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ORIGINAL ARTICLE

# Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges

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**Abstract**
*Summary* Bisphosphonate-related osteonecrosis of the jaw (BONJ) is an adverse effect of bisphosphonate use with a poorly described epidemiology in osteoporosis patients. We examined the literature and two new cohorts for BONJ. The literature suggests an incidence rate of 0.028 % to 4.3 %. Our cohort studies found an incidence of 0.02 % (95 % CI 0.004 %–0.11 %).
*Introduction* We examined the epidemiology of BONJ associated with osteoporosis dosing of bisphosphonates.
*Methods* First, we systematically searched the literature about osteoporosis BONJ. Identified studies were abstracted by two authors. Second, we attempted to estimate the relative risk of BONJ among bisphosphonate users with osteoporosis. Two different large insurance databases, one from 2005–2007 and another from 2007–2010, combined with medical record review, were searched. The older dataset did not include the International Classification of Diagnoses (ICD) diagnosis code for osteonecrosis of the jaw (ONJ; ICD 733.45). Incidence rates and relative risks were estimated using Cox regression.
*Results* The literature review produced nine studies of varying quality. The incidence rates for BONJ among osteoporosis patients varied from 0.028 % to 4.3 %. Two prior studies estimated the relative risk of ONJ related to bisphosphonates and found odds ratios of 7.2 and 9.2. Our attempts to estimate the incidence rate of BONJ encompassed 41,957 in the dataset from 2005–2007 and 466,645 in a separate dataset from 2007–2010. From the older dataset, we found 51 potential cases of BONJ using a broad definition of possible ONJ. One case was confirmed by a dentist for a prevalence of 0.02 % (95 % CI 0.004 %–0.11 %) among bisphosphonate users. From the newer dataset, we found 13 possible cases, but none could be confirmed. Most subjects with the ONJ diagnosis code appeared to have had an osteoporosis-related fracture and not ONJ.
*Conclusions* The literature suggests a broad range of possible values for the prevalence of BONJ; our estimate fell within the range from prior literature.

**Keywords** Bisphosphonate · Epidemiology · Osteonecrosis of the jaw · Osteoporosis

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## Introduction

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) is a concerning side effect of bisphosphonates. The use of these drugs has increased for cancer-related bone metastases, where dosages are relatively high (i.e., zoledronic acid,

4 mg every 4 weeks) compared with osteoporosis dosages (i.e., zoledronic acid, 5 mg annually). They are widely used among patients with osteoporosis; during 2009, 14.8 million prescriptions were written for non-generic ("branded") osteoporosis treatments [1]. During this period, there have been substantial concerns expressed in the lay press about osteonecrosis of the jaw [2, 3]. These concerns paired with the very large number of patients using bisphosphonates, especially for osteoporosis, makes understanding the epidemiology of BONJ critical.

There are important challenges to epidemiologic studies of BONJ. First, BONJ associated with osteoporosis dosing seems to be relatively uncommon [4]. Determining the epidemiology of rare diseases presents difficulties, but these problems are not insurmountable. Second, since potent amino-bisphosphonates have only been prescribed since 1995, BONJ is a relatively "new" condition without clear clinical standards. Prior conditions of the jaw have included osteonecrosis, such as phosphorous or radiation exposure; however, these have become very rare [5]. Third, the American Academy of Oral and Maxillofacial Surgeons' (AAOMS) definition of BONJ [6] has likely improved the consistency of clinical diagnosis; however, it is unclear how consistently this is applied. Moreover, until 2007, there was no specific diagnosis code in the International Classification of Diagnoses (ICD) for ONJ. This makes finding BONJ in databases that use ICD diagnosis codes challenging, a fact that is compounded by the new ICD for ONJ being very similar to a number of osteoporosis diagnosis codes.

In an attempt to estimate the risk of BONJ among osteoporosis patients and to assess the relative risk of BONJ among bisphosphonate users, we undertook two separate but related types of studies. First, we conducted a systematic review of the epidemiologic literature on BONJ associated with osteoporosis. Then, we applied this knowledge to perform cohort studies of BONJ using insurance claims data to find cases, hoping to further refine incidence rates and risk estimates for BONJ.

## Methods

### Systematic literature review

We searched Medline from 1999 to 2012 using the following search terms: osteonecrosis of the jaw and bisphosphonates and osteoporosis. Titles and abstracts were reviewed to determine an article's relevance. We then hand-searched articles' citation lists to find further references (Fig. 1).

