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Original Article

Association of Osteoporosis with Antibiotic Resistance among Postmenopausal Women with Open Tibial Fractures

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ABSTRACT

Osteoporosis is common among postmenopausal women and can complicate the healing of open tibial fractures. Antibiotic resistance is a growing concern in treatment. Yet, the connection between osteoporosis and antibiotic resistance remains unclear, needing the investigation for improved patient care. **Objective:** To explore the association between osteoporosis and antibiotic resistance among postmenopausal female patients with open tibial fractures. **Methods:** This cross-sectional study was conducted at Department of Orthopedic Surgery, Liaquat University of Medical and Health Sciences, Jamshoro, with sample size of 240 postmenopausal women with open tibial fractures and signs of infection within one week of the fracture. Participants were chosen via non-probability sampling method. Bacteriological samples for culture were obtained from secretions adjacent to the infected tissue. Data analysis was conducted using SPSS version 21.0. **Results:** The majority of osteoporotic patients experienced Road Traffic Accidents (RTA) (42.5%), followed by falls from height (35.3%), while firearm injuries were less common (22.2%). *Staphylococcus aureus* was the most common pathogen in both osteoporotic (40%) and non-osteoporotic (39.9%) patients, followed by *Escherichia coli, Methicillin-Resistant Staphylococcus Aureus (MRSA), Klebsiella, and Pseudomonas aeruginosa. Antibiotic resistance was predominantly found against S. aureus, MRSA, Klebsiella* and *E. coli.* Co-Trimoxazole exhibited the highest resistance rates across all four bacterial organisms, ranging from 34% to 50%. **Conclusions:** The study found varying antibiotic resistance patterns across various pathogens, with notable resistance observed MRSA strains. Antibiotic resistance was observed in osteoporotic group, with Co-Trimoxazole showing the highest resistance rates.

INTRODUCTION

Research indicates that by 2050, the global population aged 60 and above is expected to double, reaching 22% [1]. Among this group, many suffer from osteoporosis, a condition that weakens bones and increases the risk of fractures [2, 3]. Osteoporosis is characterized by fragile bones due to abnormal structure and reduced mass [4]. About 40% of people face a significant fracture risk, similar to heart disease [5]. This condition is a major public health concern, contributing to mortality rates, reduced mobility, and high healthcare costs [6]. As the population ages, the burden of osteoporosis is expected to grow [7]. The cessation of menstruation for one year or more in women is defined as menopause by the World Health Organization (WHO) [8]. Perimenopause, characterized by irregular menstruation before menopause, varies in duration. In Pakistan, the average age at menopause is 44.6 years, with ages ranging from 25 to 59 years [9]. Osteoporosis affects over 200 million women worldwide, and postmenopausal

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women are especially vulnerable to its severe consequences, such as osteoporotic fractures [10]. Research indicates that nearly one-third (33%) of women over 50 years old have a likelihood of experiencing osteoporotic fractures [11]. Estrogen levels have a positive correlation with Bone Mineral Density (BMD) and play a protective role against osteoporotic fractures [12]. This association may be explained by the direct effects of estrogen on bone cells, including osteoblasts, osteocytes, and osteoclasts, which contribute to maintaining a balance between bone formation and resorption [13]. Weakening of bones increases the risk of open fractures, particularly in the extremities. Previous research has highlighted the high contamination rates observed in open tibial fractures, which can result in delayed wound healing and treatment failure. Prompt administration of antibiotic prophylaxis following injury, along with urgent and thorough débridement, irrigation, and bony stabilization, is crucial to minimize the risk of infection and enhance outcomes [14]. Despite the established standard of care recommending timely irrigation and debridement within six hours post-injury for managing open tibial fractures, current evidence does not uniformly support this practice, and uncertainties persist regarding the ideal irrigation solution and pressure [15]. Information about which germs are usually found in hospitals and how they needs to be responded to antibiotics is important for giving patients the right treatment [14]. Doctors choose the right antibiotics and how long to use them based on factors like the kind of broken bone, how the injury happened, where it is, the results of tests to see which germs are present, and what kinds of germs are causing the infection. The primary goal of antimicrobial therapy is to safeguard clean tissue from infection and reduce the number of contaminating bacteria in damaged tissue until surgical irrigation and debridement can be performed [16]. However, there is a lack of clear evidence regarding the specific causative organisms and their sensitivity patterns in postmenopausal women with osteoporosis, necessitating further investigation.

