthening and deformity correction has successfully been performed on children and adults using external fixators such as the Ilizarov frame. Extensive literature has been written on limb lengthening with external fixators including complication rates.[31] More recently, limb lengthening has been described using an intramedullary nails (such as the Fitbone device). In comparison with an external frame, the nail has the benefit of being less cumbersome and having no pin site infections. The fourth chapter of this thesis, "Intramedullary Lengthening Using the Fitbone Device" provides a case series of patients undergoing limb lengthening using this intramedullary nail. This study utilized data collected prospectively over a seven-year period, but for practical purposes did not include a control group. The review assessed whether target lengths were reached, and documented the complications that occurred.

"Use of Number Needed to Treat (NNT) in the Pediatric Orthopaedic Literature: A Review" evaluates one year of pediatric orthopaedic literature, evaluating levels of evidence and use of the statistic number needed to treat. Pubmed was searched to ensure this project had not been done in the past. Subsequently, three journals were chosen: Journal of Pediatric Orthopaedics American (JPO A), Journal of Pediatric Orthopaedics British (JPO B) as well as Journal of Children's Orthopaedics (JCO). One year of publications from each journal (January 1-December 31, 2010) were reviewed. This review was performed in 2011, thus the previous year of publications was reviewed. This revealed only eight level I trials and a surprisingly high number of level 4 trials (145) and level 5 (54). This demonstrates that the majority of external evidence in pediatric orthopaedics can be classified as level 4 and 5.

Chapter 6: "Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review" questioned the exact incidence of venous thromboembolism in different subtypes of pediatric orthopaedic surgery. It details the process of creating a stringent, comprehensive protocol and search strategy to minimize bias in reviewing the literature. Although the initial plan included complex statistical analysis, the information obtained allowed for simple analysis of incidence and trends.

The goal of this thesis was to assess the current level of evidence available for the practice of Evidence Based Medicine in Pediatric Orthopaedic Surgery, and to contribute to the development of new evidence in the area deformity correction, statistical evaluation, and risk of venous thromboembolism. Two original works are presented: a level 5 case report and a level 4 case series. Subsequently, we look at the level of evidence in the current available literature and how we evaluate the quality of the highest level of evidence, randomized controlled trials, using the Number Needed to Treat (NNT). Finally, a systematic review was performed. This systematic review evaluates the incidence of venous thromboembolism in different subtypes of pediatric orthopaedic surgery. This new information is important in the development of screening protocols in the assessment of need for prophylactic treatment.

1.3 Significance of Thesis

This thesis provides a significant contribution to the literature by demonstrating the present quality of papers published in the pediatric orthopaedic literature and examines difficulties in producing higher levels of evidence in pediatric orthopaedic surgery. It provides examples of two original clinical research articles, one case study and one case series that have great clinical significance and are important adjunct to clinical expertise to help provide best care to each patient, as well as a systematic review of the literature.

Chapter 2: Co-Authorship Statement.

2.1. Physeal Arrest and Angular Deformity as a Sequelae of Guided Growth: A Case Report and Review of the Literature

i) **Design and identification of the research proposal:** The proposal was produced by thesis author and amended by Mr. Chris Harris.

ii) Practical aspects of the research: The literature search, review and development of the case report was performed by thesis author.

iii) **Data analysis:** No data analysis was performed.

iv) **Manuscript preparation:** The manuscript was prepared by the thesis author with revision recommendations made by supervisor Mr. Chris Harris.

2.2. Intramedullary Lengthening Using the Fitbone Device

i) **Design and identification of the research proposal:** The insertion of Fitbone intramedullary nails in Adelaide, Australia began in 2003 with surgeon Mr. Bruce Foster. Patients were entered into a trial prospectively beginning at that time. In 2010, a proposal was developed to review all cases performed until that time. The thesis author developed a protocol to review the twenty-one cases performed by Mr. Bruce Foster.

ii) **Practical aspects of the research:** The thesis author performed a chart review of each case, all radiograph measurements on pre-operative and post-operative radiographs and performed three surgeries with Mr. Foster. The thesis author also contacted each patient for subjective feedback.

iii) **Data analysis:** All data was accrued, and analysis was performed by thesis author.

iv) Manuscript preparation: The manuscript was prepared by thesis author with revision recommendations made by Mr. Bruce Foster.

2.3. Use of Number Needed to Treat (NNT) in the Pediatric Orthopaedic Literature: A Review

i) **Design and identification of the research proposal:** The thesis author developed the study protocol, which was amended by Dr. Kishore Mulpuri.

ii) Practical aspects of the research: All articles were reviewed by the thesis author. Identification of articles that could have Number Needed to Treat calculated were identified in partnership with Dr. Mulpuri and statistician Ruth Milner, with thesis author performing calculations.

iii) **Data analysis:** Thesis author performed all data analyses.

iv) **Manuscript preparation:** Thesis author independently prepared manuscript.

2.4. Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review

i) Design and identification of the research proposal: After a complication of a venous thromboembolism in a patient in April 2018, a review of the literature for indications of risk and need of venous thromboprophylaxis in pediatric orthopaedic patients was performed. In August 2018, a literature search of multiple databases was conducted. From this, titles were reviewed manually for duplicates, and the project was at abstract review stage when it was suggested to involve the research committee at Université Laval, which

included Dr. Olivier Costerousse. From that meeting, in March, 2019, a revised protocol was developed to include an updated search strategy employing Mesh terminology. To further develop knowledge in this methodology, the thesis author completed a Francophone Cochrane Review Course in March 2019 (3 days).

ii) **Practical aspects of the research**: In August 2019, a resident in Orthopaedic Surgery at Université Laval expressed interest in working on the project (Dr. M. Boulet). The project was reviewed with the research group at Laval, and they helped Dr. Boulet and thesis author develop a proper protocol. The resident (M. Boulet) then met with a librarian who helped determine the Mesh terms and introduced Covidence. Dr. Boulet conducted the search. Titles and abstracts were reviewed by both Dr. Boulet and thesis author.

iii) **Data analysis:** Data extraction was performed by Dr. Mathieu Boulet and thesis author. Spreadsheet of raw data was created initially by Dr. Boulet and subsequently both revised and edited by thesis author. Dr Stephane Pelet from the Université Laval Orthopaedic Surgery research group was instrumental in statistical analysis.

iv) **Manuscript preparation:** Thesis author independently prepared Chapter 6 of this thesis. A manuscript for publication has been created from this chapter by Dr. Forsythe and Dr. Boulet.

Chapter 3: Physeal Arrest and Angular Deformity as a Sequelae of Guided Growth: A Case Report and Review of the Literature[32]

3.1. Introduction:

This case report shows a complication of permanent growth arrest from a distal femur eight plate. This type of complication has not been found to have been previously reported in the literature.

Articles about therapy in the medical literature are graded in strength from Level 1 (randomized controlled trial) to level 5 (case report). The gold standard and highest quality clinical trial is the randomized controlled trial. However, this does not necessarily mean we should not pay attention to literature of lesser quality. Randomized controlled clinical trials are difficult to perform for surgical scenarios due to difficulty with blinding both surgeon and patient, and ethics of randomizing treatment to be performed. When research involves children, the issue of informed consent and parental consent to enroll their child into a prospective study increases the difficulty. [6-8]

Medical case reports can contribute valuable information to the literature. Although it is considered the lowest level of evidence (level 5), they are invaluable for reporting adverse events and medical innovation. They are important to enhance patient safety. When reporting on an adverse event, a root cause analysis should be included and findings should be discussed to develop practice and enhance patient safety. [16]

During growth, deformities can develop in long bones. When growth remains, it is an option to "guide" the growth by temporarily stopping growth of part of the growth plate. The anatomy pertaining to this technique is of importance.

The term "epiphysis" refers to the bulbous end of a long bone that includes the "growth plate" or "physis" and secondary ossification centre. The increasing length of long bones in growing children occurs at the physes. To understand physeal growth manipulation and physeal arrest, knowledge of the microscopic architecture of the physis is imperative. Traditionally, the physis is divided into four zones, from the secondary ossification centre to the metaphysis: germinal (reserve), proliferative, hypertrophic, and provisional (enchondral) calcification. Cellular proliferation occurs in the former two zones and matrix production, cellular hypertrophy, apoptosis, and matrix calcification in the latter two (i.e. Figure 3.1).[33]

At the periphery of the physis lies the Zone (groove) of Ranvier and the Perichondrial Ring of La Croix. The former contains growth cells and is responsible for peripheral growth of physis, while the latter is a fibrous structure providing mechanical stability as it connects the periosteum of the metaphysis to the epiphysis.[33]

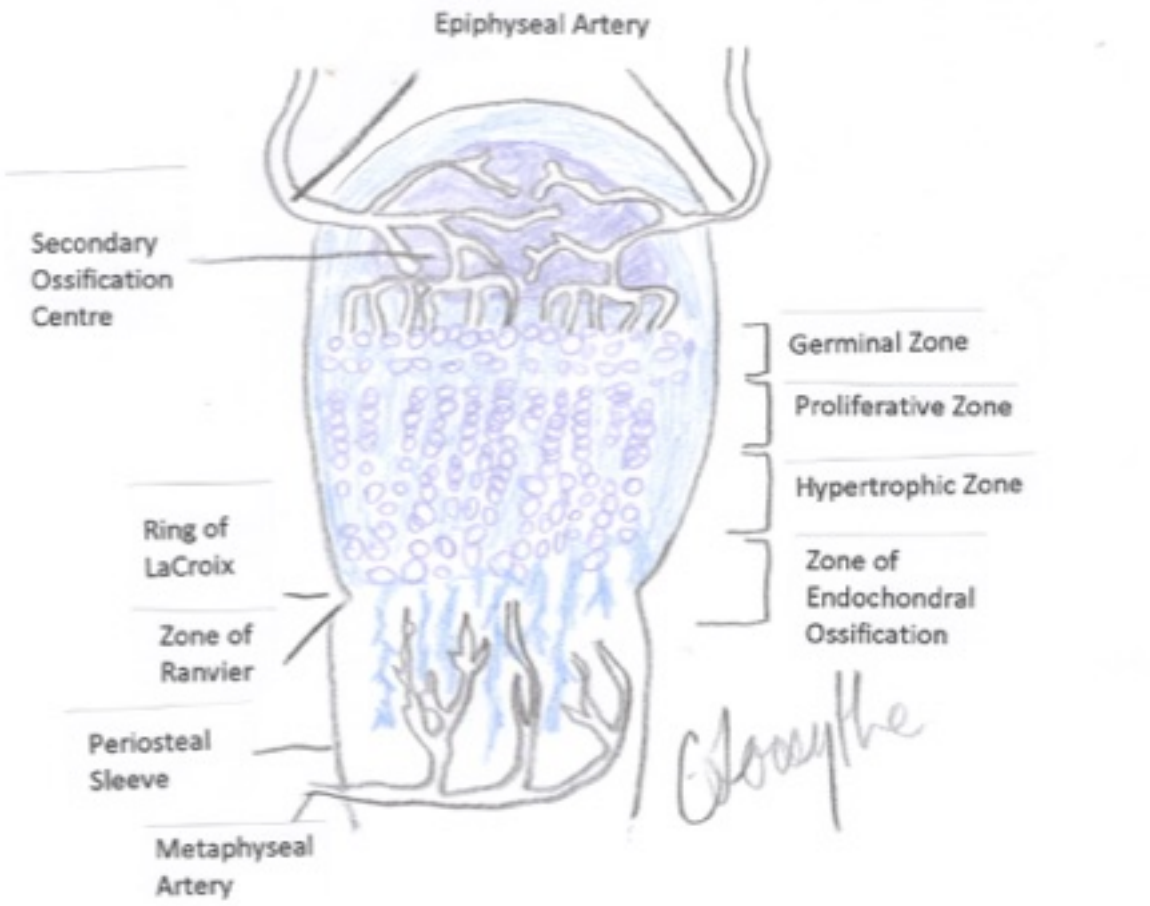


Figure 3.1: Microscopic Growth Plate Anatomy (drawn by hand by author)[33]

Disturbance of physeal growth can cause angular deformity and limb length inequality. The most common disruption to a physis is the formation of a physeal bar or bridge. A computed tomography scan (CT) can demonstrate a bar of bone spanning from the metaphysis to the epiphysis, causing growth arrest.[33]

To understand deformity and its correction, an inherent understanding of normal limb alignment is pertinent. Figure 3.2 shows normal limb alignment values for the lower extremity on the

frontal and sagittal plane. The values important in this report are the mLDFA (mechanical lateral distal femoral angle) and the aPDFA (anatomic posterior distal femoral angle).[34]

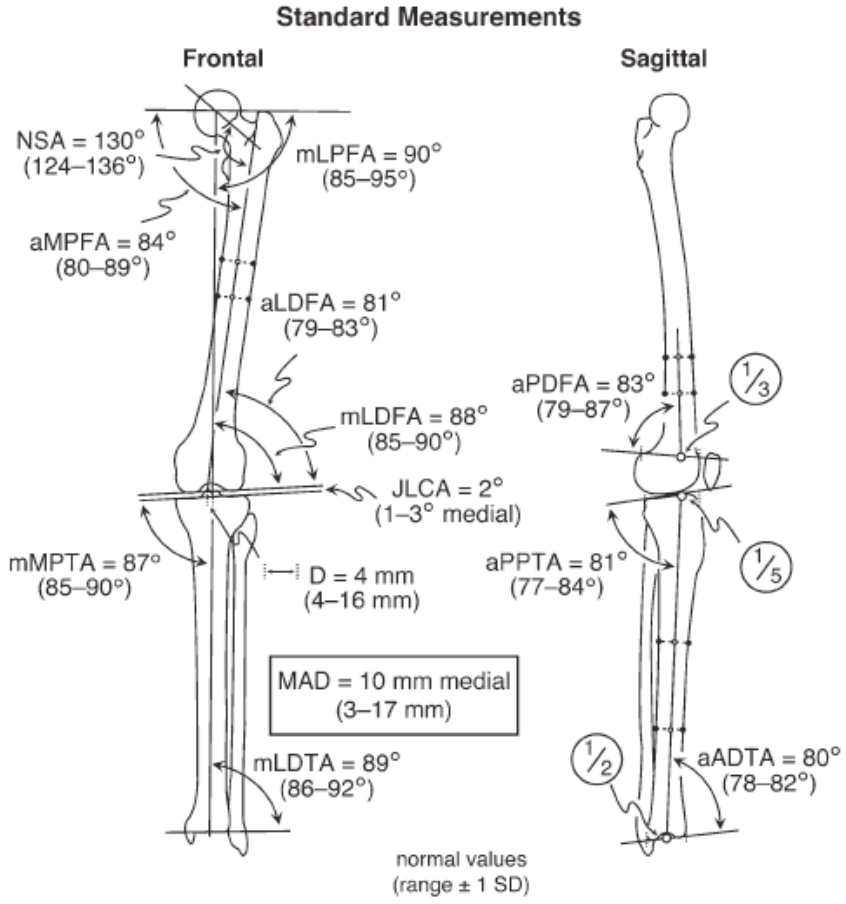
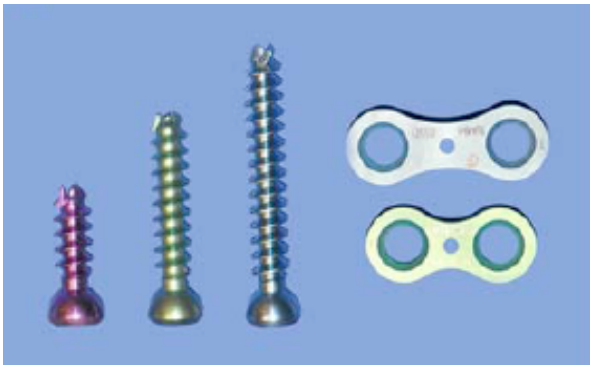


Figure 3.2: Lower Extremity Deformity Measures reprinted with permission from Feldman *et al*., J Pediatr Orthop.2007;27(2):204-208.[34]

Creating a temporary bar by placing a staple or an eight plate allows the manipulation of the growth plate to change limb deformities gradually with growth. This "guided growth" has

found widespread favour in the management of deformity in children, particularly deformities around the knee[35]. In 1945, Blount reported on the use of rigid staples to arrest or guide growth for the correction of leg length discrepancies and angular deformities. The staples were purported to allow normal resumption of epiphyseal growth after removal, a topic which remains controversial for this device.[36]

Staples remained the only implant for reversible epiphysiodesis for 60 years until Stevens[37] developed the concept of the flexible titanium plate placed at the perimeter of the physis to produce a hinge effect. Figure 3.3 shows the 8-plate (Orthofix, Verona, Italy). Is a two-hole titanium plate that is affixed with fully threaded, nonlocking cannulated or solid screws. The compression supplied by the plate is not constant as the screws diverge with correction.[35, 37] The ability of the screws to pivot creates lower pressure across the physis, which should decrease the risk of permanent physeal arrest.[38] The eight plate was felt to have less risk of spontaneous implant extrusion and less risk of hardware failure.[38, 39]



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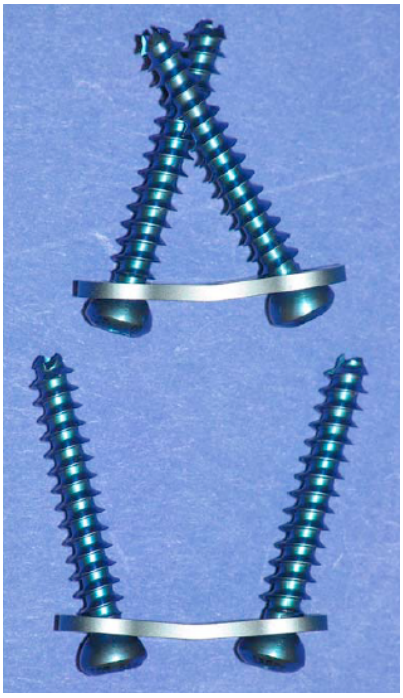

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Figure 3.3: Photographs of the 8 Plate Guided Growth System a) plate sizes 12 mm and 16 mm and screw lengths 16, 24, and 32 mm b) Photograph showing the ability of the screws to pivot greater than 45 degrees. [40] Reprinted with permission from Burghardt, R.D., et al., *Temporary hemiepiphyseal arrest using a screw and plate device to treat knee and ankle deformities in children: a preliminary report.* J Child Orthop, 2008. **2**(3): p. 187-97 DOI: 10.1007/s11832-008-0096-y.

The purpose of this report is to describe a complication of the use of the 8 plate not previously described in the literature: permanent physeal arrest. The case is discussed as well as a review of clinical and animal research on the causes of growth arrest.

3.2. Case:

Patient information:

After full ethics approval with the Department of Ethics at Royal Melbourne Children's Hospital, verbal consent from the parents and child was obtained to comply with Institutional Review Board Policy. A 7 year-old boy with a spinal muscular atrophy like disorder had eight plates applied to the anterior aspect of his left knee in late 2006 to correct a bony procurvatum deformity.