Two authors (DHS and EM) independently reviewed each article selected for inclusion. Articles were included if they contained primary epidemiologic data regarding BONJ among non-cancer patients. Case series were not included. Cohorts as well were excluded if the denominator or source population was not clear, or if it was a selected group of dental patients, i.e., dental implants. The articles were reviewed to determine their methodologic quality using a system adapted from recommendation regarding the conduct of systematic reviews (see Table 1 for quality assessment form) [7]. We abstracted, as well, information about the study procedures and results. Their designs and methodologic quality were so heterogeneous that no attempt was made to meta-analyze the studies' results.

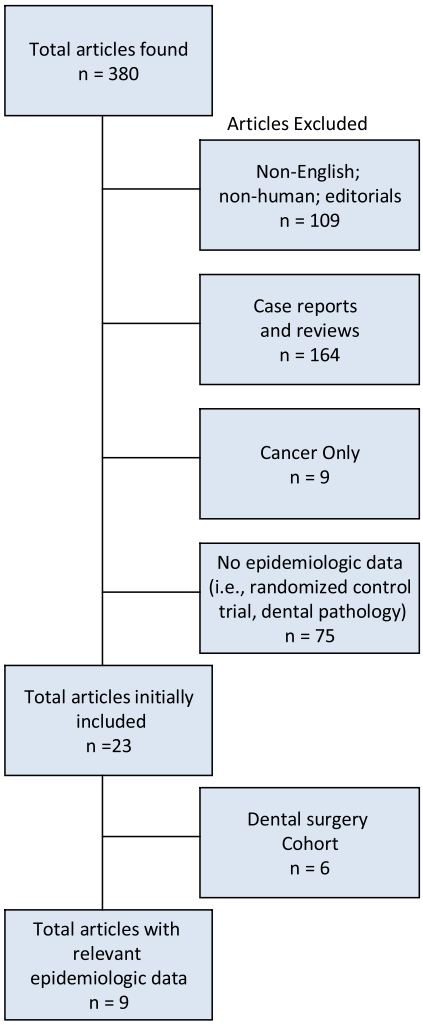


**Fig. 1** Describes the selection process for articles included in the systematic review

### Cohort studies: design

Two separate attempts were made to study the epidemiology of BONJ using large cohorts—cohorts 1 and 2. For both cohort studies, we began with large insurance-based health care claims; cohort 1 used data from a single state Blue Cross Blue Shield Plan using data from 2005–2007 and cohort 2 used data from a multi-state Commercial Insurance

**Table 1** Quality assessment measures for studies included in systematic review

| | Zero points | 1 point | 2 points |
|---|---|---|---|
| Study population | Convenience sample | Limited number of clinics | Population-based |
| Endpoint (BONJ) definition | Not BONJ (other jaw diagnoses) | BONJ by some criteria | BONJ by AAOMS criteria |
| Treatment (bisphosphonate) definition | Not patient level (i.e., marketing information) | Patient level from medical or dental records | Patient level from pharmacy or prescription records |
| Covariates included | None other than age and gender | Some variables other than age and gender included on at least cases (i.e., dental diagnoses or comorbid conditions) | Some variables other than age and gender on cases and controls |
| Design | Case-control without clear source population | Case-control with source population | Cohort study with clear source population |

*BONJ* bisphosphonate-related osteonecrosis of the jaw, *AAOMS* American Academy of Oral and Maxillofacial Surgeons

Program including data from 2007–2010. Both databases included health care and pharmacy claims for all inpatient and outpatient medical services, such as physician and surgeon visits, radiology procedures, laboratory tests, and all drug dispensings. The cohort 1 database did not include dental claims but did include all claims from participating oral and maxillofacial surgeons, whereas the database for cohort 2 included dental claims. Moreover, in cohort 2, we required eligibility for both medical and dental insurance as a pre-requisite.

Both cohorts included three groups of patients, all who could not have diagnoses for solid organ malignancy or multiple myeloma during the complete period of medical benefits: (1) those who initiated bisphosphonates; (2) those who initiated another medication for osteoporosis, such as calcitonin, raloxifene, or hormone replacement therapy; and (3) those who had a diagnosis of osteoporosis or a fracture but started no osteoporosis-related medications (see Supplementary Table 1). Thus, included subjects could not have used a bisphosphonate or another medication during the 1 year prior to the start of follow-up. This broad definition was intended to allow us to estimate the risk of ONJ in persons exposed and unexposed to bisphosphonates. These cohorts were mutually exclusive. All subjects must have had at least 12 months of concurrent medical and pharmacy eligibility prior to entering the cohort.