The aim of this study was to explore the association between osteoporosis and antibiotic resistance among postmenopausal female patients with open tibial fractures, presenting at the Department of Orthopedic Surgery, Liaquat University of Medical and Health Sciences, Jamshoro.

This study was conducted to assess the empathy scores among medical and dental students and to correlate empathy scores with demographic features like age, gender and academic year.

METHODS

A cross-sectional study was conducted at Department of Orthopedic Surgery, Liaquat University of Medical and Health Sciences, Jamshoro. A sample size of 240 cases was determined with a 90% confidence interval and a 5% margin of error, taking the prevalence of osteoporosis in postmenopausal women as 33% [11]. Non-probability consecutive sampling was utilized to select postmenopausal women with and presenting with open tibial fractures and signs of infection within one week of the fracture. Osteoporosis was diagnosed via Bone Mineral Density Method (BMD). Exclusion criteria encompassed patients presenting after seven days of the fracture, those receiving antibiotics for infection before or after the accident, women having diabetes with blood sugar levels exceeding 186mg/dl, and cases of open tibial fractures categorized as Gustilo type III C. The study lasted 1 year from Feb 2017 to Jan 2018. After obtaining informed consent, demographic information, history and examination of the patients along with assessment of wound condition was done. Radiological and microbiological investigations were performed. Bacteriological samples were obtained from secretions adjacent to the infected tissue using sterile cotton swabs and disposable syringes, which were promptly transferred to the microbiology laboratory for incubation at 37°C for 24 hours to enrich bacterial cells. Gram staining and acid-fast staining were performed on all samples, followed by sub culturing for aerobics. Isolates were identified using standard microbiological procedures and tested for antimicrobial susceptibilities via the Kirby Bauer method in accordance with Institutional Laboratory guidelines. Sensitivity patterns were determined for detected causative organisms. Data analysis was conducted using SPSS version 21.0, presenting main study variables such as causative bacterial organisms and their sensitivities in terms of frequency, percentage, and stratification for effect modifiers like, type of fracture prior to arrival at Liaquat University Hospital. Chi-square test was applied to assess associations among variables.

RESULTS

The study comprised 240 female patients with open tibial fractures with a mean age of 52.98 ± 6.479 years. 153 (63.75%) women were diagnosed with osteoporosis, while 87 (36.25%) did not show any sign of osteoporosis (Figure: 1). The duration of fracture was recorded to be 10.76 ± 3.151 hours on average, while the time from injury to the collection of culture swabs was found to be 5.9 ± 1.27 hours.

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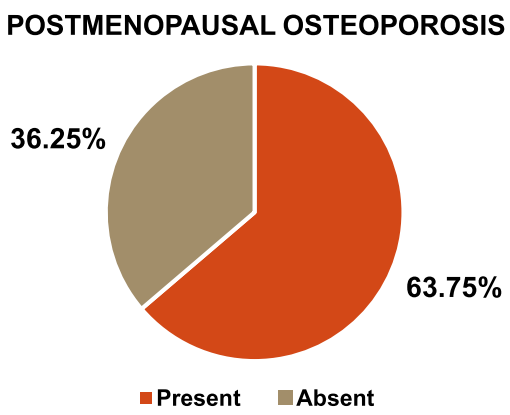

Figure 1: Postmenopausal Osteoporosis Status among Females

In table 1, regarding the mode of injury, the majority of osteoporotic patients experienced Road Traffic Accidents (RTA) (42.5%), followed by falls from height (35.3%), while firearm injuries were less common (22.2%). Conversely, non-osteoporotic patients had a higher incidence of RTA (51.7%) and falls from height (39.1%), with firearm injuries being relatively rare (9.2%). Regarding the type of fracture, osteoporotic patients predominantly presented with Type III A fractures (53.6%), whereas Type III B fractures were more prevalent among non-osteoporotic patients (70.1%). These findings suggest a potential association between osteoporosis and the severity or mechanism of injury in patients with open tibial fractures.