Clinical Findings:

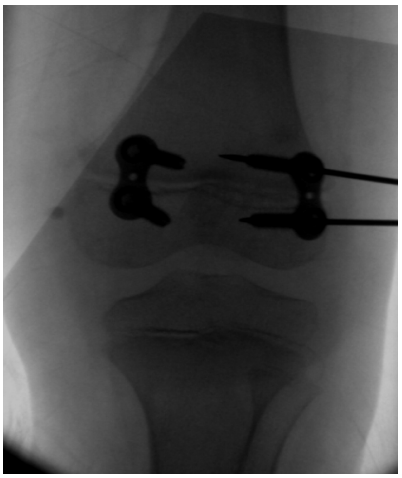
Procurvatum is a bony flexion deformity as determined on a lateral radiograph of the knee. A fixed flexion deformity exists if the anterior cortical line of the femur is not collinear with that of the tibia, and an angle with apex anterior is formed. Procurvatum of the distal femoral joint line is present if the mechanical posterior distal femoral angle (mPDFA) is less than 79 degrees. Procurvatum of the proximal tibia is present if the mechanical posterior proximal tibial angle (mPPTA) is less than 77 degrees.[41] Minimal surgery was preferred due to how the patient would tolerate this. His gait was deteriorating due to weakness from his underlying condition and altered mechanics from his fixed flexion deformity. Fixed flexion deformity of the knee is disabling, even if only a few degrees of deformity are present. Because a knee cannot be

extended to neutral or locked, the quadriceps has to work to prevent the knee from buckling and can quickly become fatigued.[42]

The surgical procedure was performed by a senior surgeon in 2006 when the patient was 7 years-old, with attention paid to preservation of the periosteum (see figure 3.4 a and b). The procurvatum corrected in a little over a year and the metaphyseal screw from each anterior eight plate was removed in 2007 when the patient was 8 years-old (see figure 3.5). This is a common method of physeal compression removal when the risk of rebound (deformity recurrence) is high. Over the next year, the knee began to develop a valgus deformity.

Diagnostic Assessment

In July 2010, when the patient was 11 years-old, the mechanical lateral distal femoral angle (mLDFA) measured 76 degrees and a medial 8 plate was inserted (see figure 3.6). After insertion of the medial 8 plate, the valgus deformity did not progress, and overall longitudinal growth was slowed, but hadn't stopped. In August 2012, when the patient was 13 years-old, a Computed Tomography Scan (CT) of leg lengths showed that the left femur was only 7 mm shorter than the right and overall the left leg was 1 mm shorter. The mLDFA was 75 degrees, essentially unchanged. In 2012, just over five years after the plate had initially been inserted, a CT scan confirmed a physeal bar and the intraosseous position of the anterolateral 8 plate (see figure 3.7).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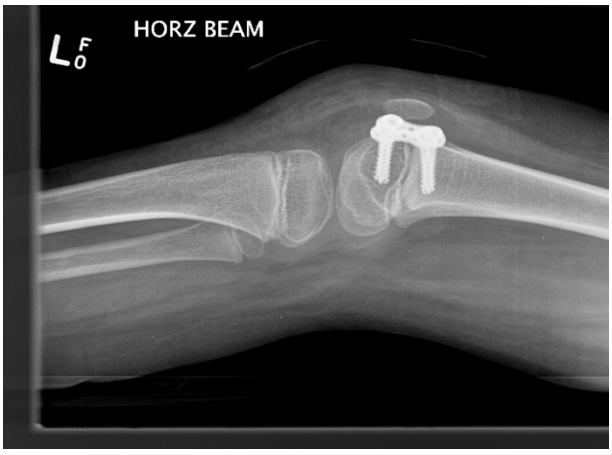

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Figure 3.4: Initial 8 plate insertion 2006 a) intraoperative fluoroscopy b) immediately post-operative radiographs (images downloaded from PACS in PDF format)

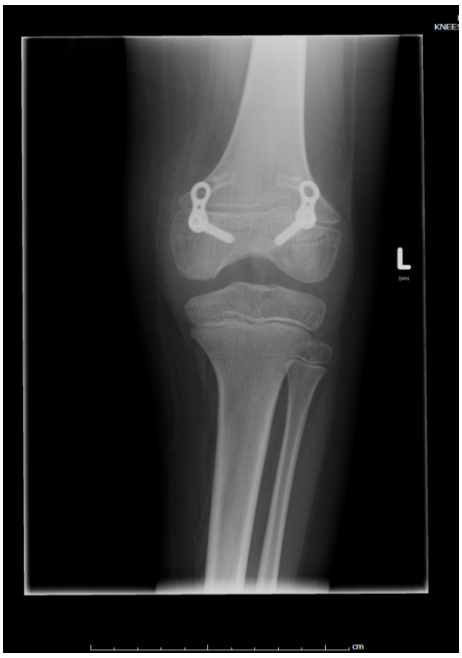


Figure 3.5: March 2008 (image downloaded from PACS in PDF format)

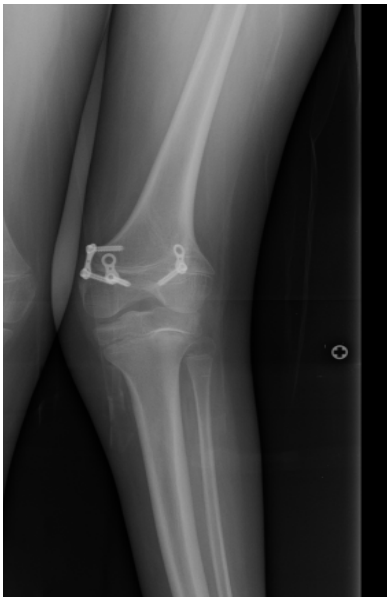
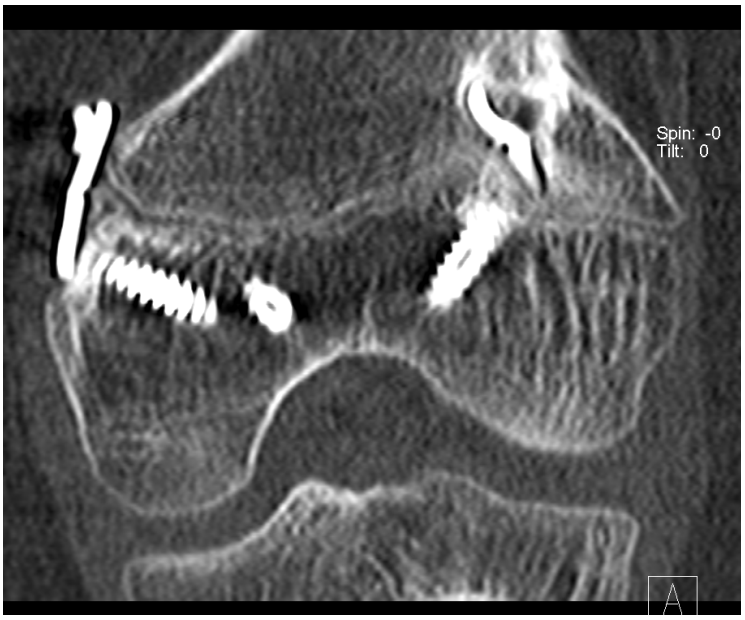


Figure 3.6: December 2011 (image downloaded from PACS in PDF format)



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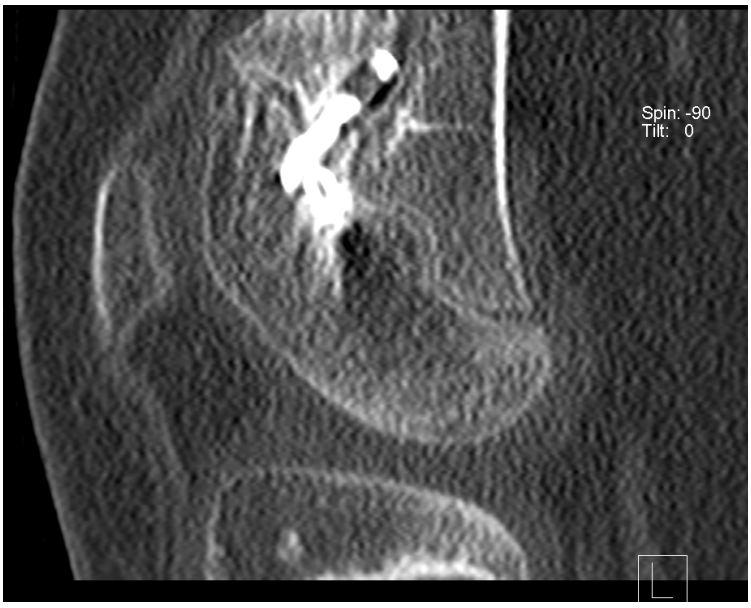

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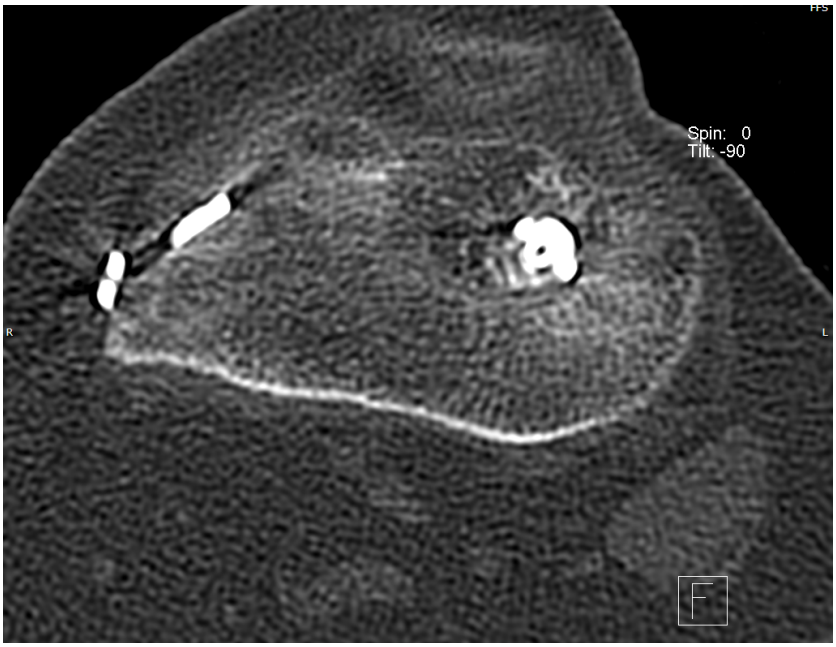

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Figure 3.7: CT 2012 a) coronal view b) sagittal view c) axial view (images downloaded from PACS in PDF format)

Therapeutic Intervention

In August of 2012, the 13 year-old patient underwent a corrective osteotomy with planned future intramedullary lengthening. (Figure 3.8 and 3.9)

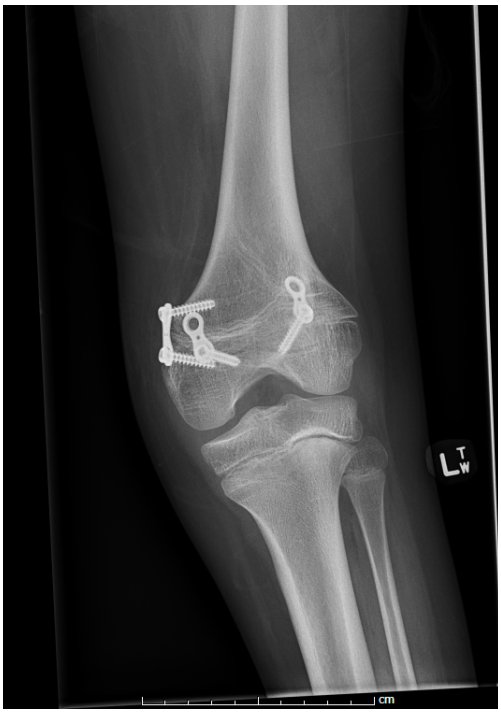


Figure 3.8: pre-op August 2012 (image downloaded from PACS in PDF format)

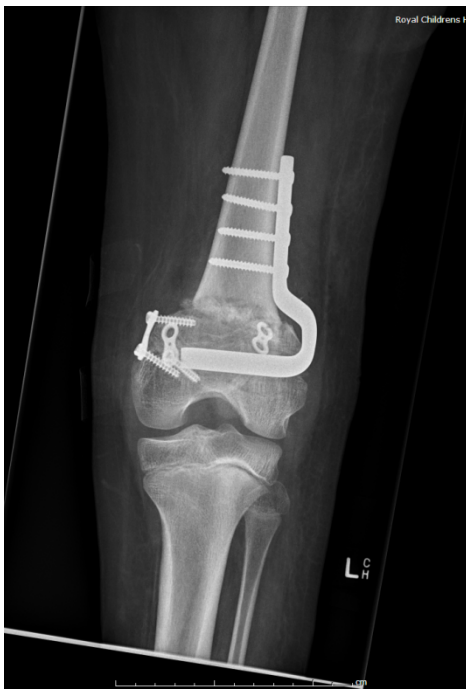


Figure 3.9: Post corrective osteotomy August 2012 (age 13 years-old) (image downloaded from PACS in PDF format

Timeline

Table 3.1 – Timeline of case events

YEAR	AGE (YEARS)	INTERVENTION
2006	7	Insertion anterior 8 plates for procurvatum deformity anterior distal femur
2007	8	Anterior metaphyseal screws removed as deformity had corrected
2008	9	Valgus deformity noted
2010	11	Medial distal femur 8 plate inserted to prevent progression of valgus deformity
2012	13	Computed tomography scan shows intramedullary position of anterolateral eight plate with physeal bar
2012	13	Corrective distal femoral osteotomy

3.3.Discussion and Review of the Literature: Case reports are important to describe adverse events and introduce novel techniques. They are subject to bias and there is the inability to infer causality of the adverse event with any certainty. [32]

In 1862, Hueter noted that diminished compression led to relatively greater bone growth.[43] In 1869, Volkmann stated that abnormal differences in compression can create asymmetrical growth of a joint.[44] Thus was coined the "Hueter-Volkmann law" which states that compression forces inhibit bone growth and tensile forces stimulate bone growth.[36]

In 1933, Phemister[45] demonstrated the ability to use epiphysiodesis to stop physeal growth. This was initially purported as a method of equalizing leg lengths but was also noted to be a possibility for angular correction. The irreversibility of the physeal arrest confined its use to children close to skeletal maturity. Accurate timing is difficult due to inaccuracies with estimation of skeletal maturity.[46]

In 1945, Haas made another advance in this field when he showed that a wire loop around the growth plate of the distal femoral canine physis could temporarily retard growth and that growth would resume with defunctioning the wire (breakage or removal).[35, 36]

Extensive research has been performed with respect to the biologic response to compression of the physis. In 1967, Goff reported on biopsies of 120 human physes, looking at histologic

changes that occur with staple insertion.[47] He showed that chondrogenesis and provisional calcification halt with staple insertion, and that growth resumed if staples were left in for less than 44 months.[47] After 49 months, staples created total physeal arrest. However, most clinicians assert that the risk of physeal bar formation increases after 24 months of staple retention.[46]

In 1996, Meikle and Stevens[46] reported on hemiepiphyseal stapling for deformity correction in children younger than ten years. Using fluoroscopy to localize the physis and using preservation of the periosteum during staple insertion and removal, they showed no growth arrest at 3 year follow up in a group of 25 children. Many authors report that growth resumption after staple or 8-plate removal has an unpredictable pattern with rebound overgrowth that is only partially compensated by earlier closure of the physis on the operated side, approximately 4-6 months earlier than the non-operated side.[48]

Several animal studies have been performed on rabbits looking at the reversibility of growth arrest after removal of staples[49-51]. In 2005, Aykut *et al.* looked at the effect of temporary stapling on bone geometry and proliferative activity of rabbit physis[49]. They inserted staples subperiosteally and extra periosteally and noted that it is of paramount importance not to disturb the periosteum during stapling to enable reversibility. They showed histologically that a bone bridge will form and permanent growth arrest will result if the staples are inserted subperiosteally.[49]

In a direct comparison of staples and 8-plates, Goyenche *et al.* [50] placed one of each device on contralateral distal femurs in New Zealand rabbits. They euthanized all rabbits at 8 weeks, with hardware still in situ. They found faster correction using conventional staples, and less inhibition of longitudinal growth with 8-plates. Histologic examination of all specimens revealed no injury to physis.

Ross *et al.* [51] compared the rate, efficacy and histologic appearance of physeal growth inhibition when using Phemister epiphysiodesis, staples, or percutaneous epiphysiodesis. They used twenty 10 week-old New Zealand rabbits, noting that by 10 weeks of age, the rabbit tibia has achieved 82% of its adult length and by 20 weeks of age, 98% of the adult length has been achieved. The rabbits were divided into four groups of five, and one of these groups had 2 staples placed medially and 2 laterally. To accurately localize the physis, the periosteum was elevated. Histology at 2 weeks showed decreased height of the physis, with a greater decrease in hypertrophic zone than proliferative. At 4 weeks, bone bridges were seen. The growth plate was nearly gone by the 6 weeks mark. Radiographic closure of the physis was seen at 3 weeks. They noted that the physeal arrest may have been due to the fact that the rabbits used were near skeletal maturity or their technique of elevating the periosteum to locate the physis. Meikle *et al*.[46] advised against direct growth plate exposure.

In 1999, Stevens *et al.* [52] retrospectively reviewed 76 patients (152 knees who underwent stapling for genu valgum). They found stapling safe and effective, with no premature physeal closures. A pre-requisite for this success they hypothesized was to leave the periosteum

undisturbed when inserting and removing staples. They noted eight knees required repeat stapling due to rebound growth.

Boero *et al*. analyzed retrospectively a group of 58 children treated with 8 plates: 30 patients had idiopathic deformities and 28 had bone dysplasias. There were no complications of physeal arrest, and only 3 rebound patients, all in the bone dysplasia group.[53]

In 2008, Burghardt *et al.*[40] reported on their first series of 11 patients who underwent treatment of angular deformities using 8 plates. This was used in patients as young as four years, 11 months. They achieved angular correction in all cases but one (who had no further growth after resection of an osteosarcoma). They did not have sufficient follow-up to comment on rebound growth or growth resumption. They did conclude that the 8 plate was superior to the Blount staple with respect to its tenacious purchase in bone, reducing the risk of extrusion and allowing fixation in younger children with mainly unossified physes.[40]

In a prospective observational study of 25 children, mean age 11.6 years, Ballal *et al.* showed no permanent growth arrests and one rebound growth[35]. They treated a total of 51 physes using 8 plates for correction of coronal plane deformities about the knee. They had one deep infection and one plate and screw migration.

In a prospective case series of 54 eight plates inserted into the limbs of 34 children by Burghardt et al. (2010), there were no demonstrated cases of growth arrest. They assessed rate of

correction and reversibility. They did show a rebound of the mechanical axis deviation of 1.0 mm per month over the 16 months of follow-up.[54]

In 2011, Guzman *et al.* [55] reported on their results of 47 valgus deformities treated with medial hemiepiphysiodesis using a tension band plate. They found faster correction with younger patients and when two plates were used instead of one. They had no complications of permanent growth arrest or plate breakage. However, they noted that they were unable to assess for rebound growth due to insufficient follow-up until skeletal maturity.

In a retrospective analysis of 35 patients treated with Blounts staples (32 extremities) versus 8-plates (29 extremities) to create temporary hemiepiphysiodesis for correction of genu varum or valgum, Jelinek *et al*. [56] noted that both methods had similar potential for correction, but there was a faster operative time for 8-plate insertion and removal. They had no complication of premature physeal closure.

Klatt *et al*.[57] retrospectively reviewed 18 patients with 29 fixed knee flexion deformities treated with a pair of anteriorly placed 8-plates for gradual correction. They had a correction rate of 1.4 degrees per month. They noted one recurrent fixed flexion deformity due to rebound growth. They reported no permanent growth arrests.

Schroerlucke *et al.* reviewed their results in treatment of proximal tibia vara with 8 plates. They had a 44% complication rate with breakage of the metaphyseal screw in 8 of 18 patients treated for Blounts disease. There were no reports of permanent physeal arrest.[58]

Stevens and Pease reported in 2006 on using hemiepiphysiodesis for postrtraumatic tibial valgus[59]. They reported on 12 patients, using either staples or a two-holed plate. They noted one episode of stapling was used in 5 patients and seven patients required two episodes of stapling (3 for recurrence, and 3 for staple migration). They recommended proximal tibial hemiepiphysiodesis if patients have persistent pathologic genu valgum more than a year after proximal tibial fracture. The authors noted they preferred using the nonlocking two holed plate which avoids premature staple migration, allowed more rapid alignment correction, and rebound growth was less likely.