The cohort studies were approved by the Partners Healthcare Institutional Review Board.

### Osteonecrosis of the jaw: endpoint definition

In the first cohort, we used a very broad set of diagnosis and procedure codes to define possible cases of ONJ (see Supplementary Table 2). This list of codes was developed based on a comprehensive review of codes that had been used for known cases of BONJ that were evaluated clinically by two of the authors (NT and SBW). After applying these codes, we then attempted to improve the accuracy of possible cases by examining the sequence of diagnosis and procedure codes. Confirmation of the final list of possible cases identified through the claims-based analysis was attempted by contacting oral and maxillofacial surgeons to confirm the diagnosis of ONJ.

In the second cohort, we attempted to find cases of ONJ using the ICD code 733.45 which had been recently developed, prior to the establishment of this cohort. The broad set of codes were not used in cohort 1 were not applied in cohort 2. We further attempted to refine the possible cases by examining the sequence of diagnosis and procedure codes surrounding the diagnosis of ONJ. In cases of visits coded with the diagnosis code ICD 733.45, we examined the claims records for a visit to an oral and maxillofacial surgeon, radiologic studies of the head and/or oral cavity, and oral procedures. If none were found, these potential cases were considered unlikely. If any evidence of possible ONJ was found, we attempted to confirm the cases through dental records.

### Statistical analyses

We considered a variety of covariates, but because of the few confirmed cases, we did not attempt any analyses adjusted for patient characteristics.

We calculated the frequency with 95 % confidence intervals (CI) of confirmed and possible ONJ cases in both cohorts. Follow-up of subjects continued until death, loss of benefits, end of study period, or ONJ diagnosis. The prevalence ratio was calculated based on comparing the prevalence among exposed cases of ONJ with unexposed cases.

## Results

### Systematic literature review

Our search yielded 374 potentially relevant papers. Further review of the titles and abstracts narrowed this to 17 papers.

**Table 2** Epidemiologic aspects and overall quality of observational studies of osteonecrosis of the jaw

| Author, year | Population source | BONJ definition | BONJ data source | Treatment route; source of data | Study design | Quality score[a] |
|---|---|---|---|---|---|---|
| Baillargeon 2011 [8] | US Medicare beneficiaries | Jaw pathology, not BONJ | ICD-9 codes | IV only (no information about oral); medical records | Cohort | 7 |
| Barasch 2011 [15] | 3 sites in US dental practice-based research network | Clear, but not AAOMS | Dental records and surveys mailed to dentists plus patient interviews | IV and oral; dental records | Case–control | 6 |
| Fellows 2011 [10] | 2 large HMO databases from the US | Clear, but not AAOMS | ICD-9 Codes, Natural Language Processing and chart review | Oral; pharmacy data | Case–control | 8 |
| Hong 2009 [17] | Hospital dental records | AAOMS definition | Medical chart review with telephone survey for missing data | Oral; pharmacy data | Case–control | 7 |
| Lo 2009 [12] | Members of Kaiser-Permanente of Northern California | AAOMS definition | Dental record review or dental examination | Oral; pharmacy data | Cohort | 9 |
| Sedghizadeh 2009 [16] | EMR at US dental school | Clear, but not AAOMS | "Radiographic evidence of an ill-defined lytic lesion of the jawbone in addition to clinical evidence of exposed necrotic bone (sequestra) with mucosal ulceration …" | Oral; dental records | Case–control | 6 |
| Cartsos 2008 [13] | Insurance database | Jaw pathology, not BONJ | ICD-9 codes | IV and oral; pharmacy data | Case–control | 5 |
| Pazianas 2008 [9] | Medstat MarketScan, insurance database | Jaw pathology, not BONJ | CPT codes for jaw surgeries from insurance claims | Oral; pharmacy data | Case–control | 7 |
| Mavrokokki 2007 [11] | Medicare database (Australia) | Clear, but not AAOMS | Surveys to members of the Australian and New Zealand Association of Oral and Maxillofacial Surgeons plus dentists | Oral; osteoporosis Population estimate | Case–control | 4 |

*BONJ* bisphosphonate-related osteonecrosis of the jaw, *AAOMS* American Association of Oral and Maxillofacial Surgeons

[a] See text and Table 1 for description of quality score

Full review revealed nine papers that provided primary epidemiologic data for osteoporosis-related BONJ.