Table 1: Mode of Injury and Type of Fracture among Patients with Open Tibial Fractures

Variables	N (%)	
	Osteoporotic (n=153)	Non-Osteoporotic (n=87)
Mode of Injury		
RTA	65 (42.5%)	45 (51.7%)
Fall from Height	54 (35.3%)	34 (39.1%)
Firearm Injury	34 (22.2%)	8 (9.2%)
Types of Fracture		
Type III A	82 (53.6%)	26 (29.9%)
Type III B	71 (46.4%)	61 (70.1%)

In table 2, the frequency of causative bacterial organisms varied between the two groups. Staphylococcus aureus (*S. aureus*) was the most common pathogen in both osteoporotic (40%) and non-osteoporotic (39.9%) patients, followed by *Escherichia coli (E. coli), Methicillin-resistant Staphylococcus aureus (MRSA), Klebsiella,* and *Pseudomonas aeruginosa (P. aeruginosa).* Interestingly, while the overall distribution of bacterial organisms was similar between the two groups, there were slight variations in the percentages, indicating potential differences in susceptibility or exposure to specific pathogens among osteoporotic and non-osteoporotic patients.

Table 2: Frequency of Various Causative Bacterial Organisms among Patients with Open Tibial Fractures

Bacterial Organisms	Total N (%)	Osteoporotic (n=153) N (%)	Non-Osteoporotic (n=87) N (%)
Staphylococcus aureus (S. aureus)	96 (40%)	61 (39.9%)	35 (40.2%)
Escherichia coli (E. Coli)	38 (16%)	24 (15.7%)	14 (16.1%)
Methicillin-resistant Staphylococcus aureus (MRSA)	33 (14%)	21 (13.7%)	12 (13.8%)
Klebsiella	24 (10%)	15 (9.8%)	9 (10.3%)
Pseudomonas aeruginosa	19 (8%)	11 (7.2%)	8 (9.2%)
Enterococcus species	9 (4%)	4 (2.6%)	5 (5.7%)
Coagulase-negative Staphylococcus (B-Staphylococcus)	9 (4%)	4 (2.6%)	5 (5.7%)
Acinetobacter	9 (4%)	4 (2.6%)	5 (5.7%)

In table 3, the investigation into antibiotic resistance patterns revealed varying degrees of resistance across the top four causative bacterial organisms. Meronem exhibited a statistically non-significant correlation with MRSA infections (p = 0.31), indicating a higher resistance rate compared to other antibiotics in the context of MRSA. Similarly, Co-Trimoxazole displayed a significant association with MRSA (p = 0.02), suggesting heightened resistance levels against this bacterial strain when treated with Co-Trimoxazole. Additionally, Co-Trimoxazole demonstrated significance in its association with *E. Coli* infections (p = 0.03), implying a potential challenge in treating *E. Coli*-related open tibial fractures with this antibiotic. Conversely, several antibiotics showed no significant correlation with any particular bacterial strain among osteoporotic patients with open tibial fractures. For instance, Avelox, Linzulin, Ceftazidime, Gentamicin, and Ceftriazone did not exhibit statistically significant associations with any of the studied bacterial organisms, highlighting potential versatility in their effectiveness across various bacterial strains
in this patient population.

Table 3: Antibiotic Resistance with Respect to Top 4 Causative Bacterial Organisms Among Osteoporotic Patients with Open Tibial Fractures

Antibiotics	Causative Bacterial Organisms			
	S. Aureus N (%) P-value	*MRSA* N (%) P-value	*Klebsiella* N (%) P-value	*E. Coli* N (%) P-value
Meronem	42 (18%) p = 0.12	68 (28%) p = 0.31	56 (22%) p = 0.41	82 (34%) p = 0.76
Pipericillin	56 (22%) p = 0.72	82 (34%) p = 0.52	68 (28%) p = 0.32	92 (38%) p = 0.73
Avelox	28 (12%) p = 0.91	56 (22%) p = 0.1	42 (18%) p = 0.23	68 (28%) p = 0.47
Linzulin	56 (22%) p = 0.82	92 (38%) p = 0.9	82 (34%) p = 0.1	108 (44%) p = 0.83