In 2007, Stevens wrote about his preliminary series using a tension band plate for "Guided growth for angular correction"[37]. He prospectively followed 34 patients with 65 deformities who underwent guided growth with a tension band plate. 32 of 34 patients (63 deformity levels) corrected to neutral at a mean 11 months. Follow up ranged from 14 to 26 months. There were no permanent growth arrests and no iatrogenic limb length discrepancies. Four patients with bilateral genu valgum experienced rebound. Two patients with adolescent Blounts disease did not fully correct.

Stevens and Klatt (2008)[60] retrospectively reviewed 14 children with rickets, ten treated with staples and four with 8-plates. There were 68 hemiepiphysiodesis performed and 35 osteotomies. In the staple group, there were 24 implant migration and 41% rebound deformity. Four patients with fifteen deformities treated with 8 plates experienced no implant migration. They noted that by switching from staples to 8 plates there was a more rapid correction and hardware migration was averted.

Stevens *et al.* (2011)[61] reported on the use of the tension band 8-plate to correct ankle valgus in 33 patients (57 ankles). They reported successful correction with none of the patients requiring osteotomy, no symptomatic ankle varus, and no premature physeal closure.

A retrospective comparison of methods of hemiepiphysiodesis about the knee was made between 39 limbs that received staples for hemiepiphysiodesis and 24 that received 8 plates. Wieman *et al.*[62], found no difference in rate of correction, complications rates. Patients with abnormal physes had higher complication rates for both groups.

Many authors recommend removal of guided growth hardware after correction or slight overcorrection has been achieved[48, 63]. Permanent physeal arrest has become uncommon, with authors recommending extraperiosteal placement and special attention not to disrupt the periosteum at time of implant removal .[63]

In the case presented, the child has a spinal muscular atrophy-like condition. This type of disorder has been found to have risk for pronounced flexion contractures at knee starting at a young age.[64] This increased the likelihood of recurrence after the correction was achieved due to muscular atrophy and weakness.

This report is important in that it describes an adverse event not previously reported in the literature. In cases where rebound of deformity is likely, it is common practice for a pediatric orthopaedic surgeon to remove the metaphyseal screw from the 8-plate and leave the rest of the construct.[65] Given the permanent growth arrest that occurred here, removal in its entirety with replacement in case of rebound is indicated. This study is limited in that it is a case report of one person having an adverse event. Thus, causality of growth arrest cannot be reliably concluded. To look at this further, a survey of multiple centres could locate other non-reported cases and a case series subsequently developed. As well, this practice of metaphyseal screw removal could be studied at an animal level.

3.4. Conclusions: Use of eight plates for guided growth has not had any reported permanent physeal arrests in the literature to date. We report on a case of physeal arrest with complication of the plate becoming intraosseous. We recommend stringent adherence to meticulous preservation of the periosteum during insertion and removal. We caution against sole removal of the metaphyseal screw once correction has been achieved.

Chapter 4: Intramedullary Lengthening Using the Fitbone Device:

A Case Series

4.1. Introduction and Aims:

Case series provide level four evidence, but still offer useful contributions to the literature. A case series describes a group of patients undergoing a similar therapy or surgical intervention, but without a comparison group. There is no hypothesis tested, but the study can be used to generate a hypothesis that can be tested in the future.[15]

There are many strengths exhibited by a case series. Case series tend to have high external validity due to a wide range of patients.[15] The investigators do not control the treatment decision process, increasing the fidelity to actual clinical practice. These studies, in comparison to randomized controlled trials, tend to be relatively inexpensive and do not take a lot of time. Given that they are often a series of patients that have been treated in one's practice, they tend to be more generalizable and relatable to clinical practice. However, limitations of case series include the fact that there is no comparison group, and studies are susceptible to selection bias and measurement bias. Prospectively designing the case series, such as this one, can help eliminate selection bias.[15]

Distraction osteogenesis occurs when two bone ends undergo gradual mechanical distraction after a low energy osteotomy. In the osteotomy gap, new bone is generated (osteogenesis). This new bone is referred to as "regenerate". [66]

The first successful bone lengthening was reported by Codvilla [31, 67]. After an osteotomy, he immediately applied traction using a calcaneal pin, with loads of medium intensity (25-30 kilograms). He described complications such as convulsions, necrosis of skin at the ankle, and limited lengthening due to pain and soft tissue problems. Ombredanne [31, 68] was the first to use an external fixator for lengthening of limbs. In his 1913 report, he described issues with skin necrosis and infection, but was able to lengthen at a rate of five millimetres per day.

In the early 1950's, Ilizarov began his work on bone lengthening in Kurgan Oblast, Siberia. He had developed a circular external fixator (Figure 4.1) to stabilize the two bone ends and researched the "rate and rhythm" of distraction, finding that distraction at a rate of 1 mm per day, divided into a rhythm of 0.25 mm every six hours gave the most favourable results for bone regeneration.[69]

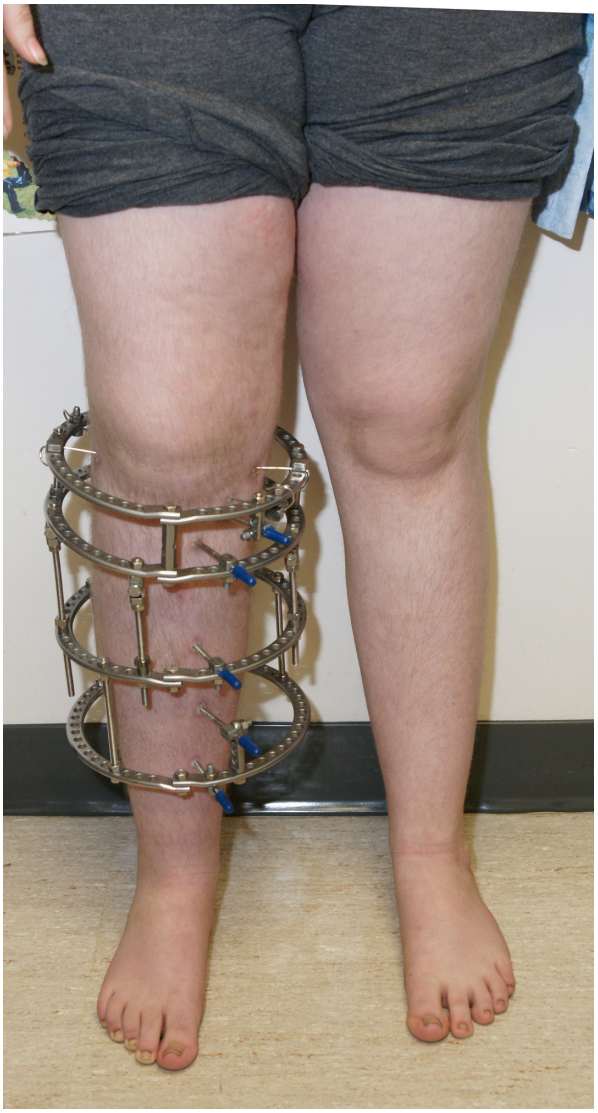


Figure 4.1: Ilizarov External fixator for tibial lengthening (photograph of patient's leg taken with personal camera).

In North America, the Wagner method (see Figure 4.2) of lengthening was most popular from 1970-1990, until details of Ilizarov's "Siberian technique" were shared with the Western world.[31, 70]. This monolateral fixator technique using 4 Schanz screws involved the patient lengthening 1.5 mm per day, at a once-a-day frequency.

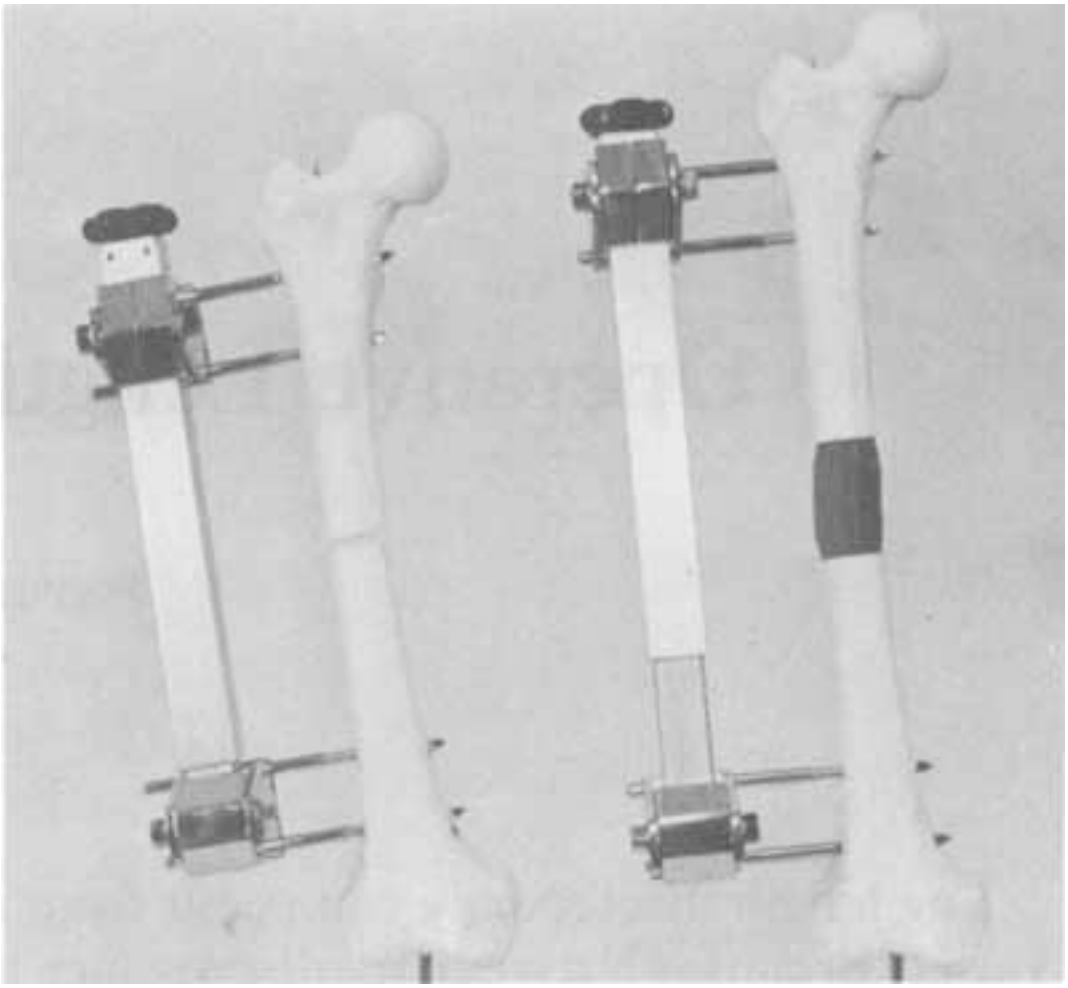


Figure 4.2: Wagner external fixation lengthening device[70] reprinted with permission from Wagner, H., *Operative lengthening of the femur.* Clin Orthop Relat Res, 1978(136): p. 125-42.

Lengthening of the lower extremities using external fixators has been fraught with complications such as pin site infection, limited rehabilitation secondary to the cumbersome frame, and fracture of the distraction callous after frame removal[71]. Antoci *et al*[72] reported in 2008, a pin tract infection rate of 96.6%.

Intramedullary lengthening avoids the use of the external frame and its complications[73]. Previous methods to eliminate problems using external fixation alone began in the 1950's when Bost and Larsen described lengthening with an external fixator combined with an intramedullary nail for stabilization[74]. This reduced the time of external fixation and thus risk of pin tract infection.

In the 1970's, several authors described various methods of leg lengthening using intramedullary devices[75-77]. Gotz *et al*.[76] described a device that used a hydraulic pressure system while Bauman *et al*.[75] described one using a spindle mechanism. Both devices needed an external component. This created the risk of direct intramedullary infection. Witt *et al*.[77] trialled an intramedullary device that was regulated by radio control. This was not continued due to technical problems.

Throughout the 1980's and 90's, several groups were designing and trialling fully implantable intramedullary distraction devices. Guichet, described the Albizzia nail which worked on a ratchet mechanism, requiring 20 degrees of rotation in each direction fifteen times to lengthen one millimetre[78]. Cole first described the use of the ISKD (Intramedullary Skeletal Kinetic Distractor)[79]. In this nail, distraction works on a ratchet mechanism and is triggered by alternating rotational movement of at least three degrees at the osteotomy site. One-hundred sixty rotational movements of three degrees leads to lengthening of 1mm. This amount of rotation should occur during normal movements[71].

Baumgart and Betz[73] first described the Fitbone in 1990. The Fitbone is a fully implantable modular nail with a motor driven actuator. A subcutaneous antenna with an external control of programmable radiofrequency customizes rate and rhythm of distraction. Energy is supplied three to four times a day, ninety seconds at a time.[80] Two types of Fitbone are available: Fitbone slide active actuator (SAA) and Fitbone telescopic active actuator (TAA). The cases described used the Fitbone TAA, which comes as a nail having shaft diameter of 10 mm and juxtaarticular diameter of 12 mm. A straight variant with continuous diameter of 13 mm is also available. A picture of the telescopic nail is shown in Figure 4.3 along with the high frequency transmitter and control unit.

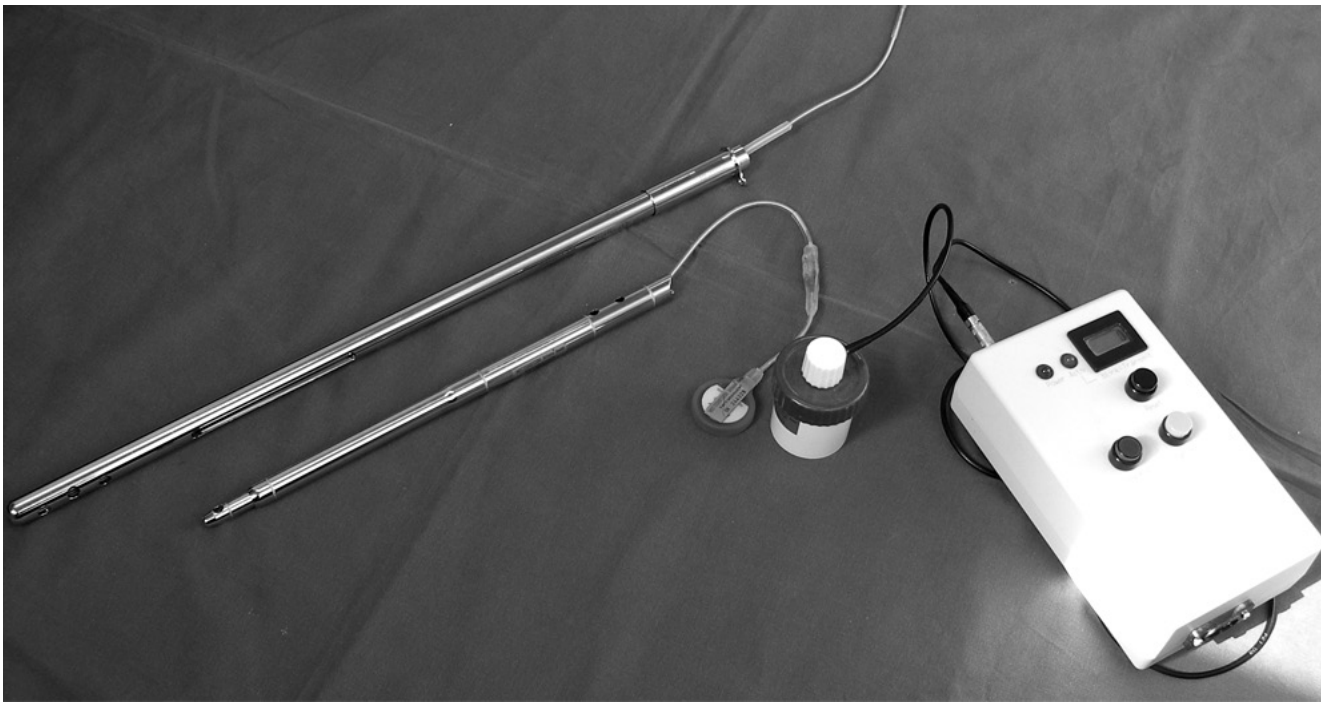


Figure 4.3 Picture of Fitbone Intramedullary Nail and External control device. Transmitter is placed on skin surface over subcutaneously placed receiver[81]. Reprinted with permission Krieg, A.H., et al., *Intramedullary leg lengthening with a motorized nail.* Acta Orthop, 2011. **82**(3): p. 344-50 DOI: 10.3109/17453674.2011.584209.

The aim of this study was to assess if the Fitbone device could provide successful lengthening with improved rehabilitation and decreased hospital stay, while achieving therapeutic aims of lengthening and correcting mechanical axis.

4.2. Method: In a prospective manner from August of 2003 to November 2010, twenty- one patients were enrolled after Institutional Review Board approval was obtained. There were six females and fifteen males with an average age of 16.6 years (+/-4.7). Prior to surgery, leg length discrepancy, mechanical axis deviation, and anatomic angles of the lower extremity were measured. Subsequently, the reverse planning method, as described by Baumgart[82], was utilized to plan corrective osteotomy and Fitbone insertion at the time of surgery.

The reverse planning method involves a detailed pre-operative analysis to develop the surgical plan. It begins with a tracing of the entire lower limb radiograph (three-foot film). The malalignment test as described by Paley[83] is first performed. For this, a line is drawn from the centre of the femoral head to the centre of the ankle. The mechanical axis deviation is then determined by measuring the perpendicular distance of this line from the centre of the knee joint. The mechanical lateral distal femoral angle (mLDFA) and mechanical medial proximal tibial angle (mMPTA) are also analyzed. When planning for a femoral osteotomy, the mechanical axis of the tibia is then continued proximally. The desired final position of femoral head is chosen (Figure 4.4).

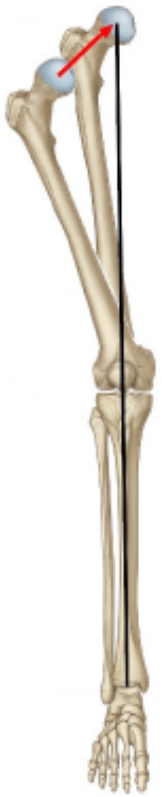


Figure 4.4: Reverse planning method. The mechanical axis of the normal tibia is continued proximally, and desired final position of femoral head is chosen reprinted with permission from Prof. Kristian Bundgaard

An osteotomy is then created at the desired level and the proximal femur is moved to its final desired position (Figure 4.5). The nail is then drawn to scale with the hip in the desired final location (Figure 4.6). The proximal femur is shifted distally along the nail to see the product to be achieved at the end of surgery (Figure 4.7)

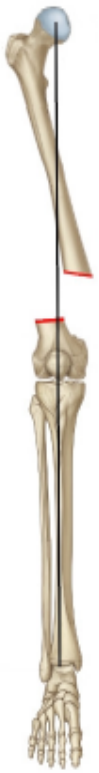


Figure 4.5: Reverse Planning Method: Femoral head moved to desired final location after osteotomy reprinted with permission from Prof. Kristian Bundgaard

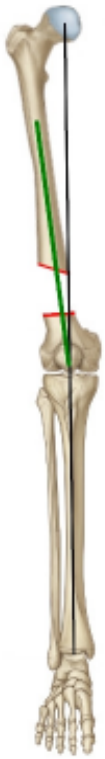


Figure 4.6: Reverse Planning Method: Fitbone nail drawn to size with hip in desired final location reprinted with permission from Prof. Kristian Bundgaard

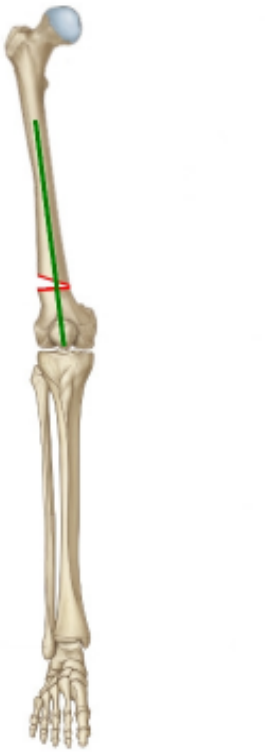


Figure 4.7: Reverse Planning Method: Proximal femur shifted distally along nail to see final surgical result: note desired angulation at osteotomy site reprinted with permission from Prof. Kristian Bundgaard

The preference at our centre is to insert the femoral Fitbone in a retrograde manner, using a transverse incision over the patellar tendon (Figure 4.8). Reaming is performed using rigid reamers by hand, and the osteotomy is performed using a 4.0 mm drill bit with completion via a small osteotome. Tibial Fitbones were inserted antegrade.

