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Treatment of Osteonecrosis in Children and Adolescents with Acute Lymphoblastic Leukemia

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Abstract

Background—Cure rates for acute lymphoblastic leukemia (ALL) have improved, but as therapy has intensified, the burden of osteonecrosis (ON) has increased. Limited data exist regarding surgical interventions for pediatric ALL patients with ON.

Materials and Methods—A multi-center cohort of children with newly diagnosed ALL was established with Pediatric Health Information System (PHIS) data from 43 freestanding children's hospitals from 1999-2011. Patients with ON identified by ICD-9 code were followed for up to 5 years after index ALL admission for the presence of ON-associated orthopedic surgical procedures.

Results—A cohort of 10,729 ALL patients was assembled, of which 242(2.33%) were identified with an ICD-9 code for ON within 5 years of ALL diagnosis. Fifty-five patients (22.7%) with ON underwent orthopedic surgical intervention aimed at joint preservation (82%) or replacement (18%) with substantial practice variation by hospital in both the rate and type of surgical intervention. The majority of patients had surgical procedures while receiving Maintenance

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therapy. None of the patients undergoing surgical intervention required ICU-level care within 14 days of surgery, and there was no associated in-hospital mortality.

Conclusions—No standard of care exists for treatment of ALL-associated ON. While considerable practice variation exists, surgical intervention appears relatively safe.

Keywords

Avascular necrosis; osteonecrosis; glucocorticoid; pediatrics; leukemia

Introduction¹

With improved treatment for acute lymphoblastic leukemia (ALL), cure rates have dramatically increased, and the importance of limiting treatment toxicities has grown. Specifically, extensive use of corticosteroids, specifically dexamethasone, and asparaginase has increased the rate of osteonecrosis (ON).¹ Reports of the incidence of ON range from 1% to 19%.^{2, 3} The Children's Oncology Group (COG) found in the high-risk phase III pediatric ALL clinical trial CCG-1961 that 143 of the 2056 patients (7.7%) had radiologic validated ON over a five-year follow up period; and in the subsequent upfront high-risk trial AALL0232, there was a 10.9% incidence of ON overall. Factors associated with ON include age greater than 10 years, female gender, and dexamethasone-based induction.^{4, 5} However, no analyses of pediatric ON have been performed using nationally representative administrative/billing data sets regardless of study enrollment. As a result, there are no published data evaluating center-level variation in ON interventions and outcomes.

Currently, there is no established standard of care for treating therapy-induced pediatric ON.⁶ Initial medical management usually includes analgesics, decreased weight bearing, and potential discontinuation of steroids.¹ When conservative ON management fails, surgery may decrease pain and improve mobility.⁷ Research from adults with ON suggests that joint decompression may be effective at preventing subsequent joint collapse, thereby preserving the native joint and decreasing pain.⁸ Arthroscopic repair, core decompression and bone grafting have all been used as attempts to prevent joint collapse.⁸⁻¹¹ Younger age has been reported as a risk factor in adults for both poor outcome and need for surgical revision when these procedures are performed in adults with similar orthopedic conditions.^{12, 13} The skeletal immaturity of the pediatric population may also complicate surgical interventions. The largest report of pediatric surgical intervention comes from the COG where 62 of the 143 patients with ON reported at least one surgical intervention with a total of 132 procedures including 55 total joint replacements and 43 core decompressions.⁵ Other reports are limited to single institution reviews and case summaries, and no data from administrative data sets have been previously reported.

We used the Pediatric Health Information System (PHIS) database to describe the incidence of ON in pediatric patients with ALL. We hypothesized that a significant proportion of children would undergo surgical intervention aimed at preventing joint collapse, that PHIS

¹Acute Lymphoblastic Leukemia(ALL), Osteonecrosis(ON), Children's Oncology Group (COG), Pediatric Health Information System(PHIS), Kids Inpatient Database(KID), Healthcare Cost and Utilization Project (HCUP), Complex Chronic Condition(CCC)

discharge diagnosis data could be used to estimate the rates of post-surgical complications and repeat procedures, and that substantial center-level variation in ON therapies would exist.