The quality of these papers and their methods were variable (see Table 2). Several used a clearly defined source population to estimate the denominator of people at risk for BONJ [8–13] while others used less well-defined cohorts (i.e., marketing data for bisphosphonates to determine the at-risk group) [14–17]. The definitions of BONJ ranged from the AAOMS criteria [17] to other clinical criteria [10–12, 14–16] or not actually BONJ, but other jaw disorders requiring surgery [8, 9, 13]. Some studies examined a broad range of patient characteristics (such as comorbidities and comedications) [8–10, 14, 15] while others did not [11, 12, 13, 16, 17].

The estimates of the incidence of BONJ from prior studies range from 0.028 % to 4.0 % (see Table 3). Two prior studies estimated the relative risk of ONJ among bisphosphonate users compared with non-users [10, 15]. These studies were conducted in large networks of dental practices with careful case-definitions but not the AAOMS definition (i.e., did not require 8 weeks of exposed bone). Similar odds ratios for the probability of bisphosphonate use among cases of ONJ were calculated for both studies, 7.2 and 9.2. Three studies using insurance claims data examined the relationship of bisphosphonate use to miscellaneous jaw lesions and found relative risks that ranged from protective (odds ratio 0.65) to elevated (odds ratio 7.8) [8, 9, 13].

## Cohort studies

The cohort 1 study had a source population of 41,957 with a mean duration of follow-up of 13 months; cohort 2 had a source population of 466,645 and a mean follow-up of 13 months as well. The mean age of cohort 1 was 38.1 years, and it was 43.9 in cohort 2. From this source population, we found 84 who had a diagnosis or procedure code that had could be associated with BONJ (see Appendix I). We further refined this group through searching each potential case for sequences of diagnosis and/or procedure codes and narrowed the list to 51 possible cases. From this list, we were

**Table 3** Results of prior observational studies of bisphosphonate-related osteonecrosis of the jaw

| Author, year[a] | Bisphosphonate users | Cases of BONJ | Results |
|---|---|---|---|
| Prevalence estimate and/or incidence rate (95 % confidence interval) | | | |
| Fellows 2011 [10] | 21,157 | 6 | 0.028 % (0.011–0.058 %) |
| Hong 2009 [17] | 2000–2008, 12,752 | 7 | 2000–2008, 0.055 % (0.0124–0.11 %) |
| | 2005–2008, 9,882 | | 2005–2008, 0.07 % (0.032–0.14 %) |
| Lo 2009 [12] | Total surveys, 13,835 | 9 | Total surveys, 0.07 % (95 % CI 0.03–0.12 %) |
| | Responders, 8,572 | | Responders, 0.10 % (95 % CI 0.0–0.20 %) |
| | | | 28 (14–53) per 100,000 bisphosphonate person-years |
| Mavrokokki 2007 [11] | 304,900 | 36 | Total cohort, 0.01–0.04 % |
| | | | Cohort with dental extractions, 0.09–0.34 % |
| Sedghizadeh 2009 [16] | 208 | 9 | 4.3 % (2.1–7.9 %) |
| Risk estimate for BONJ (95 % confidence interval) | | | |
| Barasch 2011 [15] | 111 non-cancer | 30 | OR, 7.2 (2.1–24.7) |
| Fellows 2011 [10] | 21,157 | 6 | OR, 9.2 (3.6–23.3) |
| Risk estimates for "jaw surgery" (95 % confidence interval) | | | |
| Baillargeon 2011 [8] | 9161 | 24 | HR 1.65 (0.71–3.80), adjusted |
| Cartsos 2008a [13] | Oral, 176,739 | Oral, 150 | Oral, OR 0.65 (0.54–0.79) |
| | IV, 1,742 | IV, 9 | IV, OR 4.01 (2.06–7.78) |
| Cartsos 2008b [13] | Oral,179,784 | Oral, 43 | Oral: OR 0.86 (0.59-1.26) |
| | IV, 1,849 | IV, 4 | IV: OR 7.80 (2.84-21.36) |
| Pazianas 2008 [9] | 3,505 | 697 | OR 0.91 (0.7–1.19), adjusted |