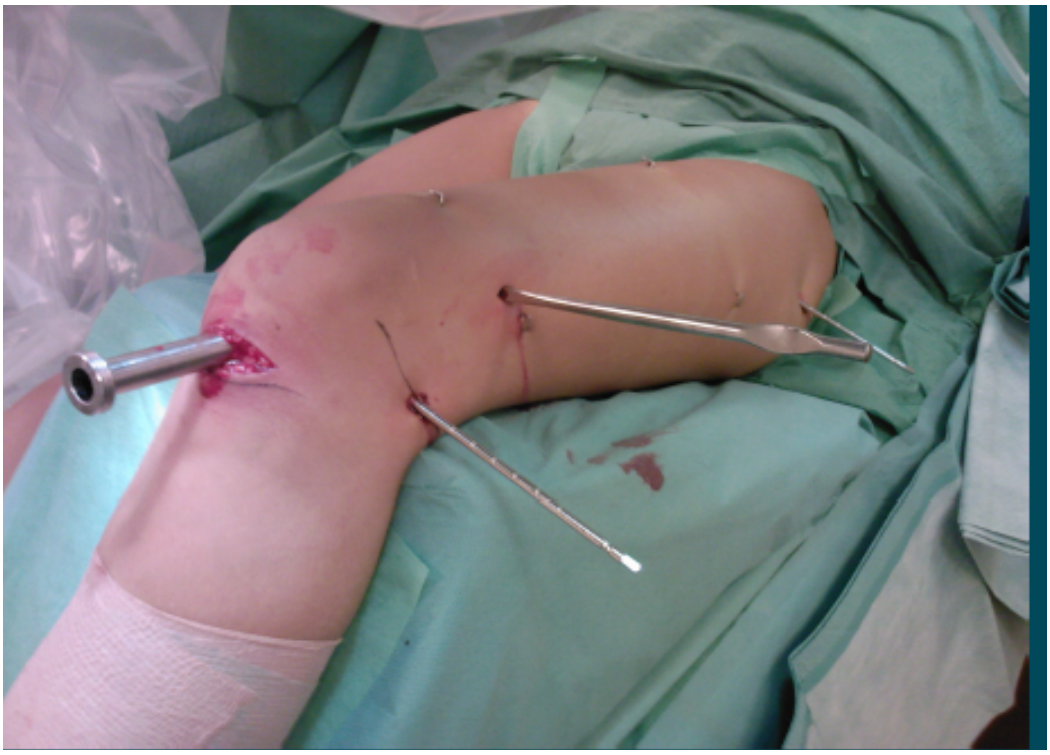


Figure 4.8: Retrograde insertion using transverse skin incision over patellar tendon reprinted with permission from Prof. Kristian Bundgaard

The preoperative level of difficulty was assessed using a scale designed by Paley *et al*.[84] (Table 4.1a) and modified by Krieg *et al*.[85] (Table 4.1b). The preoperative level of difficulty was on average 3.8 (+/- 3.7). This assessment scale looks not only at patient factors (age, medical problems), but at quality of bone and soft tissue, as well as the complexity of deformity correction associated with lengthening (angular, rotational, and displacement correction). It also considers instability of joints above and below and joint contractures. These can create complications and limit the amount of lengthening achieved.

Table 4.1a Classification scale for the level of difficulty of the femoral lengthening[84]

Parameter	0 Points	1 Point	2 Points	3 Points
Planned femoral lengthening (each cm of lengthening = 1 point)				
Age (years)	5–19	20–29	30–50	> 50
Complexity of correction of deformity at level of lengthening	None	Angulation > 5° < 20°, rotation > 10° < 30°, translation < 50% of bone diameter or MAD 1–3 cm	Angulation > 20°, rotation > 30°, translation ≥ 50% of bone diameter or MAD > 3 cm	Combination of deformities at one level or multilevel deformities
Other levels of treatment in same bone	None	One additional level mild complexity	One additional level moderate complexity	One additional level of severe complexity or ≥ 2 levels
Associated tibial lengthening (cm)	None	1–3	3.1–6	> 6
Instability of joint	None	Grade I	Grade II	Grade III
Fixed flexion deformity of the knee (degrees)	0	1–5	6–20	> 20
Flexion of the knee (degrees)	> 120	100-120	65-99	< 65
Osteoarthrosis of the joints	None	Marginal osteophytes, subchondral sclerosis	Narrowing of joint space	Loss of joint space
Quality of bone	Normal	Ollier's disease, mild osteoporosis, non-union	Radiation neurofibromatosis, osteogenesis imperfect	Osteonecrosis, infection
Quality of soft tissue	Normal	Spastic, obese muscular	Fibrotic, postradiation, small open wound	Tissue necrosis, infection, large open wound

Parameter	0 Points	1 Point	2 Points	3 Points
Medical problems and medication	None	Smoking, hypertension, rheumatoid arthritis, or other systemic arthritis	Diabetes, hemophilia, sickle cell anemia, mild immunosuppression, bone-inhibiting medications	Moderate immunosuppression, antimetabolic chemotherapy

mild = 0–6 points, moderate = 7–11 points, severe = ≥ 12 points; MAD = mechanical axis deviation. Reprinted with permission from Paley, D., et al., *Femoral lengthening over an intramedullary nail. A matched-case comparison with Ilizarov femoral lengthening.* J Bone Joint Surg Am, 1997. **79**(10): p. 1464-80 DOI: 10.2106/00004623-199710000-00003.

Table 4.1b Classification scale for the level of difficulty of the tibial lengthening[85] *,†

Parameter	0 Points	1 Point	2 Points	3 Points
Planned tibial lengthening (each cm of lengthening = 1 point)				
Age (years)	5–19	20–29	30–50	> 50
Complexity of correction of deformity at level of lengthening	None	Angulation > 5° < 20°, rotation > 10° < 30°, translation < 50% of bone diameter or MAD 1–3 cm	Angulation > 20°, rotation > 30°, translation ≥ 50% of bone diameter or MAD > 3 cm	Combination of deformities at one level or multilevel deformities
Other levels of treatment in same bone	None	One additional level mild complexity	One additional level moderate complexity	One additional level of severe complexity or ≥ 2 levels
Associated femoral lengthening (cm)	None	1–3	3.1–6	> 6
Instability of joint	None	Grade I	Grade II	Grade III
Fixed plantar flexion deformity of the ankle (degrees)	0	1–5	5-15	> 15

Parameter	0 Points	1 Point	2 Points	3 Points
Plantar Flexion of the ankle (degrees)	> 30	20-30	10-19	< 10
Osteoarthrosis of the joints	None	Marginal osteophytes, subchondral sclerosis	Narrowing of joint space	Loss of joint space
Quality of bone	Normal	Ollier's disease, mild osteoporosis, non-union	Radiation neurofibromatosis, osteogenesis imperfect	Osteonecrosis, infection
Quality of soft tissue	Normal	Spastic, obese muscular	Fibrotic, postradiation, small open wound	Tissue necrosis, infection, large open wound
Medical problems and medication	None	Smoking, hypertension, rheumatoid arthritis, or other systemic arthritis	Diabetes, hemophilia, sickle cell anemia, mild immunosuppression, bone-inhibiting medications	Moderate immunosuppression, antimetabolic chemotherapy

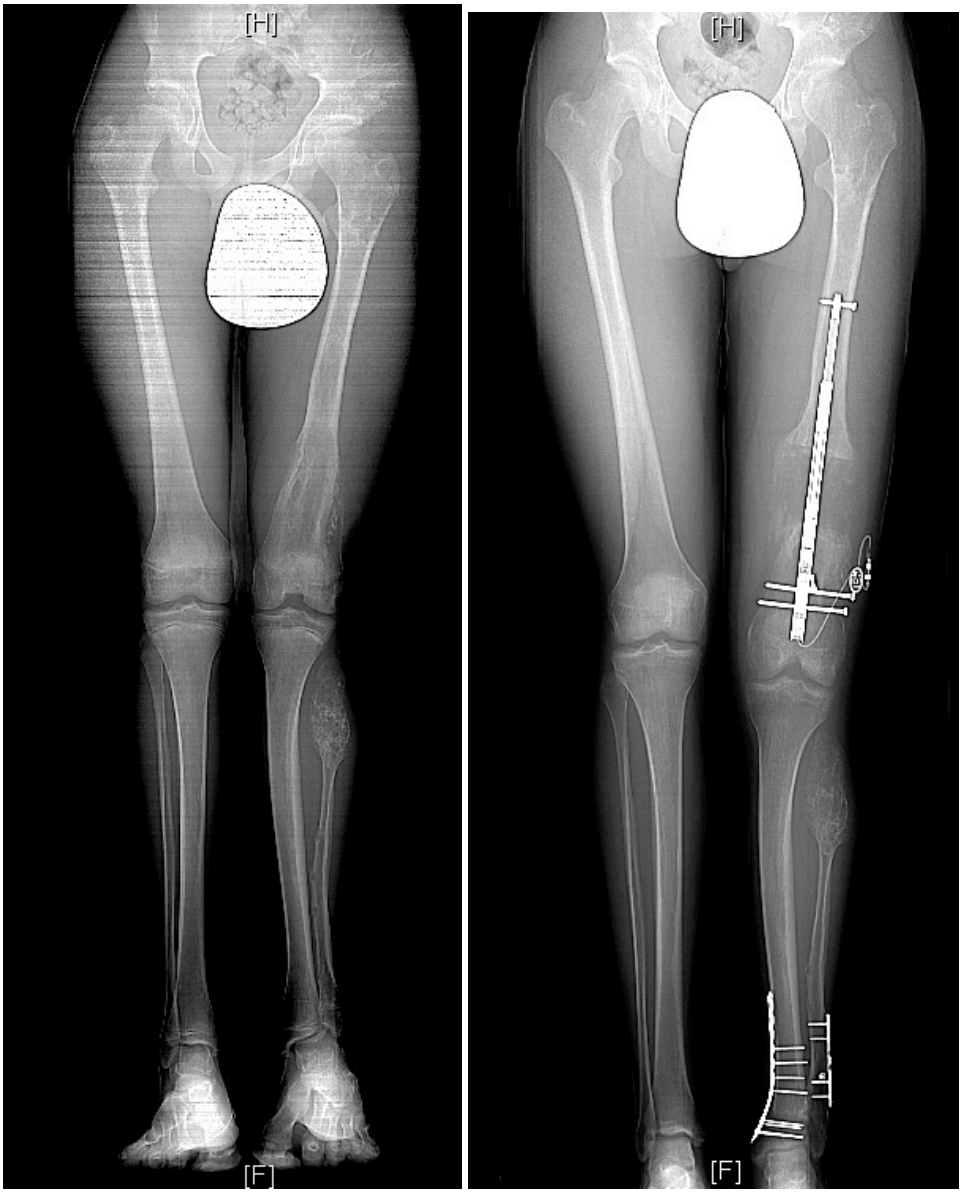
*From Paley et al.[23] classification for femoral lengthening; †mild = 0–6 points, moderate = 7–11 points, severe = ≥ 12 points; MAD = mechanical axis deviation. Reprinted with permission from Krieg, A.H., B.M. Speth, and B.K. Foster, *Leg lengthening with a motorized nail in adolescents : an alternative to external fixators?* Clin Orthop Relat Res, 2008. **466**(1): p. 189-97 DOI: 10.1007/s11999-007-0040-3.

Nails were implanted into sixteen femurs and five tibias. The average leg length discrepancy was 41.7 mm (+/- 25). Thirteen legs had a valgus deformity with an average mechanical axis deviation of 12.1 mm valgus. Leg length discrepancy was caused by trauma in six, infection in six, and congenital problems in nine. Table 4.2 summarizes patient characteristics and scores, and Figure 4.9 shows a case of a patient with Ollier's disease and a 5.5cm leg length discrepancy who underwent a 6.1cm lengthening.

TABLE 4.2: SUMMARY OF PATIENT CHARACTERISTICS AND SCORES

PATIENT	GENDER	AGE	AETIOLOGY	BONE	PRE-OP SCORE	LLD mm	PRE-OP AXIS MAD (mm)
1	FEMALE	17.8	SPINA BIFIDA	FEMUR	4	30	-9
2	MALE	16.25	FRACTURE	FEMUR	0	16	0
3	FEMALE	15.2	HIP SEPTIC ARTHRITIS	FEMUR	0	30	-8
4	MALE	17.1	FRACTURE	FEMUR	4	51	14
5	MALE	13.9	FRACTURE	FEMUR	2	33	33
6	MALE	16.5	TIBIAL HYPOPLASIA	FEMUR	3	35	27
7	FEMALE	12.75	FRACTURE	FEMUR	3	58	36
8	MALE	16.6	TIBIAL HYPOPLASIA	TIBIA	1	30	10
9	FEMALE	33	SPINA BIFIDA	TIBIA	2	32	------
10	FEMALE	13.6	CP +OSTEOMYELITIS	FEMUR	10	44	34
11	FEMALE	14.4	FIBULAR HEMIMELIA	TIBIA	3	30	18
12	MALE	16.75	AMYOPLASIA	TIBIA	2	23	5
13	MALE	15.4	PFFD + FIBULAR HEMIMELIA	FEMUR	2	40	21
14	MALE	18.1	NEONATAL HIP SEPTIC ARTHRITIS	FEMUR	2	47	0
15	MALE	16.7	OSTEOMYELITIS	FEMUR	5	55	-20
16	MALE	7.8	OSTEOMYELITIS	FEMUR	14	97	33
17	MALE	14.9	OSTEOMYELITIS	FEMUR	9	110	3

18	MALE	17.7	OLLIERS	FEMUR	5	55	35
19	MALE	22	CONGENITAL	FEMUR	0	14	0
20	MALE	64	TRAUMA	TIBIA	9	25	6
21	MALE	15.25	TRAUMA	FEMUR	0	44	5
MEAN		16.6			3.8	41.7	12.1
STANDARD DEVIATION		4.7			3.7	25.0	16.8



a) Pre-op CT scanogram b) Post lengthening CT scanogram

Images downloaded from PACS in form of PDF

Figure 4.9: Case of patient with Ollier's disease with leg length discrepancy of 5.5 cm underwent retrograde Fitbone TAA for lengthening 6.1 cm and corrective osteotomy of distal tibia.

Each patient had a Fitbone nail implanted. The nail contains a motor attached to a subcutaneous antenna that changes high frequency electric energy transmitted through the skin into a power source for the motor[73]. The motor delivers a torque that, through a gear and spindle mechanism, is transformed into axial lengthening. A stethoscope is used to discern the pitch of the motor. The physician can program the control unit to modify the daily rate of distraction, with an aim to distract 1mm per day.[69]

The surgical technique to insert the Fitbone device involved an osteotomy via a drill-hole corticotomy technique. Rotational alignment was maintained using two parallel 3.0mm Kirschner wires. Mechanical axis and joint alignment in the frontal plane was maintained using radiolucent markers attached to the operating table. The canal was reamed with straight reamers. After nail insertion, the subcutaneous receptor was connected to the motor through a thin, insulated, flexible wire.

The categorical outcome scoring system devised by Paley *et al*.[84] was utilized to grade femoral lengthening (see Table 4.3a). The scoring system as modified by Krieg *et al*.[85] was utilized for tibias (see Table 4.3b). On average, patients were seen weekly by the senior author (Prof. Bruce Foster) during distraction, and at 3, 6, 9, 12, and 18 months. Radiographs were taken at these times. At the end of the consolidation phase, gain in leg length, mechanical axis deviation, and lower extremity anatomical angles were measured on plain radiographs and via a computer program using CT scanograms.

Table 4.3a Scoring system for outcome of femoral lengthening [†,†] [84]

Parameter	Additions (number of points to be added to derive total score)				Subtractions (number of points to be subtracted from the total score)			
	Excellent (25)	Good (20)	Fair (10)	Poor (0)	Excellent (0)	Good (5)	Fair (20)	Poor (30)
Range of motion of the knee	Fixed flexion deformity = 0°, flexion > 120°, or flexion ≥ 90% of preoperative flexion	Fixed flexion deformity ≤ 5°, flexion 101°–120°, or flexion 67%–89% of preoperative flexion	Fixed flexion deformity = 6°–15°, flexion 70°–100°, or flexion 50%–66% of preoperative flexion	Fixed flexion deformity > 15°, flexion < 70°, or flexion < 50% of preoperative flexion				
Amount of lengthening	Within 1 cm of goal	Within 1.1–3 cm in goal	Within 3.1–5 cm of goal	> 5 cm of goal				
Gait (preoperative to postoperative points)[‡]	0, 1 to 0	1, 2 to 1	0 to 1 or 1, 2 to 2	0 to 2				
Lateral distal femoral angle (degrees)	85°–90°	82°–84°, 91°–93°	79°–81°, 94°–96°	< 79°, > 96°				
Pain (preoperative to postoperative points)[§]					0, 1, 2 to 0 or 1 to 1	0, 2, 3 to 1	1 to 2 or 2 to 3	0 to 2, 3 or 1 to 3
Ability to perform activities of daily living or to work (preop to postop pts)[‖]					0, 1, 2 to 0	1, 2 to 1	1 to 2 or 0 to 1	0 to 2

[†]excellent = 95–100 points, good = 75–94 points, fair = 40–74 points, poor = < 40 points; [‡]0 points = no limp, 1 point = slight limp, 2 points = moderate limp; [§]0 points = no pain, 1 point = slight pain, 2 points = moderate pain, 3 points = severe pain; [‖]0 points = full activity and full-time work, 1 point = reduced activity and work, 2 points = no activity

Table 4.3b Scoring system for outcome of tibial lengthening[85] ‡,†

Parameter	Additions (number of points to be added to derive total score)				Subtractions (number of points to be subtracted from the total score)			
	Excellent (25)	**Good (20)**	**Fair (10)**	**Poor (0)**	**Excellent (0)**	**Good (5)**	**Fair (20)**	**Poor (30)**
Range of motion of the knee	Fixed flexion deformity = 0°, flexion > 120°, or flexion ≥ 90% of preoperative flexion	Fixed flexion deformity ≤ 5°, flexion 101°–120°, or flexion 67%–89% of preoperative flexion	Fixed flexion deformity = 6°–15°, flexion 70°–100°, or flexion 50%–66% of preoperative flexion	Fixed flexion deformity > 15°, flexion < 70°, or flexion < 50% of preoperative flexion				
Amount of lengthening	Within 1 cm of goal	Within 1.1–3 cm in goal	Within 3.1–5 cm of goal	> 5 cm of goal				
Gait (preoperative to postoperative points)‡	0, 1 to 1	1, 2 to 1	0 to 1 or 1, 2 to 2	0 to 2				
Medial Proximal tibia angle (degrees)	85°–90°	80°–84°, 91°–95° or >5% deviation from pre-op	75°–79°, 96°–100° or >10% deviation from pre-op	< 75°, >100° or >15% deviation from pre-op				
Pain (preoperative to postoperative points)§					0, 1, 2 to 0 or 1 to 1	0, 2, 3 to 1	1 to 2 or 2 to 3	0 to 2, 3 or 1 to 3
Ability to perform activities of daily living or to work					0, 1, 2 to 0	1, 2 to 1	1 to 2 or 0 to 1	0 to 2

Parameter	Additions (number of points to be added to derive total score)				Subtractions (number of points to be subtracted from the total score)			
	Excellent (25)	Good (20)	Fair (10)	Poor (0)	Excellent (0)	Good (5)	Fair (20)	Poor (30)
(preop to postop pts)‖								

Modification of Paley *et al.*[84] outcome scoring system for femoral lengthening; †excellent = 95–100 points, good = 75–94 points, fair = 40–74 points, poor = < 40 points; ‡0 points = no limp, 1 point = slight limp, 2 points = moderate limp; §0 points = no pain, 1 point = slight pain, 2 points = moderate pain, 3 points = severe pain; ‖0 points = full activity and full-time work, 1 point = reduced activity and work, 2 points = no activity

4.3. Results: Since 2003, the Fitbone intramedullary lengthening device has been implanted in 21 patients in our institution. All patients have been successfully lengthened. The average lengthening was 29.7 mm (95% Confidence Interval (CI) 23.2-36.2 mm). This accounted for 87.2% (95% CI: 80.7-93.7%) planned lengthening achieved. The average distraction period was 45.5 days. Lengthening was performed in five tibial and sixteen femoral bones. The average preoperative mechanical axis deviation was 12.1 mm valgus (95% CI: 4.8-19.4mm), corrected to 0.08 mm valgus post operatively (95% CI -5.2-5.4). The average length of hospital stay was 12 days, including all complications and days for nail removal (see Table 4.4).