Materials and Methods

Study Design and Data Source

We performed a retrospective cohort study of newly diagnosed ALL patients cared for at pediatric institutions contributing data to the Pediatric Health Information System (PHIS). The PHIS database is a comparative database that includes inpatient and day surgery data from 43 freestanding children's hospitals in the United States. These institutions are affiliated with the Children's Hospital Association (CHA, Overland Park, KS) and represent 17 of the 20 major metropolitan areas nationwide. A list of participating hospitals can be found on the Children's Hospital Association website (<https://www.childrenshospitals.org/Directories/Hospital-Directory>.) PHIS data include discharge/encounter information including demographics, ICD-9 discharge diagnoses and procedure codes (up to 41 codes per admission). Hospitals submit billing data for specific resources (e.g. pharmaceutical agents) by hospital day of service. Patients are de-identified using a unique PHIS identifier that is preserved for subsequent admissions. Maintenance of PHIS data quality is a joint effort between CHA, Truven Health Analytics (data processing partner, Ann Arbor, MI), and participating hospitals. Data are subjected to reliability and validity checks before inclusion in the database.

This study received an exemption by the Committee for Protection of Human Subjects at the Children's Hospital of Philadelphia.

Study Population

Patients with ALL newly diagnosed between January 1999 and September 2011 were identified in a process previously described and validated.^{14, 15} Briefly, PHIS was screened for first admissions containing an ICD-9 code consistent with ALL (204.xx, excluding 204.02, relapsed ALL). Patients were excluded if data elements suggested an alternative malignancy or receipt of a stem cell transplant during the index ALL admission. Finally, an extensive manual review of chemotherapy billing data in PHIS was performed to identify patients with chemotherapy patterns consistent with ALL induction therapy.

Primary Outcomes

The primary study endpoint was ON, as defined by the presence of an ON ICD-9 code (733.4X). The timing of ON onset was defined by the start of the admission with the first ON-associated discharge diagnosis code.

Osteonecrosis ICD-9 Code Validation

Medical records of patients with ALL treated at the Children's Hospital of Philadelphia (CHOP) between January 1, 2004 and July 1, 2012 were reviewed to identify the presence of ON. CHOP patients included in the final PHIS cohort were matched to patients in the CHOP medical records to determine the sensitivity, specificity, positive predictive value (PPV) and

negative predictive value (NPV) of ICD-9 code for osteonecrosis in children with ALL. A systematic chart review was performed for each ALL patient in PHIS that was admitted to CHOP to establish whether the patient developed ON. Members of the study team (M.B.H.) reviewed patient's problem lists, MRI, and plain film musculoskeletal imaging reports for radiology reads consistent with ON diagnosis to determine the true presence of ON and compared with the PHIS ICD-9 code for ON (733.4X).

Covariates and confounders

Demographics—Gender, age at ALL diagnosis and race were determined based on each patient's index hospitalization. Age in years was considered as a continuous and categorical (<10 years, 10 to <16 years and >16 years) variable. Gender was analyzed dichotomously (male and female). Race was described categorically (white, black, Asian, Native American, other, and missing) by PHIS. Complex chronic conditions(CCC) were defined as described by Feudtner et al.¹⁶ Summary statistics were constructed to describe demographic characteristics using frequencies and proportions for categorical data and medians and inter-quartile range (IQR) for continuous variables. In bivariate analyses, we compared demographics and exposures of interest in patients with and without ON. For demographic variables, the Wilcoxon rank-sum and Chi-square tests were used.

Glucocorticoid Induction Regimen—Glucocorticoid induction regimen was defined based on billing data during a defined 60 day induction period to classify patients as either receiving dexamethasone, prednisone, dexamethasone and prednisone or neither glucocorticoid during induction.¹⁷ A logistic regression was built with occurrence of ON at the outcome and glucocorticoid exposure as the exposure of interest. A second analysis using age as a categorical covariate (Age<10 or Age>10yo) in the logistic regression model was performed.

Secondary Outcomes

The secondary endpoints were surgical intervention for ON as defined by ICD-9 procedure codes (Appendix 1). The 2009 Kids Inpatient Database (KID) was used to validate surgical procedures. KID is part of the Healthcare Cost and Utilization Project (HCUP) and contains data on all inpatient admissions for patients less than 20 years of age from 44 state inpatient databases. Several variables were examined at the level of surgical procedure including length of hospital stay, in-hospital mortality, ICU utilization, and bisphosphonate utilization. Intensive care unit resource utilization was defined as previously described.¹⁸

All data organization and analyses were performed using Stata statistical software version 12.0 (College Station, TX).

Statistical Analysis

Summary statistics were constructed to describe demographic characteristics using frequencies and proportions for categorical data and medians and inter-quartile range (IQR) for continuous variables. In bivariate analysis, we compared demographics and exposures of interest in patients with and without ON. For demographic variables, the Wilcoxon rank-sum and Chi-square tests were used.

