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# Pediatric Septic Arthritis and Osteomyelitis in the USA: A National **KID Database Analysis**

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Abstract Background: Prior reports suggest that osteoarticular infections may be increasing over time. Questions/Purposes: We sought to determine if incidence rates, median in-hospital costs, and length of stay (LOS) of osteomyelitis, septic arthritis (SA), and combined infections have changed over time for pediatric patients, and how they compare to previously reported rates. Methods: The Kids' Inpatient Database (KID), a US national sample of pediatric hospital discharge records from 1997, 2000, 2003, 2006, 2009, and 2012, was used to determine yearly estimated counts of infections in children 20 years of age or younger. US census data was used to calculate yearly incidence rates. Trend tests using linear contrast analysis were used to compare estimated median LOS and inflation-adjusted median costs over time for each type of infection. Results: From 1997 through 2012, the incidence rate of osteomyelitis increased from 7.9 to 10.5 per 100,000, SA was unchanged from 5.3 to 5.2 per 100, and

Level of Evidence: Level II, retrospective national database study

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combined infections increased from 0.8 to 1.3 per 100,000. Median LOS from 1997 to 2012 showed no significant change for osteomyelitis (5.0 to 4.9 days), SA (4.4 to 4.1 days), or combined infections (6.5 to 6.8 days). Median in-hospital costs from 1997 to 2012 increased for osteomyelitis (\$7735 to \$11,823), SA (\$5041 to \$10,574), and combined infections (\$12,691 to \$16,260). Conclusion: In pediatric patients, the estimated incidence rate of SA appeared stable, while rates of osteomyelitis and combined infections increased. These estimated rates fall within previously reported ranges. Despite stable LOS, costs have increased over time.

Keywords septic arthritis · osteomyelitis · osteoarticular infections · KID database · LOS · cost

## Introduction

Timely diagnosis and treatment are paramount to minimizing complications and optimizing outcomes in the treatment of septic arthritis (SA) and osteomyelitis. With appropriate treatment, many cases resolve without long-term complications, but some cases may be complicated by chronic infection, joint dislocation, growth arrest, limb deformity, avascular necrosis, deep venous thrombosis, joint degeneration, and even death [4, 19, 32, 36]. Differences in the incidence and severity of osteoarticular infections, and the costs and lengths of hospital stay for their care, may be related to local pathogen profiles, virulence of the organism, treatment regimens, drug resistance, vaccination programs, immune-modifying drugs, medical comorbidities, and other factors [9].

The incidence rate of pediatric osteomyelitis has been reported at 1.94 to 13/100,000 [6, 13, 33] and that of pediatric SA at 4 to 12 per 100,000 [11, 16, 28, 29]. The epidemiology of osteoarticular infections is primarily based on retrospective cohorts, many from single institutions [2, 13, 14, 23, 33]. A previously published single-institution study of 554 children reported a 2.8-fold increase in osteomyelitis over 20 years, with

SA rates remaining constant [13]. Another single-institution study demonstrated a 24% change in the rate of acute osteomyelitis, from 11.5 per 100,000 (95% CI = 4.15) in 1982 to 14.3 per 100,000 (95% CI = 5.12) in 2003 [23]. Although most studies suggest that SA rates are static, one study reported an increased incidence of SA over time, proposing an increased number of arthroscopic surgeries as the cause [14]. A concern with single-center studies is that the denominator is not well defined. Infections per year can easily be modified by changes in catchment area for the hospital/institution or referral patterns.

Stockman et al. previously used the Kids' Inpatient Database (KID) to assess the national US epidemiology of osteoarticular infections [38]. A 15% increase in the rate of osteoarticular infections (from 2.07 to 2.38 cases per 1000 children admitted) was reported from 1997 through 2012 [12]. The rate of osteoarticular infections was calculated by dividing the number of children admitted for osteoarticular infections by 1000 children admitted for any diagnosis. The apparent increased rate of osteoarticular infections could be due to an increase in the number of admissions for osteoarticular infections and/or a decrease in admissions for other diagnoses. Thus, this previous KID analysis does not provide a true incidence rate or optimal clinically relevant results.