The average post-operative score was 80.9 (good outcome) with 95% CI 72.7-89.1 (Paley scoring system for femurs and Krieg scoring system for tibias). The outcome score takes into account the knee range of motion, amount of lengthening achieved with respect to goal of lengthening, gait (whether or not patient limps), pain, ability to perform activities of daily living, and final mechanical lateral distal femoral angle. A perfect score is 100 points.[84]

TABLE 4.4: RESULTS

PATIENT	GAIN (mm)	% PLANNED achieved	FOLLOW UP (months)	DISTRACTION PERIOD (days)	AXIS POST-OP (mm)	POST-OP OUTCOME SCORE	LENGTH OF HOSPITAL STAY (days)
1	22	73	31	35	8	60 (FAIR)	8
2	16	100	31	31	0	95 (EXCELLENT)	7
3	30	100	28	113	3	-----	22
4	45	88	36	55	6	95 (EXCELLENT)	12
5	27	82	70	60	2.9	80(GOOD)	11
6	34	97	30	31	0	95 (EXCELLENT)	11
7	50	86	60	69	8	-------	5
8	25	83	34	36	5	95 (EXCELLENT)	10
9	32	100	40	-----	----	----------	------
10	34	77	75	45	-10	70(FAIR)	16
11	22	73	34	38	4	---------	51
12	18	78	86	29	-1.7	80(GOOD)	11
13	17	43	90	28	0	65(FAIR)	15
14	35	74	24	42	0	90(GOOD)	11
15	45	82	11	65	-33.8	85(GOOD)	8
16	42	105	33	38	23	35(POOR)	9
17	36	90	4	36	-12.8	75(GOOD)	5
18	61.5	112	16	59	15	95 (EXCELLENT)	5
19	14	100	-----	14	0	--------	----

20	25	100	18	30	-----	95 (EXCELLENT)	5
21	39	89	14	55	-15	85(GOOD)	7
MEAN	29.7	87.2	38.2	45.5	0.08	80.9 (GOOD)	12
STANDARD DEVIATION	15.1	15.2	24.9	21.4	12	16.8	10

The sixteen femoral nails had an average anatomic lateral distal femoral angle of 80.9+/-6.1 at outcome and an average mechanical lateral distal femoral angle of 87.2+/- 5.3 at outcome.

The five tibial nails had an average anatomical medial proximal tibial angle of 85+/-4.3 and an average posterior proximal tibial angle 69.8+/-2.5 at outcome.

4.3a. COMPLICATION CLASSIFICATION

A complication was defined as a deviation from the treatment plan, which leads to failure of treatment goals or development of a pathologic process if appropriate intervention is not undertaken[9]. Limb lengthening is a complex process with one of the highest complication rates of any orthopaedic procedure[86]. A recently developed classification of complications is shown in Table 4.5([87].

TABLE 4.5: COMPLICATION CLASSIFICATION SYSTEM[87]

Grade	Explanation	Examples
Category I	Treatment plan deviation was corrected within the existing treatment plan. Treatment goals were achieved with minor adjustments	Pin-tract infection, mild joint contractures, device malfunction corrected in the office
Category II	New treatment plan has to be established to correct the deviation and achieve treatment goals	Delayed consolidation required additional intervention, device-related problems needed revision, secondary deformity corrected with additional manipulation
Category IIIA	Complication led to the failure to achieve treatment goals, but the patient condition is not worse than that before the treatment	Recurrent deformity, patient incompliance resulted in ceased lengthening
Category IIIB	Complication led to the development of a new pathologic process; therefore, patient condition is worse than that before treatment	Regenerate fracture, non-union at the regenerate site, pin-tract osteomyelitis, neurologic deficit

Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Journal of Pediatric Orthopaedics B, Cerkashin *et al*. Evaluation of complications of treatment of severe Blount's disease by circular external fixation using a novel classification scheme; 24 (2): 123-130 (2015).

Complications of device backtracking and /or failure have occurred in four patients. Backtracking involved loss of length due to slipping of the gear and spindle mechanism. One femoral nail broke, requiring revision to a rigid intramedullary nail. One tibial nail required bone grafting for consolidation. One patient suffered breakage of the antenna, requiring

arthroscopic retrieval of the subcutaneous antenna and broken cable. There has been one superficial infection. Complications are summarized and classified in Table 4.6.

TABLE 4.6: COMPLICATIONS SUMMARY

PATIENT	PRE-OP SCORE	COMPLICATION	CLASS OF COMPLICATION
1	0	Superficial infection treated with antibiotics	I
3	0	1. Wound breakdown 2. Insertion new transmitter due to backtracking	I II
4	4	Motor stopped working	II
7	3	Required revision distal locking screw	II
8	1	Nail cut out proximally in tibia	III A
10	10	Decreased range of motion knee, screw and antenna removed early	III A
11	3	1. Post op pain syndrome 2. Post op hematoma 3. Revision distal locking screw 4. Bone grafting and plating for delayed union	IIIB I I II
13	2	1. Nail jammed 2. Broke Fitbone – revised to intramedullary nail	IIIA IIIB
15	5	Painful proximal locking screw	I
16	14	Reinsertion right proximal locking screw	I

Consolidation of the distraction gap was judged to have been accelerated compared to external fixation methods, with full weight bearing occurring at 3 months. Nineteen patients have had the device removed and completed consolidation within the two-year recommended time frame.

4.4. Discussion: In 1951, Ilizarov conceived his method of gradual lengthening via distraction osteogenesis. He noted there was a mechanical induction of new bone between two surfaces that were gradually pulled apart. Using an external frame, he developed a system of performing a corticotomy then beginning distraction after a latent period of seven days. Distraction rate was set at one millimetre per day. The frame was then left on for a consolidation phase.[69]

The use of external fixators has been fraught with a high complication rate from 24% - 117% [81]. In 1990, Paley *et al*. compared femoral lengthening over an intramedullary nail to Ilizarov femoral lengthening[84]. They showed reduced external fixator time by one half, decreased time to consolidation, faster improvement in range of motion, and decreased risk of refracture of distraction bone. Concomitantly occurring was the development of fully implantable distractable devices including the Albizzia nail (Depuy, Villeurbanne, France, 1983), the ISKD (Orthofix Inc, Valley, Germany, 1986), and the Fitbone (Wittenstein, Germany, 1990).

The first two aforementioned are mechanical devices. The Albizzia nail requires a large degree of rotation to engage the ratchet mechanism that causes pain and discomfort, with 22-39% requiring readmission for general anaesthesia to proceed with distraction[78, 81]. The ISKD

lengthening is achieved with physiologic gait movements to proceed with distraction. The distraction rate can thus be unpredictable with rapid lengthening of up to several millimetres per day ("run-away train"). [80, 81] The mechanically driven devices have an overall complication rate of 11-47%.[81] The Fitbone is a motorized nail that does not require any external manipulation of patient activity, allowing increased patient comfort during distraction. In a recent review by Krieg *et al*. (2011)[81], they found a complication rate of 12.5 % for their Fitbone patients, which was in keeping with the findings of Baumgart *et al.* (2006)[80] , who reported a 13% complication rate in their series of 150 patients.

Patients with limb length discrepancies often have concomitant malalignment and/or angular deformities[69]. The reverse planning method as described by Baumgart[82] is utilized for preoperative planning to accommodate for angular and axis correction. This was performed prior to each surgery. In this series, the mechanical axis deviation was corrected from 12.1 mm valgus (95% CI: 4.8-19.4mm), to 0.08 mm valgus post operatively (95% CI -5.2-5.4).

The average hospital stay was 12 days, which included all readmissions and nail removal. Most patients were weight bearing as tolerated at three months (fourteen of twenty-one) with five others full weight bearing at 4 months post operatively. Thirteen patients had full knee range of motion at 3 months. Four more had full range by six months. Two patients had extremely limited range of motion preoperatively due to osteomyelitis, thus had ongoing stiffness.

There are several limitations to this study. There were a small number of subjects in this cohort and there was no comparative group. Each patient underwent only one lengthening with Fitbone. We did not investigate the results of multiple lengthenings using this device. Small sample numbers reduce the power of a study, and the lack of control group reduces the level of evidence. To increase numbers, future studies could gather data from several centres. The level of evidence could be enhanced by use of a retrospective matched case control cohort or by developing a level one randomized control study. To achieve adequate numbers, a multicentre trial would likely be required.

The potential advantages of intramedullary lengthening devices are the reduced risk of contractures, decreased risk of infections, better maintenance of axis correction, lower rate of refracture, reduced pain and earlier return to activities of daily living[81]. One of the major advantages of an intramedullary lengthening device comes from the patient satisfaction with aspects including ease of use, increased comfort, and social acceptance, as reported verbally by our patients.

The high complication-rate of external fixators, due to pin tract infection and mobilization difficulties, is not encountered with this intramedullary device. However, complications arose in the form of motor dysfunction/backtracking, and antenna breakage, as reported in other Fitbone studies.[88]

4.5. Conclusion: The initial experience at our institution has been satisfactory. Preliminary results show good outcomes with no pin tract infection, minimal hospitalization time and early functional range of motion. A larger trial will be undertaken by our group in the future.

Chapter 5: Use of Number Needed to Treat (NNT) in the Pediatric Orthopaedic Literature: A Review

5.1. Introduction: Chapter 1 evaluated levels of evidence and the stepwise process to determine level of evidence in articles. Statistical analysis in therapeutic trials level 1-3 can be described using number needed to treat (NNT). NNT was first introduced to the medical literature by Laupacis *et al* [29, 89]. NNT is an epidemiological measure used to portray the number of patients who need to be treated to prevent one adverse outcome.[90] Statistically, it is the inverse of the absolute risk reduction.[29, 89, 91] Absolute risk reduction is the difference in risk between the group that is exposed (treatment group) and the group that is not exposed (control group).[89, 91]

The results of treatment can be expressed in relative terms or absolute terms when compared to controls. Relative risk and relative risk reduction are commonly used relative measures, while absolute risk reduction and number needed to treat are commonly used absolute terms. With dichotomous outcomes, event rates (i.e. number of deaths) can be expressed as a percentage or proportion. For the control group, this is known as the "control event rate" (CER), and "experimental event rate" (EER) for experimental/treatment group.[2, 92]

Relative risk measures include risk ratio (RR) the ratio of experimental event rates to control event rates[2, 92]:

RR= EER/CER

The relative risk reduction (RRR) is the percent reduction in risk in the treatment group compared to control group.[2, 92] This can be calculated in the following ways:

RRR = 1-RR

or

RRR= (CER-EER)/CER

The major disadvantage of using relative measures is its inability to reflect risk of event without therapy (baseline risk in placebo studies, or CER). Absolute measures consider the underlying risk.[2, 92] Absolute risk reduction is the difference in risk between the control group and the treatment group:

ARR= CER-EER

To provide meaning from this dimensionless, abstract number, we can take the inverse of absolute risk reduction, which provides number needed to treat. That is the number of patients

that need to receive treatment for the prescribed duration to prevent one adverse event.[2, 92] In order to calculate NNT, we use the following:

NNT= 1/ARR

NNT= 1/(CER-EER)

Expressing clinical results in meaningful ways is difficult. Relative risk and relative risk reduction give the effects of an intervention as a proportion. Absolute risk reduction indicates if the effect is likely to be clinically meaningful, but as a dimensionless abstract number. NNT has the advantage of taking into account the underlying risk. It provides information as to the magnitude of the treatment effect. Two studies with a similar relative risk can have an extremely different number needed to treat. A relative risk of 0.17, but two different absolute risk reductions (0.80 to 0.14 versus 0.001 to 0.00017) can have extremely different numbers needed to treat [1.5 versus 1204, respectively (see Table 5.1)]. Thus, you would need to treat 1.5 persons to achieve the therapeutic result versus treating 1204 persons for one person to achieve therapeutic effect. This expresses a much different treatment effect for the two therapies.[91]

Table 5.1: Comparison of Relative and Absolute Measures

	CER	EER	RR (EER/CER)	ARR (CER-EER)	NNT (1/ARR)
TRIAL 1	0.80	0.14	0.17	0.66	1.5
TRIAL 2	0.001	0.00017	0.17	0.00083	1204

While reporting of NNT is an important communication tool to help clinicians comprehend the effect of a treatment, it does not replace the ever-important statistical analysis, determining significance of the difference.

To assess if there is a difference, researchers develop a null hypothesis (H_0) that there is no difference between the groups, and an alternative hypothesis (H_1) that the two groups are different.[22] The study attempts to refute the null hypothesis by gathering sufficient evidence. One needs to discern the magnitude of difference in primary outcome between the two groups (Δ) that is necessary to say there is a medically important difference. The p-value for the study is the result of the statistical test and is a probability. It reflects the measure of evidence against the null hypothesis. Small p-values indicate strong evidence. When the p-value is below a pre-determined limit (typically 0.05), the results are statistically significant. The p-value gives one the likelihood of making a Type I (α) error where one concludes there is a significant difference when in fact there isn't.[26] The opposite, a Type II or β error is the probability of concluding there was no difference when in fact there was one.[22, 25] For RCTs, p-value (α-level) is

typically and arbitrarily set at $p<0.05$ and the β level 0.20. The power level ($1-\beta$) is thus arbitrarily set at 80%.

When appropriate statistical analysis for assessing a difference between the groups is performed, a p-value, which indicates a probability, is used to determine if the difference is due to a true difference between groups, or chance alone.[22] The arbitrarily chosen $p<0.05$ is used to state that the difference between two treatments is not due to chance alone, 95% of the time. In a normal distribution, 5% of values fall outside +/- 1.96 standard deviations of the mean. A $p<0.05$ indicates there is a 5% chance of stating there is a difference between the two groups when in fact there is not [Alpha (α) or Type I error]. Conversely, a Type II error [Beta (β) error] occurs when one concludes there is no difference when in fact there was one. The power of a statistical test is $1-\beta$ and is defined as being the probability of detecting a difference when there is in fact one. Factors such as small sample size can lead to a low power and the inability to conclude a difference exists.[22]

The Null hypothesis is typically accepted or rejected based on the p-value found and reflects the measure of evidence against the null hypothesis. Small p-values (<0.05) indicate strong evidence and that the probability is small that the difference can purely be assigned to chance. A p-value of less than 0.05 is typically accepted as indicating a significant result, due to the fact that the probability that the difference is due to chance alone is less than 5%. Thus, the null hypothesis (no difference between groups) would be rejected and alternative hypothesis (there is a difference) accepted. P-values do not comment about the size of difference.[26]

Using the information of α, β, and Δ, statistical calculations can detect the sample size necessary for the trial to acquire enough statistical power to detect the statistically important difference. This should be reported as a "power statement" at the beginning of the RCT.[25] A post hoc power analysis can be performed of a study to ensure adequate power. If it shows a power of less than 80%, the sample size may be too small to avoid Type II error. [6-8]

When looking at the estimate of treatment effect, it is important to determine how much of the difference is the result of treatment, and how much of the difference is due to chance alone. The precision of the estimate of treatment effect can be expressed using a confidence interval. This displays the range of estimates in which the true difference will lie 95% of the time. The 95% confidence interval is arbitrarily chosen and closely relates to the p-value of $P<0.05$ which indicates statistical significance. If the 95% confidence interval for relative risk reduction falls completely on the positive side of 0, then there is a difference with significance of $P<0.05$. If the lower end of the confidence interval falls below 0, then the P value is said to be >0.05, or not significant. Thus a study that has found no significant difference, but has an upper level of confidence interval well above 0, has truly failed to exclude an important treatment effect.[28]

NNT is a point estimate whose uncertainty must be described by a 95% confidence interval.[90] This can be constructed by simply inverting the 95% confidence interval for absolute risk reduction and reversing the order of the upper and lower numbers of the range. When the results are statistically significant, this is possible. However, if the results are not statistically significant, the 95% confidence interval for the absolute risk reduction will include 0. Thus, the

95% confidence interval for the NNT would include infinity (inverse of 0). In these cases, one may cautiously report the point estimate of the number needed to treat, albeit also reporting the results as not statistically significant.[2, 92-94]

The ideal NNT is small and approaches 1. That is to say that nearly everyone improves with treatment and few in the control group improve. A larger NNT indicates a less effective treatment.[89, 91] However, it is important to balance potential benefit of an intervention with the risks and cost of that intervention[90]. Looking at the meta-analysis by Sanmuganathan *et al*. in Heart 2001, when the coronary heart disease risk is 1.5%/year, treatment with 75mg daily aspirin gives a five-year NNT of 44 to prevent myocardial infarct, and 53 to prevent myocardial infarct without cerebral or major haemorrhage. This is a relatively inexpensive and easily implemented treatment. If one was to consider a risky surgical procedure, this NNT would not be acceptable. The benefit of aspirin is shown to outweigh the risk of harm via major bleeding episode in patients whose coronary risk is at least 1.5%/year[95].

Hildebrandt et al[96] performed an extensive literature review, searching PubMed for randomized controlled trials published in four journals: British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine, and Lancet. They included all randomized controlled trials (RCTs) published between 2003-2005. They analyzed 808 articles, 74 were excluded. 373 RCT's had time-to-event outcomes and 361 had binary outcomes. Of the 373 RCTs with time-to-event outcomes, only 34 used numbers needed to treat (NNT). Of the

361 RCTs with binary outcomes, only 28 used NNT. Furthermore, they found that only 50% of the NNT's for the time-to event outcomes were calculated properly.

NNT was first introduced by Laupacis *et al*. in 1988[29]. It was introduced as an easily understandable expression of clinical benefit. As the inverse of the absolute risk reduction, it has an advantage over relative risk reduction and odds ratio in that it expresses baseline risk without therapy and risk reduction with therapy. In studies expressing absolute risk reduction, NNT is easily calculated as an inverse of the same. For studies expressing baseline risk and relative risk reduction, tables have been devised[29, 91]. When expressing NNT for a study, it is important to ensure that the difference between the two groups is not due to chance alone and that the result is statistically significant as well as clinically. An absolute risk reduction with a confidence interval that includes zero may still give a numerical NNT, but the treatment effect may be due to chance alone[97]. In this instance, the 95% confidence interval for the NNT has an upper limit of infinity.[2, 91, 92]

A large prospective multicenter trial of the effect of treatment on outcome of Legg-Calve-Perthes Disease was published in 2004[98]. This article by Herring *et al*. is widely used to guide treatment for surgical intervention based on expansive statistical analysis. In his letter to the editor, David Little re-examined the statistics and described his findings in terms of number needed to treat and commented that comparing surgery to bracing showed a NNT of 6.25, meaning that there is a one in six chance that surgery will improve prognosis over bracing[99]. In his analysis, Professor Little noted that in comparing bracing to surgery, 16% of patients moved

from one Stulberg class to another following surgery. He noted that one would need to operate on more than six patients in order to have the Stulberg outcome improve one grade in one patient when compared to treating with bracing.[99] Although treatment of this problem remains controversial, this assists in discussions with family, particularly when one treatment option or the other is felt to be unacceptable to a family.