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Ceftazidime	42 (18%) p = 0.3	68 (28%) p = 0.2	56 (22%) p = 0.72	82 (34%) p = 0.22
Gentamicin	56 (22%) p = 0.3	82 (34%) p = 0.4	68 (28%) p = 0.63	92 (38%) p = 0.53
Ceftriazone	28 (12%) p = 0.3	54 (22%) p = 0.1	42 (18%) p = 0.21	68 (28%) p = 0.67
Co-Trimoxazole	82 (34%) p = 0.12	108 (44%) p = 0.02	96 (40%) p = 0.61	122 (50%) p = 0.03
Ofloxacin	68 (28%) p = 0.53	92 (38%) p = 0.22	80 (32%) p = 0.83	104 (42%) p = 0.9

DISCUSSION

Wound infections are a concern not only for surgeons but for everyone involved in caring for orthopedic and trauma patients. They can lead to more sickness, higher healthcare expenses, and sometimes serious consequences [17]. The types of germs causing infections in surgical wounds with implants haven't changed much over the years, except for some new germs that are resistant to antibiotics [18]. An open fracture occurs when the bone breaks through the skin, exposing it to the external environment. With the increasing population, industrialization, and firearm incidents worldwide, the incidence of open fractures has been on the rise. A study published in 2018 indicated a mortality rate of 38.5% among patients with open fractures. A report published in 2016 found a mortality rate of 36% and amputation in 28 cases out of 96 open tibial fractures [19, 20]. Before 1916, during World War I, open fractures resulted in an 80% mortality rate for femur fractures, which later reduced to 15.6% with more aggressive management. Various classification systems exist for open fractures, with Gustilo's system being commonly used. In developed countries, proper management has led to low infection rates, with reported incidences of 0.2% for Type I fractures, 2-7% for Type II, and 10-25% for Type IIIB and IIIC fractures. However, the amputation rate remains high, exceeding 50% for some types [21, 22]. In a recent study involving 50 cases, the majority were Male (74%), consistent with previous findings. The most affected age group was between 20-40 years, with a Mean age of 32.98 years. Road traffic accidents were the leading cause of injury (46%), followed by falls from height (36%) and firearm injuries (18%). This differs from other studies due to variations in lifestyle and geographical location. Type IIIB fractures were the most common (48%) in the study, followed by Type IIIA (34%), Type II (14%), and Type I (4%). These findings align with previous research, albeit with slight variations due to facility differences [23]. Infections associated with combat-related tibial fractures typically involve Gram-negative organisms, with *Staphylococcus aureus* being the most common microorganism isolated. However, the relative rates may vary across different centers. In terms of antibiotic sensitivity, certain drugs such as Meronem, Pipericillin, and Avelox were found to be highly effective against *Staphylococcus aureus* and other organisms. [24]. The investigation into antibiotic resistance patterns among *Staphylococcus aureus*, *MRSA*, *Klebsiella*, and *Escherichia coli* in orthopedic wound infections revealed significant resistance rates across various antibiotics. Our study's resistance rates for Staphylococcus aureus and *MRSA* align with trends reported elsewhere, reflecting the widespread challenge of combating these resistant strains. Variations in prevalence may occur due to differences in geographic regions and healthcare practices as explained by de Haan *et al.*, in 2015 [25]. In accordance with prior investigations, our findings demonstrate significant resistance patterns among *Klebsiella* strains [26]. This emphasizes the necessity for rigorous surveillance and infection control measures to mitigate the spread of antibiotic resistance in healthcare settings. The heightened rates of resistance observed in *Escherichia coli* echo concerns raised in similar study by *Lee et al.*, in 2015, necessitating tailored therapeutic approaches and sustained efforts to preserve antibiotic efficacy globally [27]. The widespread resistance to Co-Trimoxazole across various bacterial organisms underscores its limited clinical utility in managing orthopedic infections as described by Dombrovskiy *et al.*, in 2017 [28]. Clinicians are advised to consider local resistance profiles when selecting alternative antimicrobial agents to optimize patient outcomes [29].