All data organization and analyses were performed using Stata statistical software version 12.0 (College Station, TX).

Results

The final assembled cohort consisted of 10,729 new-onset ALL patients with a median age of 7.04 years (Range: 2.02 to 21.23 years old) (Table 1). Within 5 years from first ALL admission, 242 patients (2.3%) developed ON by ICD-9. Single institution chart review of 303 patients revealed a sensitivity of 41.2% (95% CI; 25.1-59.2%) and specificity 99.63% (95% CI; 97.6-100%) with a 93.33% (95% CI; 66.0-99.7%) PPV and a 93.03% (95% CI; 89.3-95.6%) NPV for the ON ICD-9 code within ALL patient population.

The average 5-year ON rate across hospitals was 2.33% (IQR: 0.82-2.95%). Median time from index ALL admission to first ON billing code was 1.4 years with onset within the first year of diagnosis in 85 (35%), during the second year in 75 (31.0%), third year in 58 (24%), fourth year in 12 (5%) and fifth year in 12 (5%). Table 1 summarizes demographic factors. Development of ON was significantly associated with increased age at diagnosis of ALL (6.93 years without ON vs. 12.28 years with ON $p<0.001$). Age >10 years was associated with an increased risk of developing ON compared to children <10 years, with an OR 8.3 ($p<0.001$, OR 95% CI: 6.16-11.19). Females had a 1.52-fold increase risk in development of ON ($p=0.001$, CI 1.17-1.97). Demographic characteristics were otherwise similar between patients with and without ON. Dexamethasone exposure during induction was associated with a decreased risk of ON compared with patients receiving only prednisone (OR 0.39, CI 0.30-0.53, $p<0.001$). As the Children's Oncology Group adopted an age based steroid regimen [4] we also controlled for age and steroid received. After controlling for age, dexamethasone exposure during induction was associated with an increased risk of ON compared with prednisone but was no longer statistically significant, OR = 1.36 ($p=0.08$, CI 0.96-1.92). Pegaspargase exposure during induction was not associated with development of ON ($p=0.90$).

Fifty-five of the 242 patients (22.7%) with ICD-9 diagnosed ON had at least one surgical procedure performed during the follow-up period with average time from ALL diagnosis to first surgical intervention of 2.22 years. A total of 133 ON-associated procedures were billed for in the 55 patients. Data from KID in 2009 showed 65.2% of ON-associated procedures for patients 20 years old or less were performed at children's hospitals versus adult hospitals. The percentage performed at children's hospitals varied between 35.52-77.03% by ICD-9 code.

Forty-six patients (83%) were initially managed with a joint preserving procedure compared with 9 patients (17%) who had upfront joint replacement. Of note, 34 of the 55 (61.8%) patients had at least one surgical intervention before finishing Maintenance therapy (two years from index ALL admission for girls and three years from index ALL admission for boys). Surgical interventions typically involved lower extremity procedures (Table 2). Local excision, including core decompression: total joint replacement, and bone grafts were the most common interventions (Table 3). Fifteen patients required one or more joint replacements accounting for 22 total joint replacements. Of these 15 patients, 6 patients had

2 hip replacements, 8 patients had 1 hip replacement and 1 patient had a hip and shoulder replacement. Average time from ALL diagnosis to total hip replacement was just over 3 years. Six patients had an ON associated procedure prior to total hip replacement.

The 80 admissions associated with an ON surgical intervention ranged from 2-67 days with an average length of stay of 7.92 days. Prolonged stays may reflect slow recovery time or may reflect Complex chronic condition (CCC) codes other than malignancy were present in 70% of surgical admissions with an average number of 2.1 CCC codes per patient.¹⁶ The most common CCC code present was hematologic/immunologic (n=21) and metabolic (n=20). No patients required ICU-level care within 14 days of surgical procedures, and no deaths occurred during hospitalizations for ON procedures. Nineteen patients required a second surgical intervention an average of 6 months after initial surgical intervention (range 2-686 days). Four patients required 3 surgical interventions and 2 patients required 5 surgical interventions each. Of those undergoing surgical intervention 17 (30.9%) had a subsequent surgery involving the same joint type initially operated on. Inpatient bisphosphonate billing codes were observed in 14 of the 242 patients who had an ON diagnosis. None of the 55 patients who underwent surgical interventions also had pharmacy bisphosphonates billing codes.