The purpose of this study was to review one year of pediatric orthopaedic literature to assess the use of number needed to treat as an adjunct to statistical analysis. Secondarily, the level of evidence was evaluated. Thirdly, where possible, number needed to treat was calculated for articles not expressing this statistic.

5.2. Methods: Using online resources, articles from one year of publication (January 1-December 31, 2010) of three respected pediatric orthopaedic journals: Journal of Pediatric Orthopaedics American (JPO A), Journal of Pediatric Orthopaedics British (JPO B) as well as Journal of Children's Orthopaedics (JCO) were reviewed. 2010 was the year chosen as the review was performed in 2011. The use of "numbers needed to treat" as an adjunct to statistical analysis was determined. Level of evidence as described by Wright *et al*., 2003[8], was determined for each article. In two papers, numbers needed to treat was calculated as examples of the ability to use this statistic to enhance interpretation of data.

5.3. Results: A total of 316 articles were reviewed from the three journals. There was little use of Number Needed to Treat in the pediatric orthopaedic literature. JPO A had one article in which this analysis was calculated[93]. There was one article calculating Number Needed to Harm [100]. JPO B and JCO did not have any articles in which either value was calculated. Table 5.2 shows the Level of Evidence[8] for each journal, and Table 5.3 shows the types of studies found in each journal.

TABLE 5.2: Level of Evidence

LEVEL OF EVIDENCE	JPO A 2010	JPO B 2010	JCO 2010
I	3	1	5
II	36	7	6
III	34	16	9
IV	69	43	33
V	13	40	1

TABLE 5.3: Type of Study

TYPE OF STUDY	JPO A 2010	JPO B 2010	JCO 2010
PROSPECTIVE	44	22	18
COHORT	13	9	7
RCT	7	1	3
SYSTEMATIC REVIEW	4	1	3
THERAPEUTIC	84	102	41

Of note, JPOA had one level one therapeutic trial, and two level one diagnostic trials. JCO had three level one therapeutic trials, one level one prognostic, and one level one diagnostic. The one level one article in JPOB was therapeutic.

5.4. Discussion: NNT was introduced as a summary statistic comparing the differing effects of treatment over control[29, 91]. It is purported to convey both clinical and statistical significance in a simple format. NNT is felt to be an effective way to use literature to guide treatment.[89] In this review, we sought to look at one year of pediatric orthopaedic literature and the use of numbers needed to treat during the year 2010. In cases where possible, we sought to calculate NNT to provide a differing interpretation of data.

There was a paucity of use of NNT in the pediatric orthopaedic literature. In 2010, JPO B and JCO did not have a single article that calculated this statistic. JPO A had one article which calculated NNT: "The Utility of Posterior Sloping Angle in Predicting Contralateral Slipped Capital Femoral Epiphysis" [93]. In this retrospective case control study, the authors looked at the ability to use posterior slip angle (PSA) to predict subsequent contralateral slip after slipped capital femoral epiphysis (SCFE). Looking at the PSA in girls, they found a statistically significant higher PSA in girls with bilateral slip (p=0.002). Using a receiver-operating curve, they found a positive predictive value of 76% for contralateral slip in girls with PSA greater than 13 degrees. Further calculation revealed a NNT of 2.2. The benefit of this number is to communicate with families and other physicians that if all girls with SCFE's having PSA greater than 13 degrees had the contralateral hip pinned, pinning 2.2 hips would prevent 1 hip from progression to bilateral slip.

"Iatrogenic Ulnar Nerve Injury After the Surgical Treatment of Displaced Supracondylar Fracture of the Humerus: Number Needed to Harm, A Systematic Review"[100] discussed the "evil twin" of NNT, number needed to harm which looks at comparison of treatments in terms of potential adverse outcomes[101]. They looked at 32 studies comparing crossed wires with lateral wires only in the treatment of supracondylar fractures of the humerus in children. The results showed that there was a pooled risk difference of iatrogenic ulnar nerve injury of 0.035 (95% CI 0.014-0.056), with higher incidence in the cross pinning groups. The calculated NNH was 28, with the conclusion stating that there is an iatrogenic ulnar nerve injury for every 28 patients treated with crossed pinning compared to lateral pinning.

Of the 316 articles reviewed, only one expressed NNT and one Number Needed to Harm. There are several reasons this may have occurred. Firstly, the majority of articles, 145, were level 4 (case series with no control group) and 54 were level 5 (case report). Thus, NNT could not be calculated. For other trials, some showed no clinically significant difference. In some cases, the lack of calculation demonstrates an under-utilization of this statistic. If all level I and II studies calculated NNT, it would have been utilized 58 times.

5.5. Calculation of NNT, 2 Examples: The following two papers presented statistics not including NNT. From the available data, NNT was calculated. "Medial and Lateral Pin Versus Lateral-Entry Pin Fixation for Type 3 Supracondylar Fractures in Children: A Prospective, Surgeon Randomized Study"[102] looked at a comparison of loss of reduction in Gartland three supracondylar fractures. Supracondylar fractures are common pediatric fractures of the distal humerus. Gartland classified these fractures involving an extended distal fragment into three groups: Type 1 with no displacement, Type 2 hinged with an intact posterior cortex and Type 3 with no cortical contact.[102]

Loss of reduction is challenging to define. Bauman's angle changes by six degrees for every ten degrees of humeral rotation. Some authors arbitrarily pick a change in Bauman's from five degrees to twelve degrees to represent a loss of reduction[102]. In a recent randomized control trial, Kocher *et al.* categorized loss of reduction as: no displacement (change of Bauman's less than six degrees), mild displacement (change of Bauman's between six and twelve degrees), and

major loss (change of Bauman's angle greater than twelve degrees)[103]. The study by Gaston *et al*. concluded that there was not a statistical difference in the radiographic outcomes of the two groups[102]. However, when further looking at the data, the authors state that twelve of the 47 lateral-entry pin patients had loss of reduction greater than 6 degrees in Baumann's angle versus 10 of 57 in the cross pinning group. This was not statistically significant (p=0.32). Calculation of NNT reveals NNT=14. This means that for every 14 patients receiving cross pinning compared to lateral pins only, there is a prevention of loss of reduction in Baumann's angle of 6 degrees. This of course is of questionable clinical significance. A change in Bauman's angle of six degrees may not create any clinical difference in range of motion or carrying angle (cosmetic appearance). This study did not look at clinical outcomes.

NNT is a point estimate whose uncertainty must be described by a 95% confidence interval. This can be constructed by simply inverting the 95% confidence interval for absolute risk reduction. When the results are statistically significant, this is possible. However, if the results are not statistically significant, the 95% confidence interval for the absolute risk reduction will include 0. Thus, the 95% confidence interval for the NNT would include infinity (inverse of 0). In these cases, one may cautiously report the point estimate of the number needed to treat, albeit also reporting the results as not statistically significant.[2, 92] In this case, the confidence intervals for the absolute risk reduction were not available, thus a point estimate is given, albeit cautiously as the 95% confidence interval for the NNT of 14 inherently includes infinity.[2, 91, 92, 94]

Bales *et al.* looked at "The Effects of Surgical Delay on the Outcome of Pediatric Supracondylar Humeral Fractures"[104] by dividing prospectively treated children into two groups: those treated in less than 21hours and those treated in more than 21 hours with closed reduction and percutaneous pinning of supracondylar humerus fractures. There was no statistical difference between type 3 fractures treated within 21 hours and those treated after 21 hours in terms of length of surgery, carrying angle, Baumann angle, avascular necrosis (AVN) and unsatisfactory outcome. From the data presented, we were able to look more closely at avascular necrosis and unsatisfactory outcome. Despite the lack of statistical significance between the two groups, the NNT for both groups was 29. From this, one could interpret that for every 29 patients delayed more than 21 hours, one patient will have a poor outcome or AVN. Again, it is important to note that the two groups did not reach statistical difference for either outcome. Thus, any difference between the two groups may be due to chance alone. Given that there were only forty-two Gartland type three fractures followed for more than eight weeks, (nineteen treated within 21 hours, and twenty-three treated later than 21 hours), this study may not be adequately powered to determine if the difference seen in these two groups is indeed due to chance alone.

One must also be aware of the undesirable properties of NNT. Results of comparing treatments often don't exclude the possibility of no difference. There is no value of NNT that corresponds to no difference. This would give an absolute risk reduction of zero and thus a number needed to treat of infinity. "Number" needed to treat also implies a precise number, rather than the reality of an element of probability in a range of confidence interval. However, it is possible to calculate the 95% confidence interval for the number needed to treat by taking the inverse of the 95% confidence interval for the absolute risk reduction and reverse the order of the upper and

lower numbers.[92, 94] NNT for an intervention depends on nature of treatment and underlying risk for the patient. It is not a fixed quantity. An NNT reported in the literature for a group with a certain base-line risk can be adjusted to provide accurate data given your patient's base-line risk.[91]

Simple calculations using proportions are only appropriate in studies with binary outcomes.[105] Time to treat analysis require more sophisticated statistical analysis[96]. Thus, incorrect calculation and misinterpretation of NNT often occurs. NNT is only able to be calculated for dichotomous outcomes at a specific point in time and thus does not tell about trajectory of improvement[101]. NNT should be reported in terms of the comparison group (underlying risk) for which it was calculated, the desired outcome, and the defined period of treatment.[91]

In a recent article, Froud *et al.*[106] reported the number needed to treat by estimating from continuous outcome variables in a statistical analyisis of the UK BEAM trial. By converting continuous outcomes into binary data, they calculated number needed to treat. Although the mean differences originally reported in the BEAM trial were small, the numbers needed to treat were relatively small, indicating how well the treatment works and the relatively small effort needed to invest to achieve the outcome. They concluded that reporting numbers needed to treat may help with result interpretation by showing effect size.

5.6. Limitations: There are limitations to this study. A relatively small number of articles were reviewed due to the fact that very few number needed to treat or harm analysis were located during the period studied. The p-value is currently reported for most comparison articles, and determines whether results are due to chance alone.[2] Unlike NNT, it does not give any information about effect size.[94] The smaller the NNT, the larger the effect size difference between treatments[101].

These limitations could potentially be addressed by reviewing articles over a five-year period to provide more articles to review. Disseminating the benefits of number needed to treat reporting in the medical literature may encourage authors to use this tool. Finally, the journals reviewed could be encouraged to mandate improved reporting guidelines that require authors to provide analysis of significance testing as well as report their results with NNT and a 95% confidence interval where appropriate.

5.7. Conclusion: NNT describes treatment effect and takes into account underlying risk. It provides information on the effort needed to achieve the desired outcome.[92] It must be viewed in conjunction with the statistical significance as shown by the p-value. Using p-value on its own has limits, as it does not tell you about effect size, only how likely the result is not due to chance alone.[2] Combined with statistical significance is the importance of clinical relevance.[94] This statistical tool is felt to be a simple way to enhance comprehension of the literature and patient communication. This study has found a definite underutilization of number needed to

treat in the pediatric orthopaedic literature. In future research projects, this statistical analysis should be utilized when possible.

Chapter 6: Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review

6.1 Introduction:

Over the last ten years, the pediatric orthopaedic community has become more aware of venous thromboembolisms (VTE) after procedures in children.[107] The frequency of VTE, either deep venous thrombosis (DVT) or pulmonary embolisms (PE), was shown to increase in general pediatric literature. [108, 109] The incidence of thrombotic complications in pediatric orthopaedics remains unclear.[110] The morbidity and mortality of these rare events [109] and the risk factors inherent of orthopaedic procedures makes VTE a subject of interest for the pediatric orthopaedic surgeon.

A few authors have looked retrospectively at the incidence and risk factors of VTE in different administrative datasets of children going through various orthopaedic procedures. The incidences reported in these articles go from 0,05% - 0,68%, although rare, there is a 13-fold difference depending on the studied orthopaedic subtype. [110-116] We have not found a systematic review on the incidence of VTE in the different subtypes of pediatric orthopaedics.

In 2020, a survey was conducted by Murphy and al. in the Pediatric Orthopaedic Society of North America (POSNA) group. A majority of members responded that they were unaware of their institution protocol for VTE prophylaxis. Most participants agreed that a form of prophylaxis should be used in children undergoing trauma, spine or hip surgeries.[107] This general idea of "a

need for prophylaxis" might be explained by the unawareness of the true incidence of VTE in pediatric orthopaedics.

The aim of this systematic review was to properly assess the incidence of VTE in pediatric orthopaedics by using a thorough and sensitive search of the literature and to assess risk factors. We evaluated the frequency of this complication in the different subtypes of pediatric orthopaedics. Improved knowledge of thrombotic events by subgroups of patients (trauma, spine, elective surgeries, etc.) could help surgeons in their practice and guide them when prescribing prophylaxis for their patients.

6.2 Methodology:

Development of Protocol: Prior to embarking on this systematic review, a stringent protocol was developed and submitted to PROSPERO. (Appendix A)

Methodology of Systematic Review

We conducted a systematic review on VTE complications in the pediatric orthopaedic population in accordance with The Cochrane Handbook for Systematic Reviews of Interventions [117] methodological recommendations and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23]. A protocol for this study was registered in PROSPERO (CRD42020185339) and we followed the PRISMA guidelines.

We searched four important databases: Ovid (MEDLINE), Embase, Web of Science, and Cochrane. We consulted with search specialists at our institution to create a sensitive strategy. We used three major search concepts: "pediatrics", "orthopaedic surgery/trauma" and "VTE complications". These concepts were broken down in MeSH, EmTree and their free vocabulary synonyms for proper literature review. (Appendix A)

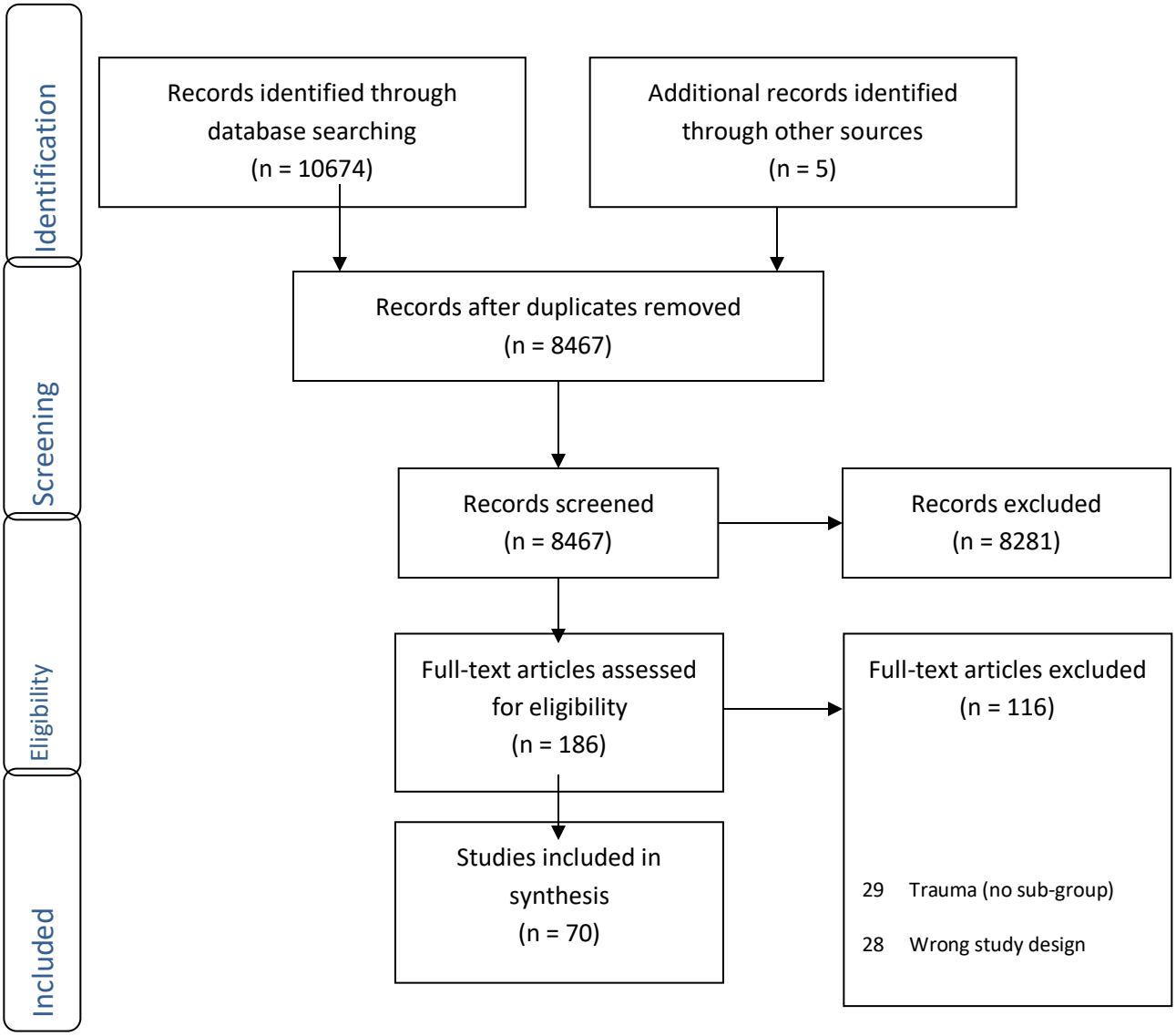
The inclusion criteria were: (1) orthopaedic intervention documented in prospective or retrospective studies (2) reporting the incidence of VTE (3) at least 80% of pediatric patients <18-years-old (4) trauma studies with a clear subgroup of orthopaedic patients were included (5) English or French written articles without time restriction. The exclusion criteria were: (1) non-pediatric orthopaedic studies (2) small cohort studies <30 patients (3) studies on cohorts of patients with coagulation disorders exclusively (4) not enough data for VTE incidence (5) trauma studies without a distinctive orthopaedic subgroup.

The initial search was conducted on December 18, 2019 and updated on February 8, 2021 and included more recent articles. The results were uploaded to *Covidence* software for de-duplication, title/abstract and full text screening. A total of 10 679 articles were found, 2212 duplicates were removed, resulting in 8467 unique articles. (Figure 6.1)

Two authors (Mathieu Boulet & Caroline Forsythe) independently screened titles and abstracts for inclusion. A third author (Etienne Belzile) was consulted for final decision in conflicting cases.

After the screening process, 186 articles met the inclusion criteria for full-text review. References of included articles were examined to ensure no additional papers were missed by our search strategy. Following full text screening, 70 articles were included in our review for data analysis. **Figure 6.1** outlines the results of our search including reasons for exclusion at the full text level.[118]

Figure 6.1: Flow-chart of included studies (based on PRISMA[118])



Data extraction was made by two authors and reviewed together. As suspected before our extraction, the heterogeneity of the articles (mostly Level III) prevented the realization of a proper meta-analysis based on the PRISMA principles.[118] Therefore, statistical analysis of risk factors (age, sex, BMI, comorbidities, etc.) was not possible. We extracted the values for VTE incidence calculation in the articles. Studies were divided based on their orthopaedic subtypes: trauma, spine, elective surgery (hip reconstruction, limb alignment, arthroscopy, etc.), musculoskeletal infection and mixed studies. We performed analysis by subgroups: VTE as a primary outcome, study size over 1000 patients and all articles.