Length of stay (LOS), costs, and resource utilization relating to osteoarticular infections have been documented in the past. The median LOS for patients with osteomyelitis treated in 1982 to 1983 was 50 days and for patients treated in 2002 to 2003 was 29 days, although both time points could be considered historic [23]. The National Inpatient Sample demonstrated a trend toward decreased health care utilization for pediatric patients with SA from 1988 to 2000, but inflation-adjusted total charges increased over time, from a median total charge of \$10,098 in 1988 to \$11,155 in 2000 (p < 0.05); LOS was shorter for patients of higher socioeconomic status (p < 0.05) [12]. This previous analysis on financial aspects of osteoarticular infections was limited by reporting of charges, not costs.

The primary objective of the current study was to determine if national US incidence rates of osteomyelitis, SA, and both infections combined have increased over time and how they compare to previously reported rates. Secondary aims were to determine median in-hospital costs and LOS for each diagnosis and to assess how these have changed over time.

## Methods

Data was sourced from the KID, a part of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP). This all-payer inpatient database contains a US national weighted sample of more than seven million hospital admissions from approximately 1000 US hospitals for patients younger than 21 years of age. The traditional National Institutes of Health definition of *pediatric* is age less than 21 years; this database includes only pediatric patients. Datasets have been published for 1997, 2000, 2003, 2006, 2009, and 2012, and all published years were included in this study. Unweighted, the KID contains approximately three million discharge records each year. Based on sampling and weighting parameters, it is possible to determine national and regional estimates, despite the fact that not every US admission is included in this dataset. The database contains over 180 variables, including diagnoses by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), procedures by ICD-9-CM, patient and hospital demographics, total charges, and LOS. A cost-to-charge ratio is provided in order to convert charges to costs. Diagnosis codes for osteomyelitis and SA and relevant procedure codes are listed (see Online Resource 1).

Yearly incidence rates of osteomyelitis, SA, and combined infections were ascertained using weighted frequency data from the KID database with population estimates calculated from intercensal bridged-race population estimates from the US Census and National Center for Health Statistics (NCHS) from the years 1990 to 2014 [39–42]. Incidence rates for each type of infection were calculated by age. Incidence rates by race could not be calculated accurately due to incomplete reporting of race in the KID.

Median LOS and inflation-adjusted costs were calculated for each infection type for each year. Total hospital charges were converted using hospital-level cost-to-charge ratios supplied by HCUP to estimate the cost of hospital stays. The costs were further adjusted to 2012 dollars by applying the medical care component of the consumer price index [7]. Procedures performed on included patients were also analyzed and compared over time. Trend tests using linear contrast analysis were used to compare estimated median LOS and inflation-adjusted cost over time for each type of infection. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Significance was set at p = 0.05.

# Results

From 1997 to 2012, annual estimated cases increased for osteomyelitis (6524 to 9134), SA (4379 to 4485), and combined infections (624 to 1167), p < 0.05. Weighted frequencies for patient sex are listed in Table 1. For each year and each diagnosis, there were more males admitted than females. There were significantly more males with septic arthritis than females (p = 0.002), while distributions of osteomyelitis and combined infection between the sexes were not statistically significant (p = 0.155 and p = 0.062, respectively). Median age, LOS, and total cost are also presented (Table 1). The incidence rate of hospitalized cases of osteomyelitis increased by 33%, from 7.9 to 10.5 per 100,000 (p = 0.015); SA hospitalization incidence rates were unchanged, at 5.3 to 5.2 per 100,000 (p = 0.917), and combined infections increased 63%, from 0.8 per 100,000 to 1.3 per 100,000 (p = 0.016; Fig. 1).

The incidence rates of osteoarticular infections by age are illustrated in Fig. 2. Post hoc pairwise comparison of mean age from year to year showed a significant increase in age between years 1997 to 2000 and 2000 to 2003 for OA and SA hospitalizations, but no increase in age from 2003 to 2006, 2006 to 2009, and 2009 to 2012. For hospitalizations for combined disease, there was no significant difference in mean age for each subsequent year of data.