Abbreviations: *BONJ* bisphosphonate-related osteonecrosis of the jaw, *OR* odds ratio (crude, unless noted to be adjusted), *HR* hazard ratio

[a] Relevant notes about each study

Hong: seven hospital cases used as numerator for calculations

Lo: the 13,835 survey recipients for minimal estimate and 8,572 respondents for reported estimate

Cartsos: results compared with the ratio of bisphosphonate-naïve patients presenting with the same inflammatory condition; results "a" outcome was surgery for inflammatory lesions of the jaw and "b" other jaw surgery

Baillargeon: Of 24 total cases found, nine used a bisphosphonate

Pazianas: Of the 697 cases found, 96 used a bisphosphonate

only able to confirm one case from dental records and dentist responses. Thus, from our list of 4,934 bisphosphonate users, we found one case of dentist-confirmed BONJ, for a prevalence of 0.02 % (95 % CI 0.004 %–0.11 %). With only one case, we were unable to pursue further analyses of relative risks or risk factors.

The second cohort was from a study period that included the period after the ICD diagnosis code for ONJ was established. From our source population of 466,645, we found 13 with a possible diagnosis of BONJ. We hand-searched the diagnosis and procedure codes for these possible cases and further defined a small list as probable cases, based on visits with relevant providers (dentists or oral and maxillofacial surgeons), procedures related to the oral cavity, or radiographs of the head and mouth areas. However, we could not confirm any of these cases as definite BONJ based on further review of dental records. We were not able to get complete records for nine of the 13 possible cases, and none of the dentists or oral and maxillofacial surgeons confirmed BONJ when surveyed.

We calculated prevalence rates using possible (unconfirmed) cases based on the ICD diagnosis (see Table 4). The estimated prevalence of BONJ among bisphosphonate users was 0.007 % (95 % CI 0.0007 %–0.014 %). No possible cases were found among the non-bisphosphonate osteoporosis drug users. The estimated incidence rate among the osteoporosis and fracture cases which did not start a medication was 0.002 % (95 % CI 0.0008 %–0.004 %). The unadjusted prevalence ratio was 4.10 (95 % CI 1.37–12.2).

## Discussion

Osteonecrosis of the jaw remains a major concern for many patients using bisphosphonates. While there have been

**Table 4** Prevalence rates of confirmed and possible osteonecrosis of the jaw cases from two different health care claims-based cohorts

| Cohort definition | Confirmed cases | Total subjects exposed | Prevalence (95 % CI) | Prevalence ratio (95 % CI) |
|---|---|---|---|---|
| Cohort 1 | | | | |
| Bisphosphonate users | 1 | 4934 | 0.02 % (0.004 %–0.11 %) | NA |
| No use of bisphosphonates | 0 | 780 | NA | – |
| Non-users of osteoporosis medications | 0 | 18,294 | NA | – |
| Cohort 2[a] | | | | |
| Bisphosphonate users | 7 | 100,109 | 0.007 % (0.0007 %–0.014 %) | 4.10 (1.37–12.2) |
| No use of bisphosphonates | 0 | 14,913 | NA | – |
| Non-users of osteoporosis medications | 6 | 351,623 | 0.002 % (0.0008 %–0.004 %) | Reference |

[a]Cohort 2 had no confirmed cases, so these represent possible cases

important advances in the diagnosis and treatment of BONJ, the epidemiology is still poorly understood. We conducted a systematic review of the BONJ epidemiology literature related to osteoporosis and found variable quality in prior studies. Moreover, estimates of the incidence rate vary considerably, likely because of very different methodologies. Our attempt to further this field through using large insurance claims databases for case-finding proved largely unsuccessful.

Our literature search found several examples of other methods for studying BONJ. Studies that surveyed oral medicine specialists and maxillofacial surgeons have the advantage of available and relevant records, however, it is unclear if all cases really met similar criteria for BONJ and whether all cases were included [11, 12]. Many times, the sampling was done in a convenience sample and not at a population-level [11, 16, 17]. Furthermore, such studies often relied on imprecise estimates of exposure based on bisphosphonate sales data [11]. The large study from Kaiser-Permanente may provide the most reliable incidence rate estimates [12]. The investigators found potential cases through a survey of patients with possible BONJ based on diagnoses. Cases were then confirmed by oral medicine specialists or the dental records. Bisphosphonate exposure data were obtained directly from pharmacy dispensing data from Kaiser-Permanente.