The quality of the articles was evaluated using the MINORS criteria.[119] We used medians to present incidences in the subgroups because of high variability. We avoided the effect of outliers that could have skewed mean incidences. We calculated confidence intervals of 95% and standard deviations.

6.3 Results:

Articles distribution and demographics

The 70 articles yield a total of 845010 participants. The total number of VTE events was 1619, the estimated proportion were 80.9% for DVT and 19.1% for PE. The majority of the articles were on pediatric spine 33/70 (47%) representing the quarter of the participants in this review (212951 kids: 25.2%). Trauma studies were less numerous 16/70 (23%) but included half the children in our analysis (401553 kids: 47.5%). Overall, the children in this review had a mean age of 12.3

years (SD 2.73) and the female proportion was calculated at 54.6%. **Table 6.1** illustrates articles distribution, demographics by orthopaedic subtypes and quality assessment with MINORS.

	Number of articles	Articles proportion (%)	Number of patients	Patients proportion (%)	Mean age	SD age	Female proportion (%)	Mean MINORS (value / 16)	SD MINORS
Trauma	16	22.86	401553	47.52	10.21	2.42	32.74	7.1	2.14
Spine	33	47.14	212951	25.20	13.53	1.66	71.69	7.9	2.9
Elective	11	15.71	154562	18.29	13.87	2.83	44.72	7.9	2.6
MSK infection	5	7.14	7831	0.93	8.57	1.81	36.44	7.4	1.1
Mixed	5	7.14	68113	8.06	10.52	2.57	51.88	9	1.4
Total	70	100	845010	100	12.30	2.73	54.59	7.8	2.f5

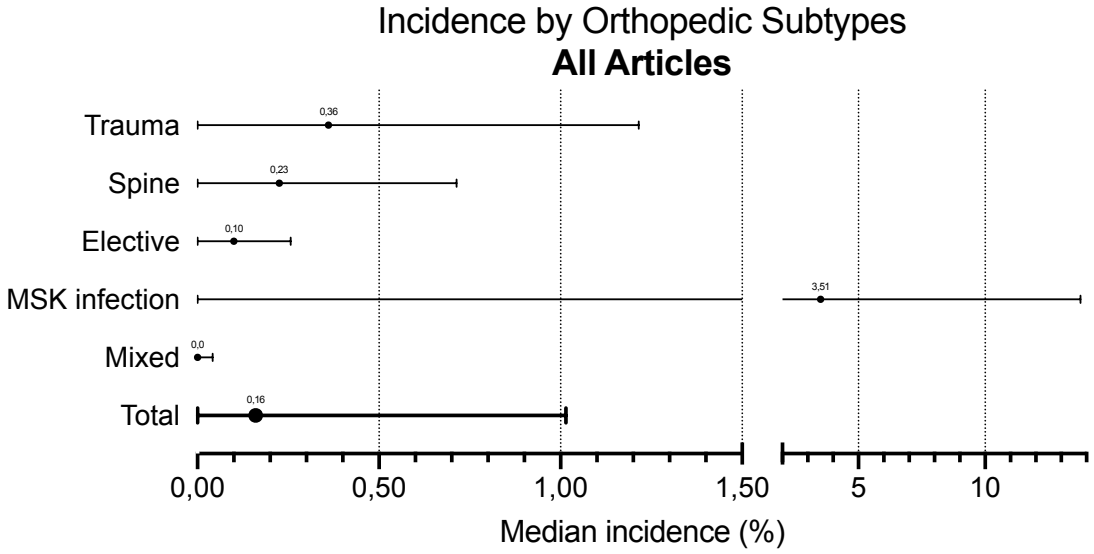
Table 6.1: Articles distribution and demographics by orthopaedic subtypes

All articles

The gross overall incidence of VTE calculated in this review was 0.19%; this is however a value that must be interpreted with caution. We calculated the median incidence for all the articles at 0.16% [95%CI 0.0 – 1.01%]. Subgroup analysis by orthopaedic subtypes was performed, these included all articles. A higher incidence was calculated in trauma at 0.36% [95%CI 0.0 – 1.22 %]. Musculoskeletal infection articles had the highest median incidence with 3.51% [95%CI 0.0 – 13.8%], this was 22 times higher than the overall incidence established. Pediatric spine articles

yielded an occurrence of 0.23% [95%CI 0.0 – 0.71%]. **Figure 6.2** illustrates median incidence by orthopaedic subtypes for all articles.

Figure 6.2: Median incidence for all articles by orthopaedic subtypes

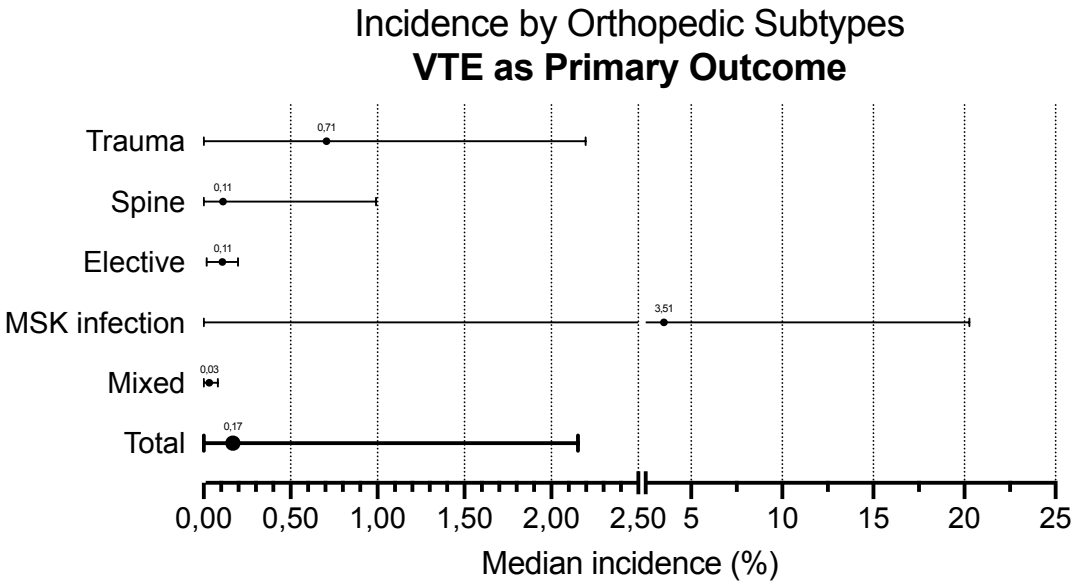


Articles with "VTE as primary outcome"

With the intention of using articles that were focusing mainly on thrombotic complications, we performed a subgroup analysis with the studies that used VTE as a primary outcome in their research question. The "VTE as primary outcome" articles represented 29/70 studies with a population weight of 74.7% of the children included in the overall analysis. The median incidence including all subtypes had a small increase at 0.17% [95%CI 0.0 – 2.15%]. A noticeable increase in VTE was seen in trauma studies: 0.71% [95%CI 0.0 – 2.20%]. In pediatric spine, these shortlisted articles lowered the median incidence at 0.11% [95%CI 0.0 – 0.99%]. Elective

surgeries, MSK infections or mixed studies kept similar incidences with this selection of articles. **Figure 6.3** illustrates median incidence by orthopaedic subtypes for articles with "VTE as primary outcome".

Figure 6.3: Median incidence for articles with VTE as primary outcome



Articles with more than a thousand patients

Since VTE are rare complications, we selected articles over a thousand patients as we thought they could represent the reality more accurately. The majority of the articles including over a thousand children used coded national databases to obtain large cohorts (NIS, KID, PHIS, etc.). A total of 28 studies were included in this subgroup that weighted for 98.7% of the children in this review. When compared to all the articles, a decrease in VTE events was seen as a tendency. Larger articles yield a median incidence of 0.10% [95%CI 0.0 – 0.34%] for all subtypes. A median VTE incidence

of 0.22% [95%CI 0.0 – 0.46%] was seen with large trauma cohorts. In spine and elective surgeries articles, the incidences were two times lower at 0.11% [95%CI 0.02 – 0.20%] and 0.05% [95%CI 0.0 – 0.13%] respectively. Only one large study on MSK infections was included in this subgroup with its incidence at 3.51%. **Figure 6.4** illustrates median incidence by orthopaedic subtypes for articles including >1000 children. **Table 6.5** summarizes VTE incidence by subgroups.

Figure 6.4: Median incidence for articles with >1000 patients

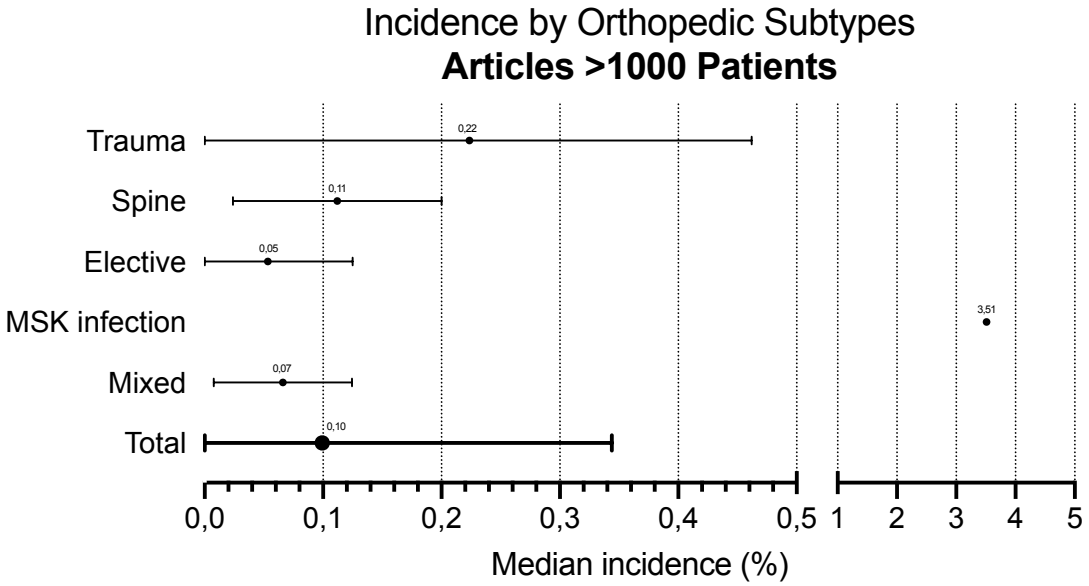


Table 6.2: Summary of VTE incidence by subgroups

	Gross Incidence (%)	Median Incidence (%)	Confidence Interval (95%)
Trauma	0.238	0.361	0.854
Spine	0.121	0.225	0.488
Elective	0.068	0.100	0.156
MSK infection	3.244	3.514	10.247
Mixed	0.072	0.00	0.042
Total **All Articles**	0.192	0.160	0.854
Total **VTE as Primary outcome**	0.183	0.168	1.99
Total **>1000 patients**	0.219	0.099	0.244

6.4 Discussion:

In this systematic review, an overall median incidence of 0.16% [95%CI 0.0 – 1.01%] can be calculated with the available orthopaedic literature reporting VTE complications in children. Small variations in median incidences were seen in the subgroup analysis based on articles characteristics. This review illustrates that VTE complications are not exceedingly rare and that surgeons should be attentive for these events in children and teenagers. Our results show a slightly higher incidence than recent estimations of thrombotic risk in children undergoing orthopaedic surgery, where incidence was estimated at less than 1%.[120, 121] This supports the need for the development of thromboembolism prophylaxis algorithms to identify pediatric orthopaedic surgical patients at high risk VTE potentially benefiting from thromboprophylaxis.[120]

We advocate for risk stratified usage of thromboprophylaxis. These measures come with costs and risk of bleeding complications. [122] The advantage of chemical or mechanical thromboprophylaxis is well documented in adult surgery,[123] but its universal use is discouraged in children where it is not supported by strong evidence on lesser morbidity and mortality, and low incidence VTE.[124, 125] No prospective randomized literature is available on the efficacy and utility of thromboprophylaxis in pediatric orthopaedics. The utilization extent and advantage of VTE prophylaxis cannot be assessed in this review. Only a few studies reported data on prophylaxis usage, and it is not possible to know if children with VTE were on prophylaxis or not. Some authors performed retrospective studies in trauma and neuromuscular orthopaedics and realized that around 14.6% to 15.5% of children receive prevention measures (mechanical or chemical).[126, 127] New screening protocols to guide thromboprophylaxis in pediatric orthopaedic

or trauma are being proposed.[120, 122, 128-130] [They results in higher detection of patients at risk while decreasing unnecessary thromboprophylaxis prescriptions.[120, 122, 128]

With screening tools being implemented, clinicians should be aware of the thrombotic risk factors reported in the pediatric orthopaedic literature. A positive family history of VTE increase the odds ratio by 2.2 for thrombotic complications, parents should be questioned for such conditions.[131] Age is also known to increase the incidence of VTE. In trauma, teenagers >16 years have an 8-fold increase of VTE compared to children <12 years.[132] Some predisposing factors are age related: smoking, oral contraceptives (OCPs) and obesity. They should be identified in teenagers undergoing orthopaedic procedures.[128] Female adolescents are at higher risk than males, those using OCPs are 3 to 5-times more likely to develop a VTE.[121, 133] Children with neurological, hematologic, renal or intestinal comorbidities should be considered at high risk. [110, 120] Immobilization >48h, used in surgical and conservative orthopaedic treatments, also puts children at risk.[120] Long hospital stays, treatments in the ICU and presence of a CVC are risk elements frequently highlighted in the literature. [107, 113, 121, 124]

An interesting aspect found in this review was the considerably higher median incidence found in MSK infection studies at 3.51% [95%CI 0.0 – 13.8%]. Musculoskeletal infections (septic arthritis, osteomyelitis, deep abscess, etc.) puts children at higher risk of VTE. [110, 134-136] This association can be explained by the coagulation cascade hyper-activated by inflammatory mediators of the host.[135, 136] Baker and al. also reported the higher risk of VTE with children treated for osteomyelitis. Their team observed thrombotic events in 1.2% of the septic cases, more than 10-

fold the incidence of VTE in their overall analysis.[110] Methicillin-resistant *Staphylococcus aureus* (MRSA) was proposed by a few authors to accentuate the development of VTE compared to methicillin-sensitive *Staphylococcus aureus* (MSSA).[134, 137] Surgeons should be careful as VTE complications may even happen before surgeries for irrigation and debridement. Observation and screening are advised for children with deep infections; thromboprophylaxis could be indicated for these patients.[110, 134]

Stress induced by trauma brings a hypercoagulable state. However, this effect is lower in children than adults. [132, 138] In this review, the median incidence of VTE was 0.36% [95%CI 0.0 – 1.22 %] for trauma articles. With a lower VTE rate at 0.17% in their retrospective cohort study, Greenwald and al. consider safe withholding thromboprophylaxis.[125] Guzman and al. found a higher incidence of VTE after trauma in the 2012 KID database. They described that 0.68% of the patients had thrombotic complications with the age being a significant risk factor (the mean age was 5 years older for kids with VTE).[113] With the PHIS database, Murphy and al. proposed a lower VTE incidence of 0.058%. They concluded that age >12 years and kids with femoral fractures were at higher risk.[116]

In spine articles, the median incidence was 0.23% [95%CI 0.0 – 0.71%]. Jain and al. studied VTE in pediatric spinal fusions from the NIS database. They reported 21 events per 10 000 cases (0.21%) which were more prevalent in syndromic scoliosis and traumatic spinal fractures. The risk for children with adolescent idiopathic scoliosis (AIS) fusion seems to be lower (0.04% based on their work).[114] In this review, many pediatric spine papers studied the usage of antifibrinolytics

to reduce surgical blood loss. A meta-analysis from Gausden and al. concluded that antifibrinolytics reduce intra-operative blood loss and the risk of transfusion. However, the incidence of VTE was too low in their work for conclusions on such events.[139]

Elective surgeries seem to impose a lower risk for VTE events with a median incidence of 0.10% [95%CI 0.0 – 0.26%]. Two recent papers looked at thrombotic complications after pediatric knee arthroscopies, they presented similar incidences of 0.25% and 0.27%[112, 115] Arthroscopic procedures were more often performed in teenagers over 15 years,[112, 115] this could explain a similar rate of VTE than adult arthroscopic procedures.[112] Both authors concluded that early mobilization should be encouraged and thromboprophylaxis measures only considered in high-risk patients. Georgopoulos and al. presented a 0.063% incidence of VTE and assumed that underlying diagnoses (metabolic disorders, syndromes, obesity, etc.) are more predictive of VTE than the type of elective procedure.[111]

The strength of this review was its methodology. A stringent protocol was developed with a thorough search strategy that resulted in 8467 articles (after duplicates removed) and included 70 articles to be screened. This entailed reporting on 845010 participants. Our stringent process gives a more accurate overview of VTE incidence in the pediatric orthopaedic literature. However, the main limitation of this study comes from the quality of the included articles (most of them being retrospective database Level III studies). The high heterogeneity precluded the realization of a meta-analysis nor quantification of risk factors. A semi-quantitative review was performed with articles that presented recall or detection bias.

6.5 Conclusion:

Thrombotic complications are rare events in pediatric orthopaedics. In this review, VTE median incidence for all orthopaedic subtypes was 0.16% [95%CI 0.0 – 1.01%]. Musculoskeletal infection articles showed greater occurrence of VTE and seems to be a subtype of pediatric orthopaedics more at risk for such events. Surgeons should have knowledge of VTE risk factors present in their patients as these events can occur in children undergoing orthopaedic treatments. New protocols for VTE-screening are being proposed and studied. [120, 122, 128-130] The use of screening tools could pinpoint patients in need of prophylaxis and reduce unnecessary prescriptions for children at lower risk.

Chapter 7: Summary

7.1: Summary:

In Pediatric Orthopaedic Surgery, like all medical specialties, one must incorporate the use of evidence- based medicine into the practice of clinical application. This involves five simple steps[2]:

1. Asking a question
2. Finding the current best evidence
3. Assessing the evidence for its validity and applicability
4. Integrating critical appraisal into practice
5. Self-evaluation

In Chapter 6, "Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review", a detailed plan and search strategy was able to screen all available literature and limit bias in the evaluation. Due to the low quality of the studies recovered, a meta-analysis was not able to be realized.

Use of Number Needed to Treat (NNT) in the Pediatric Orthopaedic Literature: A Review (Chapter 5), shows that current pediatric orthopaedic literature consists mainly of level 4 evidence. It also demonstrated that in instances where statistical analysis number needed to treat

could be utilized, it often wasn't. This demonstrated the need to be able to assess for instances where number needed to treat could be calculated and doing the same to enhance communication with patients. It also showed that although the level of evidence is low, many of these articles have large clinical significance and are an important part of critical appraisal of current best evidence.

The most common type of study in the orthopaedic literature is therapeutic. Looking at Level of Evidence for a therapeutic study, Level 1 is the pinnacle of studies, the high-quality randomized control trial. If a randomized controlled trial is poorly randomized, it has less than 80% follow up, or has insufficient blinding of evaluators, it becomes a level 2. As well, if a post hoc power analysis shows a power of less than 0.8, the study drops to level 2. A comparison trial will be a level 2 if it is prospective (prospective cohort study), or a level 3 if it is retrospective. A case-controlled study is retrospective. This is where the outcomes ("cases" and "controls") are compared. The "cases" have had an outcome of interest, and controls have a different outcome. Once the groups are identified, treatment regime differences are investigated.[6-8]

Level 4 therapeutic studies are either prospective or retrospective case series with no control group. While level 5 studies are considered expert opinion (see Table 6.1)[6].