Characteristic*	1997	2000	2003	2006	2009	2012
Osteomyelitis <sup>a</sup>	6524 (6020, 7200)	7507	7737	9367	9579 (8417 10 942)	9134
Female sex	(0029, 7200) 2474 (38%)	(0810, 8501) 2744 (37%)	(0985, 8055)	(8200, 10,081)	(3417, 10, 942) 3531 (37%)	(8135, 10,450)
Age, years	7.8 2 3–12 3	9.4 (2.7-13.9)	10.2 4 5–14 7	10.0 (3.9–14.7)	10.2 (3.7-15.2)	10.5 (5.0-15.0)
Length of stay, days	5.0 (2.8-9.0)	4.9	5.1	5.2 (2.8-9.4)	5.3 (2.9–9.6)	(3.6° 13.6) 4.9 (2.8–8.7)
Total cost USD, 2012 adjusted	\$7735 (\$4531-19.553)	\$6175 (\$3819-11.081)	\$8484 (\$5226-14.854)	\$9825 (\$5832-17 389)	\$10,945 (\$6358-19,714)	\$11,823 (\$7079-21,294)
Septic arthritis <sup>a</sup>	(\$4379 (4152, 4680)	(4508 5142)	(\$5220-14,854) 4719 (4437 5050)	(\$3832-17,389) 5172 (4832,5568)	(\$0538-19,714) 4871 (4570 5222)	(\$7079-21,294) 4485 (4241 4795)
Female sex	1799 (41%)	1797 (37%)	1668 (36%)	1798 (35%)	1790 (37%)	1631 (36%)
Age, years	5.2	6.5	7.6	7.4	7.1	8.2
	(1.0-10.6)	(1.4 - 12.7)	(2.0-13.3)	(1.9 - 14.3)	(1.8 - 14.2)	(2.8 - 14.4)
Length of stay, days	4.4 (2.6–7.3)	4.5 (2.7–7.0)	4.3 (2.5–7.1)	4.3 (2.5-7.2)	4.4 (2.5-7.4)	4.1 (2.5–7.0)
Total cost USD, 2012 adjusted	\$5.041 (\$3876-9704)	\$6.113 (\$3.941_9.757)	\$7843 (\$4988-11 944)	\$8607 (\$5444-14 422)	\$10,103 (\$6258-16,926)	\$10,574 (\$6684-17,644)
Combined infections <sup>a</sup>	(\$3876-976 <del>4</del> ) 624 (619, 630)	(\$3.941-9.757) 703 (698, 711)	(\$4988-11,944) 780 (781, 798)	(0.000) $(0.000)$ $(0.0$	(\$0238-10,920) 1277 (1258, 1302)	(1151, 1189)
Female sex	239 (38%)	218 (31%)	262 (34%)	375 (36%)	511 (40%)	406 (35%)
Age, years	4.7	5.3	7.1	7.7	6.5	8.2
	(0.4–9.8)	(0.4 - 11.7)	(1.6 - 11.6)	(1.8 - 12.1)	(1.3 - 11.7)	(2.8 - 14.4)
Length of stay, days	6.5	6.5	6.9	7.0	7.6	6.8
	(4.1 - 11.0)	(4.2–11.3)	(4.1 - 13.0)	(4.3–13.4)	(4.5 - 13.8)	(4.1 - 12.1)
Total cost USD, 2012 adjusted	\$12,691 (\$8839-29,375)	\$9430 (\$6278-13,635)	\$11,382 (\$7290-19,369)	\$14,123 (\$9378-27,519)	\$17,314 (\$10,158-32,410)	\$16,260 (\$10,103-30,264)

 Table 1
 Weighted descriptives of demographic, length of stay, and charge characteristics of pediatric hospitalizations for osteoarticular infections in the USA, 1997–2012

\*Age, length of stay, and total cost presented as weighted median (interquartile range)

<sup>a</sup> Overall weighted frequency (95% confidence interval)

In 1997, 51% of osteomyelitis patients underwent one or more surgical procedures. Procedures included bone debridement (59%), diagnostic biopsy/aspiration (45%), other debridement (24%), joint debridement (19%), and implant removal (6%) (Table 2). Of those with SA, 78% underwent a surgical procedure, including joint debridement (53%) and diagnostic biopsy or aspiration (44%), and 81% of patients with combined osteomyelitis and SA underwent a procedure; the most common were joint debridement (54%), followed by diagnostic biopsy or aspiration (44%) and bone debridement (36%) (Table 2). There was no significant change in proportion of patients undergoing a surgical procedure over the course of the study for osteomyelitis (p = 0.766) or combined infections (p = 0.399). However, there was a small but significant increase in the proportion of patients undergoing a surgical procedure for SA (p = 0.003) over the 15-year study period.