Surgical intervention was reported at 21 institutions of the 37 PHIS hospitals that had at least 1 patient with ON reported by ICD-9. Hospitals varied not only in the rate of surgical intervention (Figure 1) but also in the type of surgical intervention performed (Figure 2). In the hospitals performing surgery the most common intervention was joint preservation with 18 (85.7%) billing at least one type of joint preserving surgeries, 10 (47.6%) billing a joint replacement, and 7 (33.3%) billing both joint replacements and joint preserving surgeries. Some of the procedures may have been combined procedures for example excision with grafting which in the PHIS database would be counted as two procedures. Of the 37 institutions reporting at least one ON diagnosis, 11 also reported bisphosphonate use. Six PHIS institutions did not have any reported patients with ON; these institutions also had the fewest ALL patients over the study period (0-108.)

Discussion

To our knowledge this is the first report using a nationally representative administrative database to study ON in children with ALL. The overall ON rate is consistent with previously reported ON rates, however, based on the sensitivity of the ICD-9 code for ON may substantially underestimate the true ON incidence. The age distribution of both the overall cohort and patients with ON is consistent with previous reports. In previous cohorts of patients with ALL, dexamethasone has been reported as a risk factor for the development of ON.^{1, 3} While our initial analysis identified dexamethasone as being associated with a decreased rate of ON, this likely reflects the change in practice to only use dexamethasone in younger children. After controlling for age, dexamethasone was no longer significant and supports the continued use of an age-based induction regimen.

The substantial variation in the rate of ON by center was unexpected as the vast majority of children with ALL in the United States are treated on clinical trials or receive clinical trial

like chemotherapy creating a cohort of patients with a fairly uniformly defined exposures. Many institution level variables may account for differences in reported ON rates. No standard exists for screening for ON and institutional differences in screening may account for the observed variability. Additionally, PHIS data are limited to resources used in the inpatient or day surgery setting and therefore, institutional preference for management in an inpatient hospital setting vs. outpatient management would affect the rate of ON detected.

Previous studies have focused on the development of ON within three years of diagnosis with only retrospective self-reports suggesting a continued risk of developing ON after 3 years.² A strength of PHIS data permits a long-term analysis of a large cohort of patients. Greater longitudinal follow up showed a small but clinically significant rate of new ON 4-5 years after ALL diagnosis. While PHIS data allow for longer-term monitoring for complications, the database relies on ICD-9 codes. Single institution chart review found the ICD-9 code for ON had low sensitivity but high specificity suggesting that while the cohort may not encompass all ALL patients with ON the patients included are very likely to truly have ON. Previous cohort studies using ICD-9 codes have suggested a greater sensitivity and specificity for more severe disease.¹⁹ Unfortunately, we are unable to determine onset of pain which makes it difficult to directly compare our data with previously published data.

Greater longitudinal follow-up and a comprehensive surgical activity data found in PHIS permits a more in depth look at surgical interventions for ON at pediatric children's hospitals. The overall ON-related surgical rate of 22.7% is similar to that reported previously in COG trials. Surgical intervention typically involved large weight bearing joints, and the majority of procedures were joint preserving surgeries.

Our analysis shows institution-level variation occurred in the utilization of surgical intervention. While these analyses cannot determine "appropriate" surgical intervention, the more than eight-fold variation in surgical intervention (Figure 1) suggests that either 1) some hospitals are undertreating patients with ON; 2) some hospitals are exposing patients to unnecessary surgical interventions, or 3) different pediatric orthopedic expertise is available at differing institutions, resulting in referrals outside the hospital for surgical interventions. A limitation of PHIS database is that data is limited to freestanding children's hospitals and does not include the treatment of patients referred to adult hospitals or dedicated orthopedic surgical centers. The 2009 Kids Inpatient Database (KID) was used to assess the proportion of ON associated procedures performed in adult hospitals that would not be captured by PHIS compared the pediatrics hospital similar including PHIS and similar institutions. KID is part of the Healthcare Cost and Utilization Project (HCUP) and contains data on all inpatient admissions for patients less than 20 years of age from 44 state inpatient databases. The KID data suggests freestanding children's hospitals possess the orthopedic expertise to perform surgical intervention for ON but that our data may underestimate the true rate of surgical intervention.