CONCLUSIONS

The study found that among postmenopausal women open tibial fractures have a high prevalence of osteoporosis i.e., 63.75%. S. aureus was found to be most common pathogen present in both groups. Antibiotic resistance patterns vary across these pathogens, with notable resistance observed particularly in MRSA strains. Antibiotic resistance was observed in osteoporotic group, with Co-Trimoxazole showing the statistical significant highest resistance rates.

Authors Contribution

Conceptualization: RAB
Methodology: RAB, LDM, AA, MFJ, AGA
Formal analysis: RAB, LDM, MFJ, AGA
Formal analysis: RAB, LDM
Writing, review and editing: RAB, LDM, AA, MFJ, AGA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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REFERENCES

[1] Newgard CB and Sharpless NE. Coming of age: molecular drivers of aging and therapeutic opportunities. The Journal of Clinical Investigation. 2013 Mar; 123(3): 946-50. doi: 10.1172/JCI68833.

[2] Clynes MA, Harvey NC, Curtis EM, Fuggle NR, Dennison EM, Cooper C *et al.* The epidemiology of osteoporosis. British Medical Bulletin. 2020 May; 133(1): 105–17. doi: 10.1093/bmb/ldaa005.

[3] Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N *et al.* Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. Journal of the American Medical Association (JAMA) Network Open. 2021 Aug; 4(8): e2121106. doi: 10.1001/jamanetwork open.2021.21106.

[4] Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. 2019; 393(10169): 364–76. doi: 10.1016/S0140-6736(18)32112-3.

[5] Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002 Jun; 359(9321): 1929–36. doi: 10.1016/S0140-6736(02)08761-5.

[6] Kanis JA, Svedbom A, Harvey N, McCloskey EV. The osteoporosis treatment gap. Journal of Bone and Mineral Research. 2014 Sep; 29(9): 1926-8. doi: 10.1002/jbmr.2301.

[7] Bae G, Kim E, Kwon HY, Ha YC, An J, Park J *et al.* Burden of osteoporotic fractures using disability-adjusted life years in South Korea. Asia Pacific Journal of Public Health. 2020 Mar; 32(2-3): 111-7. doi: 10.1177/1010539520916376.

[8] Kadam NS, Chiplonkar SA, Khadilkar AV, Khadilkar VV. Prevalence of osteoporosis in apparently healthy adults above 40 years of age in Pune City, India. Indian journal of endocrinology and metabolism. 2018 Jan; 22(1): 67-73. doi: 10.4103/ijem.IJEM_438_17.

[9] Rana MYB, Kulsoom O, Ali HS, Istiaq S, Sultana S, Hussain R *et al.* Factors Influencing the Age of Menopause Among Pakistani Women. Journal of the Society of Obstetricians and Gynaecologists of Pakistan. 2021 Oct; 11(3): 214-6.

[10] Kang HY, Yang KH, Kim YN, Moon SH, Choi WJ, Kang DR *et al.* Incidence and mortality of hip fracture among the elderly population in South Korea: a population-based study using the national health insurance claims data. BMC Public Health. 2010 Dec; 10: 1-9. doi: 10.1186/1471-2458-10-230.

[11] Lin J, Zhu J, Wang Y, Zhang N, Gober HJ, Qiu X *et al.* Chinese single herbs and active ingredients for postmenopausal osteoporosis: From preclinical evidence to action mechanism. Bioscience Trends. 2017 Oct; 11(5): 496-506. doi: 10.5582/bst.2017.01216.

[12] Yoo JE, Shin DW, Han K, Kim D, Yoon JW, Lee DY *et al.* Association of female reproductive factors with incidence of fracture among postmenopausal women in Korea. Journal of the American Medical Association (JAMA) Network Open. 2021 Jan; 4(1): e2030405. doi: 1001/jamanetworkopen.2020.30405.