Median LOS from 1997 to 2012 showed no significant change for osteomyelitis (5.0 to 4.9 days, p = 0.141), SA (4.4 to 4.1 days, p = 0.478), or combined infections (6.5 to 6.8 days, p = 0.575) (Fig. 3; Table 1).



Fig. 1. Incidence of osteomyelitis, septic arthritis, and combined infections, 1997–2012 (error bars indicate 95% confidence intervals; error bars for combined infections are not visible due to small error ranges)

2 ٥ 11 12 13 9 15 16 17 <1 2 10 14 1 8 Age

-Osteomyelitis ----Septic Arthritis ----Combined Infections Fig. 2. Osteomyelitis, septic arthritis, and combined infection rate by age, for all years, 1997–2012

Adjusted median in-hospital costs in 1997 were \$7735 for osteomyelitis, \$5041 for SA, and \$12,691 for combined infections. By 2012, these costs increased to \$11,823 for osteomyelitis (p < 0.001), \$10,574 for SA (p < 0.001), and \$16,260 for both infections (p < 0.001). Controlling for inflation, costs increased significantly over the study period for all infection types (p < 0.001; Fig. 4).

#### Discussion

The incidence rate of pediatric osteomyelitis increased by 33%, while SA rates were stable, and combined infections increased by 63% from 1997 to 2012. Despite stable LOS in all subgroups, costs for SA, osteomyelitis, and combined infections increased dramatically over the study period.

This study has a number of limitations. First, the administrative nature of the KID increases the possibility of misclassification due to hospital coding errors. However, multiple sources have validated the use of this database. which has been used to study temporal trends in various populations and validated against other sources [21, 37]. If misclassification were to occur, the most likely scenario is that a case of true infection was coded as unspecified infection or unspecified arthritis and thus would not have been included in our analysis. This would have resulted in underreporting of infection rates; therefore, the numbers reported here could be considered conservative. Second, because the KID database is cross-sectional and does not include longitudinal follow-up, it was not possible to assess for recurrence, late development of osteomyelitis, or additional surgical procedures required beyond the index admission.

Table 2 Procedures performed for osteoarticular infection, 1997–2012

Infection type	Procedure <sup>a</sup>	1997	2000	2003	2006	2009	2012
Osteomyelitis	Procedure performed	3302 (51%)	3725 (50%)	3795 (49%)	4580 (49%)	4840 (51%)	4602 (50%)
	Bone debridement	1942 (59%)	2199 (59%)	2385 (63%)	2841 (62%)	3105 (64%)	2916 (63%)
	Diagnostic biopsy or aspiration	1501 (45%)	1637 (44%)	1522 (40%)	1780 (39%)	1902 (39%)	1804 (39%)
	Other debridement	799 (24%)	818 (22%)	859 (23%)	874 (19%)	858 (18%)	899 (20%)
	Joint debridement	615 (19%)	681 (18%)	742 (20%)	940 (21%)	1058 (22%)	1043 (23%)
	Removal of implant	214 (6%)	322 (9%)	370 (10%)	407 (9%)	529 (11%)	464 (10%)
Septic arthritis	Procedure performed	3400 (78%)	3850 (80%)	3790 (80%)	4085 (79%)	3979 (82%)	3707 (93%)
	Bone debridement	629 (14%)	689 (14%)	793 (17%)	921 (18%)	1051 (22%)	1026 (23%)
	Diagnostic biopsy or aspiration	1923 (44%)	1932 (40%)	1912 (41%)	1984 (38%)	1887 (39%)	1778 (40%)
	Other debridement	408 (9%)	343 (7%)	346 (7%)	419 (8%)	367 (8%)	407 (9%)
	Joint debridement	2338 (53%)	2796 (58%)	2784 (59%)	3033 (59%)	3040 (62%)	2820 (63%)
	Removal of implant	17 (0%)	36 (1%)	58 (1%)	66 (1%)	72 (1%)	68 (2%)
Combined infections	Procedure performed	507 (81%)	575 (82%)	669 (85%)	833 (80%)	1055 (83%)	992 (85%)
	Bone debridement	224 (36%)	225 (32%)	287 (36%)	326 (31%)	521 (41%)	480 (41%)
	Diagnostic biopsy or aspiration	268 (43%)	304 (43%)	346 (44%)	397 (38%)	532 (42%)	474 (41%)
	Other debridement	90 (14%)	82 (12%)	85 (11%)	89 (9%)	120 (9%)	156 (13%)
	Joint debridement	337 (54%)	398 (57%)	463 (59%)	583 (56%)	743 (58%)	690 (59%)
	Removal of implant	3 (0%)	9 (1%)	13 (2%)	17 (2%)	25 (2%)	21 (2%)