There was also great variability in the type of surgery performed with centers vastly differing in their use of joint replacement versus joint-preserving procedures. For instance, bone grafts have been reported in case studies as an adjuvant to excisional procedures and were performed at 8 institutions but more commonly performed at centers where a greater

percentage of patients were managed surgically.⁸ The majority of surgical interventions were joint-preserving surgeries, but there was great variability of the type of joint-preserving surgery performed. The patients who received joint-preserving surgical interventions had a shorter time period from diagnosis to complete joint replacement than those who went straight to joint replacement. Patients who received early surgical intervention aimed at joint preservation may have had more severe disease warranting clinicians to pursue more aggressive early management since there are no guidelines for treatment of symptomatic ON.¹⁶ Bisphosphonates have been proposed as another form of early intervention, but bisphosphonate use during and after therapy did not seem to be widespread during the years of this cohort

Regardless of institutional-level variation the absence of post-operative mortality or ICU-level resource utilization suggests that surgical intervention for ON can be performed safely during ALL therapy. A significant portion of the cohort underwent surgical intervention while still on treatment and had a high number of CCCs at the time of intervention without undue complications. Data supporting the safety of surgical intervention despite continued chemotherapy for ALL, and presence of CCC is of particular importance given the potential for early intervention to preserve joints and stop disease progression.^{8, 17, 20} While there is some data to suggest earlier intervention is more efficacious, no large scale studies have examined this.^{1, 7, 8, 17, 20} Joint-preserving surgeries could potentially halt the progression of disease and improve quality of life, but such interventions are only possible before joint collapse. As surgical intervention appears safe, efficacy trials are warranted. The duration of surgical admissions was longer than expected which may suggest prolonged rehabilitation or that surgical procedures may have been performed as part of admissions with other purposes.

This analysis of an administrative database provides complimentary evidence to the current ON literature. This is the first data to support the safety of early surgical intervention. Given the demonstrated safety and the potential to prevent disease progression, further efforts should focus on prospective studies to assess the efficacy of early intervention. We identified significant practice variation between hospitals in ascertainment of and surgical intervention for ON. Further research should prospectively examine the efficacy of joint-preserving surgeries as treatment for ON to allow for an evidence-based standard of care and consistent treatment to optimize outcomes.

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Appendix 1. ICD-9 codes for ON associated Orthopedic Procedures

Procedure contents/Description	ICD-9
Revision of hip replacement, both acetabular and femoral components	0070
Revision of hip replacement, femoral component	0072

Procedure contents/Description	ICD-9
Resurfacing hip, total, acetabulum and femoral head	0085
Resurfacing hip, partial, femoral head	0086
Resurfacing hip, partial, acetabulum	0087
Wedge osteotomy of radius and ulna	7723
Wedge osteotomy of femur	7725
Wedge osteotomy of tibia and fibula	7727
Wedge osteotomy of tarsals and metatarsals	7728
Wedge osteotomy of other bone	7729
Local excision of lesion or tissue of scapula, clavicle, and thorax [ribs and sternum]	7761
Local excision of lesion or tissue of humerus	7762
Local excision of lesion or tissue of radius and ulna	7763
Local excision of lesion or tissue of femur	7765
Local excision of lesion or tissue of tibia and fibula	7767
Local excision of lesion or tissue of other bone	7769
Excision of bone for graft, unspecified site	7770
Excision of scapula, clavicle, and thorax [ribs and sternum] for graft	7771
Excision of humerus for graft	7772
Excision of femur for graft	7775
Excision of tibia and fibula for graft	7777
Excision of other bone for graft	7779
Other partial ostectomy, unspecified site	7780
Other partial ostectomy of carpals and metacarpals	7784
Other partial ostectomy of femur	7785
Other partial ostectomy of patella	7786
Other partial ostectomy of tibia and fibula	7787
Other partial ostectomy of other bone	7789
Total ostectomy of tarsals and metatarsals	7798
Bone graft of scapula, clavicle, and thorax (ribs and sternum)	7801
Bone graft of humerus	7802
Bone graft of carpals and metacarpals	7804
Bone graft of femur	7805
Bone graft of patella	7806
Bone graft of tibia and fibula	7807
Bone graft of tarsals and metatarsals	7808
Bone graft of other bone	7809
Other repair or plastic operations on tibia and fibula	7847
Other repair or plastic operations on tarsals and metatarsals	7848
Removal of implanted device from humerus	7862
Removal of implanted device from radius and ulna	7863