One of the included studies deserves special discussion. This study came from one academic dental practice and estimated an incidence rate ten times larger than any other study (see Table 3) [16]. The investigators described including consecutive dental patients and having pharmaceutical information available on all included patients. While the availability of dental records was a clear strength of this study, sampling patients in a dental practice may have biased towards bisphosphonate users with oral pathology (i.e., referral bias). As well, this study examined a relatively small sample, reducing the stability of the estimate. This outlier result should be viewed with caution.

The vagaries of the BONJ diagnosis code and the difficulty obtaining all relevant medical and dental records made our cohort study challenging. Even after the ONJ ICD code establishment in 2007, we found that this was not a useful way of identifying BONJ cases as the claim sequence for many of these potential cases had nothing to suggest oral pathology, i.e., no visits with oral medicine specialists, no procedures involving the oral cavity, and no radiographs of this anatomic area. This project speaks to the importance of validation studies with adequate medical and/or dental records, especially early after establishment of a diagnosis code. We also found it surprising that the majority of the dental claims that we reviewed had no diagnosis codes, but only Common Procedural Terminology used for billing. This severely limits the ability to find BONJ cases primarily seen at a dental practice. As more research is performed using insurance claims data, it will be important to attempt to link dental claims including diagnoses with other insurance claims. Furthermore, linking dental and medical records with full insurance claims would facilitate the study we conducted.

It is worthwhile to consider other methods for studies of uncommon or poorly defined outcomes like BONJ. The importance of a standard and well-accepted case definition cannot be under-estimated. While the AAOMS and others [6, 18] developed case definitions of BONJ early on, it is unclear whether this has been widely used in practice and whether it adequately excludes other diagnoses, such as a retained sequestrum. Post-marketing surveillance registries—using combination of written, telephone, and/or Internet communication—of all patients exposed to a given drug can be very useful tools to identify potential cases which can then be verified with review of appropriate records. Such registries have been used for many vaccines and biologics. It is not clear why such an effort was never undertaken for bisphosphonates, despite the substantial concerns raised regarding their potential association with various adverse events.

Six case series prospectively followed patients undergoing dental procedures for post-operative BONJ [14, 19–23]; they were not included in the primary results because of this specialized source population. While these studies cannot be used to estimate incidence rates because they do not represent a general population, they do offer some insights into the potential relationship between dental procedures and BONJ. Four of the six studies found no cases of BONJ, and two found a total of five cases; thus the incidence of BONJ ranged from 0.0 % to 7.8 %. The large discrepancy in incidence rates may be explained by random variation across studies with small populations, or it may be that differences in the source populations (i.e., lower versus higher risk) explained the heterogeneity in results.

We attempted to estimate the incidence rate of BONJ related to the use of bisphosphonates for osteoporosis. The literature was systematically reviewed, and two cohort studies were attempted. We encountered important impediments to the cohort studies that we could not overcome in the setting of this study, such as difficulty defining the BONJ outcome using claims as a sampling method. It is likely that as the diagnosis code for ONJ is used in a more standard manner over time, health care claims will provide opportunities for BONJ epidemiology. Currently, access to oral medicine records is critical for confirming the diagnosis of BONJ.

**Conflicts of interest** Dr. Solomon receives research support from Amgen and Lilly.

## Appendix 1

Possible diagnosis codes for osteonecrosis of the jaw

| ICD-9-CM Diagnosis Code | Description | ICD-9-CM Diagnosis Code | Description |
|---|---|---|---|
| 730.08 | Acute osteomyelitis involving other specified sites | 733.9 | Disorder of bone and cartilage, unspecified |
| 730.00 | Acute osteomyelitis, site unspecified | 526.4 | Inflammatory conditions of jaw |
| 733.40 | Aseptic necrosis of bone, site unspecified | 528.9 | Other and unspecified diseases of the oral soft tissues |
| 733.49 | Aseptic necrosis of other bone sites | 733.99 | Other disorders of bone and cartilage |
| 730.18 | Chronic osteomyelitis involving other specified sites | 526.89 | Other specified diseases of the jaws |
| 730.10 | Chronic osteomyelitis, site unspecified | 526.9 | Unspecified disease of the jaws |
| 730.20 | Unspecified osteomyelitis, site unspecified | 525.9 | Unspecified disorder of the teeth and supporting structure |
| 733.45 | ONJ (since 10/1/07) | | |

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