<sup>a</sup> See Appendix A for categorization of procedures





Fig. 3. Length of hospital stay for osteomyelitis, septic arthritis, and combined infections, 1997–2012

Third, the KID database does not provide accurate information on causative bacteria, as ICD-9 codes do not exist for every type of bacterial infection. Even where codes do exist for infection due to a specific bacteria (for example, septic arthritis of the knee caused by Staphylococcus aureus [ICD-9 code 711.06 and 041.10], or septic arthritis of the knee caused by methicillin-resistant S. aureus [MRSA; ICD-9 code 711.06 and 041.12], we believe it would not be coded accurately because many clinicians/coders would likely select the more general code (septic arthritis of the knee, ICD-9 code 711.06), without the additional code specifying the bacterial type. Fourth, despite an attempt to accurately calculate national incidence rates, the US Census numbers used for incidence rate calculations do not include undocumented residents, thus the actual denominator could be larger than indicated by census data. Fifth, information on length of antibiotic treatment, transition times to oral antibiotics, and intensive care unit (ICU) admission were not available in the KID database. Finally, this study may not have captured changes in practice that could have resulted from recent studies documenting shorter treatment regimens, as the most

recent year included in the KID dataset was 2012.

Although we used the same data set as Stockmann et al. [38], the analyses differ significantly. Stockman et al. identified cases using the ICD-9-CM codes 711.0 (pyogenic arthritis), 730.0 (acute osteomyelitis), and 730.2 (unspecified osteomyelitis), as compared to the extensive list of ICD-9-CM codes related to osteoarticular infections included in the current study (Online Resource 1). In addition, Stockmann et al. reported rates as cases per 1000 hospital admissions, which is perhaps a less useful statistic than an incident rate reported per 100,000 children.

The osteomyelitis rate identified in the current study was 7.9 to 10.5/100,000, which falls within the ranges reported in other series in developed countries, 1.94 [13] to 13 [33]/100,000 [6, 13, 33]. Our reported rates are lower than those found in some populations, such as children from New Zealand or of Polynesian or Maori descent (43/100,000) [34] and Aboriginal Australians (almost 200/100,000) [15].

The SA rate identified in this study was 4.3 to 5.2/100,000, within but at the low end of the range reported in



Fig. 4. Total cost associated with osteomyelitis, septic arthritis, and combined infections, 1997–2012

other series, 4 to 12/100,000 [11, 16, 29]. The current series is limited only to infections treated in-hospital and does not include cases that may have been treated on an out-patient basis. However, it is unlikely that we have missed any significant cases of osteomyelitis, SA, or combined infections because they are typically treated in-hospital for at least a few days.

This study builds on previous studies similarly identifying an increasing rate of osteomyelitis and combined infections [2, 13, 23]. Although increasing bacterial virulence or some other factor may be causing this increase in osteomyelitis and combined infections, another likely explanation is that magnetic resonance imaging (MRI) evaluation is more accessible, making it easier to identify subtle disease, providing an apparent increase in the national rate of osteomyelitis and combined infections. Experts suggest that musculoskeletal infection imaging workup should include MRI rather than ultrasound, provided that imaging can be performed in a safe and timely fashion [24]. Additionally, when MRI is performed for suspected osteomyelitis, dedicated imaging of the neighboring joints should routinely be included.