Procedure contents/Description	ICD-9
Removal of implanted device from femur	7865
Removal of implanted device from tibia and fibula	7867
Removal of implanted device from other	7869
Arthrotomy for removal of prosthesis of hip	8005
Other arthrotomy of shoulder	8011
Other arthrotomy of elbow	8012
Other arthrotomy of hip	8015
Other arthrotomy of knee	8016
Other arthrotomy of ankle	8017
Other arthrotomy of foot and toe	8018
Other arthrotomy of other specified site	8019
Arthroscopy of shoulder	8021
Arthroscopy of elbow	8022
Arthroscopy of hip	8025
Arthroscopy of knee	8026
Arthroscopy of ankle	8027
Other local excision or destruction of lesion of shoulder joint	8081
Other local excision or destruction of lesion of elbow joint	8082
Other local excision or destruction of lesion of wrist joint	8083
Other local excision or destruction of lesion of hip joint	8085
Other local excision or destruction of lesion of knee joint	8086
Other local excision or destruction of lesion of ankle joint	8087
Other local excision or destruction of lesion of joint of foot and toe	8088
Other local excision or destruction of lesion of joint of other specified site	8089
Other excision of elbow joint	8092
Other excision of hip joint	8095
Other repair of knee	8147
Total hip replacement	8151
Partial hip replacement	8152
Revision of hip replacement	8153
Total knee replacement	8154
Arthroplasty of metacarpophalangeal and interphalangeal joint without implant	8172
Total shoulder replacement	8180
Partial shoulder replacement	8181
Total elbow replacement	8184
Other repair of elbow	8185
Pedicle or flap graft, not otherwise specified	8670
Attachment of pedicle or flap graft to hand	8673
Attachment of pedicle or flap graft to other sites	8674

Procedure contents/Description	ICD-9
Revision of pedicle or flap graft	8675

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Clinical Practice Points

- Extensive use of corticosteroids and asparaginase has increased the rate of osteonecrosis after treatment for ALL.
- Surgical intervention can decrease pain and improve mobility but there is no established standard of care for treating therapy-induced pediatric ON.
- In our analysis we found rates of ON consistent with previous reports but marked institutional variation in rate of ON and surgical intervention.
- Our data showed a continued risk of ON after three years from diagnosis of ALL
- Surgical intervention for ON is safe even in patients with complex conditions and patients continuing to receive Maintenance therapy for ALL.

Figure 1. Rates of ON and Surgical Intervention by PHIS Hospital

Figure 2. Type of Procedure by PHIS Hospital

Table 1

Demographics

	ALL Patients with out ON (n=10,487)		ALL Patients with ON (n=242)		P
Age	n	%	n	%	
<1 year	295	(2.8)	0	(0)	<.0001
1 to <10 years	7,515	(71.7)	65	(26.9)	
10 to <19 years	2,557	(24.4)	169	(69.8)	
19 years	120	(1.1)	8	(3.3)	
Sex					0.2009
Male	5,893	(56.2)	126	(52.1)	
Female	4,594	(43.8)	116	(47.9)	
Race					0.1219
White	7,927	(75.6)	193	(79.8)	
Black	774	(7.4)	17	(7.0)	
Asian	321	(3.1)	5	(2.1)	
Native American	121	(1.2)	6	(2.5)	
Other	1,019	(9.7)	14	(5.8)	
Missing	325	(3.1)	7	(2.9)	
Region					0.0527
Midwest	2,742	(26.2)	63	(26.0)	
Northeast	1,042	(9.9)	19	(7.9)	
South	3,478	(33.2)	67	(27.7)	
West	3,225	(30.8)	93	(38.4)	
Medication use during induction *					
Prednisone	4,252	(40.6)	152	(62.8)	<.0001
Pegaspargase	6,540	(62.4)	150	(62)	0.9041
Dexamethasone	6,378	(60.8)	104	(43)	<.0001
Concurrent Dex & Pred	600	(5.7)	17	(7)	0.3892

*** Induction is defined as 60-day period from ALL admission

Table 2
Type of Orthopedic Procedure

Type of Surgical Intervention	N	%
Excision	59	44.4%
Graft	32	24.1%
Total joint replacement	22	16.5%
Arthrotomy	11	8.3%
Arthroscopy	10	7.5%
Other joint repair	5	3.8%
Partial joint replacement	2	1.5%

Table 3**Site of surgical intervention**

Site of surgical intervention	N	%
Femur	47	35.3%
Hip	35	26.3%
Knee	22	16.5%
Humerus	8	6.0%
Tibia/fibula	6	4.5%
Elbow	3	2.3%
Foot and toe	1	0.8%
Ankle	1	0.8%
Other	1	0.8%
Shoulder	1	0.8%