[13] Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends in Endocrinology & Metabolism. 2012 Nov; 23(11): 576-81. doi: 10.1016/j.tem.2012.03.008.

[14] Khosravi AD, Ahmadi F, Salmanzadeh S, Dashtbozorg A, Montazeri EA. Study of bacteria isolated from orthopedic implant infections and their antimicrobial susceptibility pattern. Research Journal of Microbiology. 2009 Jul; 4(4): 158-63. doi: 10.3923/jm.2009.158.163.

[15] Mundi R, Chaudhry H, Niroopan G, Petrisor B, Bhandari M. Open tibial fractures: updated guidelines for management. The Journal of Bone and Joint Surgery Reviews. 2015 Feb; 3(2): e1. doi: 10.2106/JBJS.RVW.N.00051.

[16] Naeemullah HS, Khan AH, Gul H, Baz KA. Common organisms and their sensitivity, in open fractures of the extremities. Pakistan Journal of Surgery. 2012; 28(3): 186-92.

[17] Ahmed MI. Prevalence of nosocomial wound infection among postoperative patients and antibiotics patterns at teaching hospital in Sudan. North American Journal of Medical Sciences. 2012 Jan; 4(1): 29. doi: 10.4103/1947-2714.92900.

[18] Singh A, Sikka R, Maggu NK, Deep A, Chaudhary U, Gill PS *et al.* Prevalence and antibiotic sensitivity pattern of bacteria isolated from nosocomial patients. Journal of Orthopaedics. 2010 Jul; 7(2): e3.

[19] Olson M, O'Connor M, Schwartz MI. Surgical wound infection, a five-year prospective study of 20,193 wounds at Minneapolis V.A. Medical Centre. Annals of Surgery. 1984 Mar; 199: 253–259. doi: 10.1097/00000658-198403000-00001.

[20] Volkmann R. Die Behandlung der complizierten fracture. Zentralblatt fur Chirurgie. 2018; 5: 649.

[21] Gustilo RB. The Fractures Classification Manual. 1st Edition. United States; CRC Press: 1991.

[22] Moore TJ, Mauney C, Barron J. The use of quantitative bacterial counts in open fractures. Clinical Orthopaedics and Related Research. 1989 Nov; 248: 227-30. doi: 10.1097/00003086-198911000-00036.

[23] Orwoll ES, Parimi N, Wiedrick J, Lapidus J, Napoli N, Wilkinson JE *et al.* Analysis of the associations between the human fecal microbiome and bone density, structure, and strength: the osteoporotic fractures in men (MrOS) cohort. Journal of Bone and Mineral Research. 2020 Dec; 37(4): 597-607. doi:

DOI: https://doi.org/10.54393/pjhs.v5i04.1497

10.1002/jbmr.4518.

[24] Cheng S, Qi X, Ma M, Zhang L, Cheng B, Liang C *et al.* Assessing the relationship between gut microbiota and bone mineral density. Frontiers in Genetics. 2020 Jan; 11: 6. doi: 10.3389/fgene.2020.00006.

[25] de Haan K, Groeneveld AJ, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Critical Care. 2014 Dec; 18: 1-8. doi: 10.1186/s13054-014-0660-4.

[26] Leung RY, Cheung BM, Nguyen US, Kung AW, Tan KC, Cheung CL *et al.* Optimal vitamin D status and its relationship with bone and mineral metabolism in Hong Kong Chinese. Bone. 2017 Apr; 97: 293-8. doi: 10.1016/j.bone.2017.01.030.

[27] Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC *et al.* Risk of aortic dissection and aortic aneurysm in patients taking oral fluoroquinolone. The JAMA Internal Medicine. 2015 Nov; 175(11): 1839-47. doi: 10.1001/jamainternmed.2015.5389.

[28] Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Critical Care Medicine. 2007 May; 35(5): 1244-50. doi: 10.1097/01.CCM.0000261890.41311.E9.

[29] Allen MR. Skeletal accumulation of bisphosphonates: implications for osteoporosis treatment. Expert Opinion on Drug Metabolism and Toxicology. 2008 Nov; 4(11): 1371-8. doi: 10.1517/17425255.4.11.1371.