LOS for osteoarticular infections has certainly improved from historic reports of 50 days in 1982 to 1983 [23] but has been stable at approximately 5 days over the course of this study. LOS is lower than in other recent reports, including a retrospective cohort study in Israel that found an overall LOS of  $9.2 \pm 6.5$  days [6]. The decrease in LOS between previous reports and the current study period may be attributed in part to shorter IV antibiotic regimens, as SA traditionally was treated with a 2to 4-week treatment of IV antibiotics [8, 27, 44], while traditionally osteomyelitis was treated with antibiotics for 1 to 2 months, IV for the first 1 to 2 weeks. A recent Finnish randomized, controlled trial (RCT) treated children with 2 to 4 days of IV antibiotics then randomized children with SA to 10 or 30 days of clindamycin or a first-generation cephalosporin (intravenously for the first 2 to 4 days) [30]. Given no difference in outcomes between treatment arms, this regimen of short-course IV antibiotics followed by 10 days of oral antibiotics has been recommended [29].

In a similar Finnish RCT of children with culturepositive acute hematogenous osteomyelitis (AHOM), children were treated with 2 to 4 days of IV antibiotics, followed by randomization to clindamycin or a first-generation cephalosporin for 20 versus 30 days [31]. In an Australian prospective study of pediatric SA and osteomyelitis, 59% of patients could be converted to oral antibiotics at 3 days and 86% at 5 days, with median LOS at 5 days [20]. Although these studies were completed in Finnish and Australian populations, their findings may influence osteoarticular treatment practices beyond those countries' borders.

With the Finnish studies including only uncomplicated SA and osteomyelitis cases, with no MRSA cases [30, 31], some may question the external validity of this study. When MRSA is present or C-reactive protein levels are persistently high despite antibiotic treatment, longer courses of IV antibiotics may be needed [22]. With these previous studies being performed in Europe and Australia, and results not having been replicated in North America or other countries, these shorter IV regimens may not have been fully adopted worldwide.

Early diagnosis, improved surgical management, more effective antibiotics, or greater access to home IV programs may also factor in the decreased LOS seen in previous studies, although the current study cannot prove this, since procedure rates were stable over the study period. Realistically, LOS probably cannot be reduced much beyond 5 days, since patients typically require at least 2 to 4 days of IV antibiotics, and most clinicians prefer to observe for fevers and C-reactive protein re-evaluation before discharge on oral antibiotics [3, 5].

Despite stable LOS over the study period, costs have increased over time in the USA, higher than the 3.0% national growth rate in per-capita healthcare expenditures, specifically compared to the overall annual expenditure per capita from 2010 to 2011, 2011 to 2012, and 2012 to 2013, which was 4, 3.7, and 3.9%, respectively [1] (7.9, 4.5, and 4.6%, respectively, in the 18 and younger population). This is consistent with the Nationwide Inpatient Sample study [12] that found that although efforts to reduce SA-associated LOS have been successful, they have not resulted in decreased hospital charges-perhaps partly due to the larger number of therapeutic procedures, diagnostic tests, or increased incidence of MRSA or other more virulent infections [10, 17, 18, 35, 43]. The emergence of MRSA in hospitals has been associated with increased rates of bacteremic infections caused by difficult-to-treat pathogens [25]. Patients with MRSA more commonly have sequelae from their musculoskeletal infections, often requiring ICU admission [35]. Assertions that decreasing LOS by promoting earlier hospital discharge would significantly reduce the overall hospital charges [26] are not supported by our current analysis.

In conclusion, pediatric osteoarticular infections are responsible for significant resource use. Across the USA, the incidence rate of SA was stable, while rates of osteomyelitis alone and combined infections increased. Despite stable LOS over the past 15 years, costs have increased. This study demonstrates the most accurate and current population-level data available on the incidence of osteoarticular infections in children and the changes in rates, LOS, and costs over time in the USA. Understanding current practices and the financial impact on our healthcare system may help in designing studies and public health initiatives aiming to optimize treatment and costs for patients with osteoarticular infections.

#### **Compliance with Ethical Standards**

**Conflict of Interest:** Gabriella Safdieh, MD, Jason Silberman, BA, Joseph Nguyen, MPH, Shevaun Doyle, MD, John Blanco, MD, David Scher, MD, Daniel Green, MD, MS, Roger Widmann, MD, and Emily Dodwell, MD, MPH, FRCSC, declare that they have no conflict of interest. Joseph Nguyen, MPH, reports grants from Clinical Translational Science Center (CTSC), National Center for Advancing Translational Sciences (NCATS), outside the submitted work.

Human/Animal Rights: N/A

Informed Consent: N/A

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

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