Table 7.1: Levels of Evidence[6]

	Types of Studies			
	Therapeutic Studies—Investigating the Results of Treatment	**Prognostic Studies—Investigating the Effect of a Patient Characteristic on the Outcome of Disease**	**Diagnostic Studies—Investigating a Diagnostic Test**	**Economic and Decision Analyses—Developing an Economic or Decision Model**
Level I	• High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review[b] of level I randomized controlled trials (and study results were homogeneous[c])	• High-quality prospective study[d] (all patients were enrolled at the same point in their disease with ³80% follow-up of enrolled patients) • Systematic review[b] of level I studies	• Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference gold standard) • Systematic review[b] of level I studies	• Sensible costs and alternatives; values obtained from many studies; multiway sensitivity analyses • Systematic review[b] of level I studies
Level II	• Lesser quality randomized controlled trial (eg, <80% follow-up, no blinding, or improper randomization) • Prospective[d] comparative study[e] • Systematic review[b] of level II studies or level I studies with inconsistent results	• Retrospective[f] study • Untreated controls from a randomized controlled trial • Lesser quality prospective study (eg, patients enrolled at different points in their disease or <80% follow-up) • Systematic review[b] of level II studies	• Development of diagnostic criteria on the basis of consecutive patients (with universally applied reference gold standard) • Systematic review[b] of level II studies	• Sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analyses • Systematic review[b] of level II studies
Level III	• Case control study[g] • Retrospective[f] comparative study[e] • Systematic review[b] of level III studies	• Case control study[g]	• Study of nonconsecutive patients (without consistently applied reference gold standard) • Systematic review[b] of level III studies	• Analyses based on limited alternatives and costs; poor estimates • Systematic review[b] of level III studies
Level IV	• Case series[h]	• Case series	• Case control study • Poor reference standard	• No sensitivity analyses
Level V	• Expert opinion	• Expert opinion	• Expert opinion	• Expert opinion

This chart was adapted from material published by the Centre for Evidence-Based Medicine, Oxford, United Kingdom. For more information, please see www.cebm.net.
[a]A complete assessment of the quality of individual studies requires critical appraisal of all aspects of the study design.
[b]A combination of results from 2 or more prior studies.
[c]Studies provided consistent results.
[d]Study was started before the first patient enrolled.
[e]Patients treated one way (eg, with cemented hip arthroplasty) compared with patients treated another way (eg, with cementless hip arthroplasty) at the same institution.
[f]Study was started after the first patient enrolled.
[g]Patients identified for the study on the basis of their outcome (eg, failed total hip arthroplasty), called "cases," are compared with those who did not have the outcome (eg, had a successful total hip arthroplasty), called "controls."
[h]Patients treated one way with no comparison group of patients treated another way.

Reprinted with permission DeVries, J.G. and G.C. Berlet, *Understanding levels of evidence for scientific communication.* Foot Ankle Spec, 2010. **3**(4): p. 205-9
DOI: 10.1177/1938640010375184.

The gold standard and highest quality clinical trial is the randomized controlled trial. However, this does not mean we should not pay attention to literature of lesser quality. Randomized controlled clinical trials are difficult to perform for surgical scenarios due to difficulty with blinding both surgeon and patient. When research involves children, the issue of informed consent and parental consent to enroll their child into a prospective study increases the difficulty. All these factors contribute to difficulties in performing the highest level of evidence in pediatric orthopaedic surgery.

The two original clinical works: "Physeal Arrest and Angular Deformity as a Sequelae of Guided Growth: A Case Report" and "Intramedullary Lengthening Using the Fitbone Device" are level five and level four evidence, respectively. Although level 5 is simply "expert opinion", when an unusual case or complication occurs, a case report is a valuable way to disseminate important information. The level four case series is stronger than a case report in that it shows outcomes over multiple sequential cases. However, a method to strengthen this report would have been to

gather more subjects, or look at subjects previously treated with an ilizarov frame for lengthening and develop a match case control group. The latter would provide level three evidence.

Physeal Arrest and Angular Deformity as a Sequelae of Guided Growth: A Case Report and Review of the Literature demonstrates how a collective group of surgeons identify a problem that has not previously been reported. This led to and exhaustive literature search and the development of a case report that included an extensive review of literature including animal studies that demonstrate the importance of respecting the periosteum during surgery, a technical pearl important to all surgeons performing this type of surgery.

Intramedullary Lengthening Using the Fitbone Device is a level four evidence original article that reviews cases of this innovative device performed over an eight-year period. Each patient was followed for many years, often waiting until skeletal maturity for an intramedullary lengthening to allow canal size to be large enough and in cases of retrograde femoral lengthening, to avoid early closure of the distal physis. Leg length discrepancy caused by congenital or traumatic reasons evolve over many years of growth, requiring many years to accrue data as demonstrated. Prior to 2003, patients at this institution were treated with external fixator (ilizarov frames) for leg length discrepancies and deformity correction. It would be impossible to perform a randomized control trial of an external fixator to an intramedullary nail (for obvious reasons), a retrospective case controlled comparison would have improved the level of evidence of the study.

And the final addition to this thesis was a systematic review of the literature. "Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review" was initially intended as a meta-analysis. The protocol was developed with the statistical analysis plan, but the articles included did not allow for this component. The stringent protocol and systematic step-wise process allowed all literature to be searched with all relevant articles included for analysis. This stringent, detailed process helps reduce bias in literature reviews. The aim of this systematic review was to properly assess the incidence of VTE in pediatric orthopaedics by using a thorough and sensitive search of the literature and to assess risk factors. We evaluated the frequency of this complication in the different subtypes of pediatric orthopaedics. Improved knowledge of thrombotic events by subgroups of patients (trauma, spine, elective surgeries, etc.) could help surgeons in their practice and guide them when prescribing prophylaxis for their patients. Thrombotic complications are rare events in pediatric orthopaedics. In this review, VTE median incidence for all orthopaedic subtypes was 0.16% [CI 0.0 – 1.01%]. Musculoskeletal infection articles showed greater occurrence of VTE and seems to be a subtype of pediatric orthopaedics more at risk for such events.

The four original articles included in this thesis demonstrate how clinicians can ask a question, appraise the literature, and develop original work to answer questions or document scenarios not currently described in the literature.

Critically appraising the literature and developing works to answer questions when none currently exists is only the first part of evidence-based medicine. From there, one must assess the applicability to patients and integrate into practice.

How do we use these original works in our practice? In the case of eight-plate insertion, one should now be more conscientious of respecting the periosteum and maximum length of time the plate should be left in before significant increase of permanent physeal arrest. The case series of intramedullary lengthening showed successful lengthening. When discussing the option of intramedullary versus external frame lengthening with patients, when feasible, most choose intramedullary lengthening.

There is a definite underutilization of number needed to treat in the pediatric orthopaedic literature. This statistical tool is felt to be a simple way to enhance comprehension of the literature and patient communication. It must be viewed in conjunction with the statistical significance as shown by the p-value. Using p-value on its own has limits as it does not tell you about effect size, only how likely the result is not due to chance alone. Surgeons should have the ability to calculate NNT in instances where appropriate to help enhance their understanding of the original work, and to help communicate with patients effectively.

The final step in practicing evidence-based medicine is to constantly re-evaluate one's own performance with steps 1 to 4. Each clinician must constantly assess their own ability to ask the

appropriate questions, search the existing literature thoroughly, effectively, and efficiently, assess validity and applicability to their own patient population, and integrate findings into practice.

When developing original works, one can look at ways to improve level of evidence for the study you are performing. If you have a case report of an adverse event, reaching out to other centres might locate other such events that could be developed into a case series.

When designing a case series, prospective collection with stringent inclusion and exclusion criteria can help limit selection bias. Adhering to an accurate, valid form of measurement for outcomes can reduce measurement bias. Blinding outcome evaluators by having different evaluators collect patient characteristics and other evaluators collect outcome data can help reduce bias. [15]

Finally, by adding a control group, one can elevate the level of evidence.

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Appendix A: Protocol for Chapter 6: Venous Thromboembolism in Pediatric Orthopaedics: A Systematic Review

Development of Protocol: Prior to embarking on this systematic review, a stringent protocol was developed and submitted to PROSPERO. Following is the methods section of the protocol.

Protocol and registration

The protocol of this review was registered in PROSPERO

(http://www.crd.york.ac.uk/prospero) CRD42020185339.

Purpose: The purpose of this review is to conduct a systematic review of cohort studies and randomized control trials reporting VTE in pediatric patients following orthopaedic surgery or musculoskeletal trauma

Study design

We will conduct a systematic review in accordance with The Cochrane Handbook for Systematic Reviews of Interventions [117] methodological recommendations and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23].

Eligibility Criteria

Since we are interested in the incidence of post-intervention VTE and its risk factors, our systematic review will include prospective and retrospective cohort studies as well as randomized controlled trials. Pediatric patients (children and adolescents ≤18 years) experiencing a post-intervention VTE, as reported by authors (symptomatic and/or diagnosed with ultrasound examination), following an orthopaedic intervention (surgery or non-operative intervention) will be considered. In case of a mixed aged population, at least 80% of patients included in a specific study have to respect the age criterion for the study to be eligible. Reported data on post-intervention VTE incidence will be required for study inclusion. Since we expect that few studies will report precisely if patients were diagnosed with VTE at the exit of the operating room or of any department of care, we will not restrict inclusion to immediate post-intervention patients but rather consider a population-based approach of post-intervention care. Studies that are reviews and case reports will be excluded. **Table A.1** and **Table A.2** present the structured study question and inclusion and exclusion criteria, respectively.

Table A.1 Structured study question

Population	Pediatric patients (children and adolescents) undergoing orthopaedic surgery or musculoskeletal trauma
Comparison or control	None
Outcome	Venous thromboembolism post-event
Secondary interests	Risk factors
	Peri-operative thromboprophylaxis (chemical)
	Antithrombotic (mechanical)
	Hospital length of stay
	All other reported clinical outcomes

Table A.2 Study eligibility criteria

Inclusion criteria	Cohort studies (both prospective and retrospective) and randomized controlled trials
	Orthopaedic intervention (indication: trauma or elective)
	Reporting the incidence of post-intervention VTE (deep vein thrombosis or pulmonary embolism)
	At least 80% of pediatric patients (≤18 years old)
	At least 80% of patients with orthopaedic intervention
	At least 30 patients in cohort
Exclusion criteria	Non-orthopaedic intervention
	Patients with congenital hereditary blood or circulatory disorders (e.g. Factor V Leiden thrombophilia, Factor II Mutation)
	Patients with coagulation disorders (e.g. Von Willebrand disease, hemophilia, thrombotic thrombocytopenic purpura)

Information sources

We will systematically search MEDLINE, Excerpta Medica database (EMBASE), and The Cochrane Library for eligible studies. References of included articles and abstracts presented at major conferences (Pediatric Orthopaedic Society Of North America [POSNA] and European Paediatric Orthopaedic Society [EPOS]) (within the last 5 years) will be screened to identify additional potentially eligible studies. Clinical Trials database will be searched for results of studies not yet published. Experts in orthopaedic surgery, not members of our team, will also be contacted to identify additional ongoing studies.

Search strategy

Our search strategy will be based on keywords related to VTE and orthopaedic surgery and non-operative intervention, as well as children and adolescents. Clinicians, investigators with expertise in orthopaedic intervention or in vascular medicine, and information specialists will be consulted to verify the search strategy, identify synonyms and additional search terms. Relevant index terms (Medical Subject Headings and Emtree) will be added to the strategy. The search will be limited to human studies. No language or date of publication restriction will be used.

The search strategy will be first designed for Medline and Embase, and will be adapted for other electronic databases afterwards. Resulting references will be imported into EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) and duplicates will be removed. References will then be exported to a Microsoft Excel 2016 (Microsoft, Redmond, WA, USA) spreadsheet in order to complete the selection process.

Study selection

Two independent reviewers will screen all retrieved citations to determine eligibility in a two-step process, first from titles and abstracts, and then based on full text evaluation for studies that could be potentially eligible for inclusion in the systematic review. In case of disagreement on the inclusion of a study, a third reviewer will be consulted for arbitration. Reasons for exclusion at the full-text stage will be recorded and presented. After selection is complete, the reference lists of included studies will be reviewed to identify any additional eligible studies. A translation will be obtained for articles published in languages other than English or French.

Data collection

Two reviewers will independently extract data into a standardized data abstraction form. In case of discrepancy, consensus will be reached through discussion or the involvement of a third reviewer. The initial data abstraction form will be piloted on five studies to ensure robustness, with subsequent modifications for thoroughness if necessary.

Table A.3 lists the set of data that will be extracted from each study. Authors will be contacted if relevant data is missing or clarification is needed. To avoid duplication, if the same study is published more than once, the most complete article will be retained.

Table A.3 List of data to be extracted

Study characteristics	Authors, design, date of completion, year, setting, study type, intervention type, sample size, inclusion and exclusion criteria, follow-up period, funding sources, and conflicts of interest
Patient characteristics	Age, sex, comorbidities (e.g. obesity, smoking, drinking alcohol), prothrombotic conditions and medications, use of oral contraceptives, and orthopaedic intervention indication
Therapeutic and supportive measures	Co-interventions (type, timing), use of thromboprophylaxis, and pharmacological treatment
Characteristics of the orthopaedic intervention	Duration of the intervention, traction use and duration, indication (trauma or elective), anatomical region (e.g. foot, ankle, knee, hip, back, shoulder), use and duration of tourniquet, infections and other complications, and length of hospital stay
Post-intervention characteristics	Length of follow-up, VTE diagnosis and tests, deep vein thrombosis, pulmonary embolism, presented in relation to intervention characteristics, such as localization, type, and VTE extension, weight-bearing and mobility restriction

Missing data

Original authors will be contacted in event of missing data.

Risk of bias in individual studies

Risk of bias of included RCTs will be assessed using The Cochrane Collaboration tool for assessing the risk of bias [117]. Risk of bias in cohort studies will be assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool [117].

Synthesis of results

Data will be presented in a descriptive manner. Nominal variables and count data will be reported using proportions while continuous variables will be presented as either means with standard deviations or medians with interquartile ranges. If reported, effect measures will be presented in both their adjusted forms and unadjusted forms where possible.

P-values for global and trend tests will be computed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA, November 2018).

We will pool cumulative incidences of patients experiencing VTE in the course of their hospital stay following orthopaedic surgery or non-operative intervention. Variances of cumulative incidences of VTE from all studies will be stabilized using a Freeman-Tukey transformation and proportions will be pooled with DerSimonian and Laird random-effects approach [140] using R statistical software (version 2.15.1: R Development Core Team, R Foundation for Statistical Computing June 2012, Vienna, Austria).

Results from randomized controlled trials allocating patients to different pharmacological strategies will be pooled separately, if deemed appropriate.

If meta-analysis is possible, risk ratio analyses will be conducted with Cochrane Review Manager (RevMan) version 5.3 computer program (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) using Mantel-Haenszel random-effect models. Pooled effect sizes and their 95% confidence intervals will be reported. We will pool mean differences or risk ratios to evaluate the association between VTE and potential determinants or patient-oriented outcomes (e.g. continuous or ordinal variables such as age, duration of intervention or immobilization, severity of the orthopaedic condition, hospital length of stay). Mean differences will be pooled using the inverse variance method with random effects. A two-sided 5% type I error will be considered for all analyses.

Statistical heterogeneity will be measured using the Cochran's Q-test and I^2 statistics. The I^2 statistics will be interpreted via the recommended standard categorization of negligible (<40%), moderate (30–60%), substantial (50–90%), or considerable (75–100%) [117]. Where permitted by the data available, sensitivity and subgroup analyses will be undertaken to explore sources of heterogeneity and test the robustness of the results. Such analyses will be performed in regard to minimal age of inclusion, severity of orthopaedic condition, comorbidities, timing of VTE assessment, pharmacological strategies, and study risk of bias. Visual analysis of funnel plots will be used to evaluate the presence and degree of publication bias.

Risk of bias

We will evaluate the risk of publication bias by visual exploration of funnel plots. We will also evaluate the risk of selective reporting of outcomes within studies by searching for previously published protocols on registration website (http://www.controlled-trials.com and clinicaltrials.gov).

The ability of a study to answer the review question will be evaluated in terms of applicability. Applicability concerns relate to deviation of a study from the ideal study designed to answer our research question (in relation to our primary outcome). For instance, a study recruiting patients with mixed surgeries, therefore including patients with a surgery other than orthopaedic surgery that might not be admitted to the study, will be considered as having high applicability concerns.

Additional analyses

Subgroup and sensitivity analyses

A priori planned subgroup and sensitivity analyses will be conducted to explore potential statistical and clinical heterogeneity according to design of studies (cohort versus randomized controlled trials), severity of orthopaedic injury or condition, type of intervention, age of patient, timing of intervention (duration of intervention in operating room, overall hospital stay, or other timing), presence of comorbidities (by categories of comorbidities if data available), type of thromboprophylaxis given as a co-intervention (if any), presence or absence of specific pharmacological intervention, low applicability concerns and risk of bias. Subgroup analysis

taking into account whether VTE was specifically reported as a studied exposure or outcome will be conducted, as we will consider that these studies might have more complete data pertaining to VTE.

GRADE of evidences

We will use the GRADE methodology to evaluate the quality of evidences of our findings [141].

List of Keywords/ MESH

((((((Pediatric*[Title/Abstract] OR Adolescent*[Title/Abstract] OR Adolescence[Title/Abstract] OR Teen*[Title/Abstract] OR Teenager*[Title/Abstract] OR Youth*[Title/Abstract] OR Female Adolescent*[Title/Abstract] OR Male Adolescent*[Title/Abstract] OR Child*[Title/Abstract])))) OR (((((Pediatrics[MeSH Major Topic]) OR Child[MeSH Major Topic]) OR Adolescent[MeSH Major Topic]) OR Infant[MeSH Major Topic]) OR Minors[MeSH Major Topic]))) AND (((((((Thrombophlebitis[MeSH Major Topic]) OR Venous Thrombosis[MeSH Major Topic]) OR (Embolism and Thrombosis[MeSH Major Topic])) OR Thromboembolism[MeSH Major Topic]) OR Pulmonary Embolism[MeSH Major Topic])) OR ((Phlebothrombos*[Title/Abstract] OR Venous Thrombos*[Title/Abstract] OR Deep Vein Thrombos*[Title/Abstract] OR Deep-Venous Thrombos*[Title/Abstract] OR Deep-Vein Thrombos*[Title/Abstract] OR Deep Venous Thrombos*[Title/Abstract] OR Embolism*[Title/Abstract] OR Embolus*[Title/Abstract] OR Pulmonary Embolism*[Title/Abstract] OR Pulmonary Thromboembolism*[Title/Abstract] OR Thrombophlebiti*[Title/Abstract] OR Thromboembolism*[Title/Abstract] OR Thromboprophylaxis[Title/Abstract])))) AND (((((((Traumatology[MeSH Major Topic]) OR Fractures, Bone[MeSH Major Topic]) OR (Wounds and Injuries[MeSH Major Topic]))) OR ((Surgical Traumatology[Title/Abstract] OR Traumatology[Title/Abstract] OR Trauma*[Title/Abstract] OR Injur*[Title/Abstract] OR Broken Bone*[Title/Abstract] OR Bone Fracture*[Title/Abstract] OR Bone Fracture*[Title/Abstract] OR Fracture*[Title/Abstract])))) OR ((((Orthopedics[MeSH Major Topic]) OR Orthopedic Procedures[MeSH Major Topic])) OR ((Orthopedic*[Title/Abstract] OR Orthopedic Surger*[Title/Abstract] OR Orthopedic Procedure*[Title/Abstract] OR Orthopedic Surgical Procedure*[Title/Abstract] OR Orthopaedic*[Title/Abstract] OR Orthopaedic Surger*[Title/Abstract] OR Orthopaedic Procedure*[Title/Abstract] OR Orthopaedic Surgical Procedure*[Title/Abstract]))))