Trends in the Epidemiology of Osteomyelitis

A Population-Based Study, 1969 to 2009

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Background: The epidemiology of osteomyelitis in the United States is largely unknown. The purpose of this study was to determine long-term secular trends in the incidence of osteomyelitis in a population-based setting.

Methods: The study population comprised 760 incident cases of osteomyelitis first diagnosed between January 1, 1969, and December 31, 2009, among residents of Olmsted County, Minnesota. The complete medical records for each potential subject were reviewed to confirm the osteomyelitis diagnosis and to extract details on anatomical sites, infecting organisms, etiological risk factors, and outcomes.

Results: The overall age and sex-adjusted annual incidence of osteomyelitis was 21.8 cases per 100,000 person-years. The annual incidence was higher for men than for women and increased with age (p < 0.001). Rates increased with the calendar year (p < 0.001) from 11.4 cases per 100,000 person-years in the period from 1969 to 1979 to 24.4 per 100,000 person-years in the period from 2000 to 2009. The incidence remained relatively stable among children and young adults but almost tripled among individuals older than sixty years; this was partly driven by a significant increase in diabetes-related osteomyelitis from 2.3 cases per 100,000 person-years in the period from 1969 to 1979 to 7.6 cases per 100,000 person-years in the period from 2000 to 2009 (p < 0.001). Forty-four percent of cases involved *Staphylococcus aureus* infections.

Conclusions: The reasons for the increase in osteomyelitis between 1969 and 2009 are unclear but could comprise a variety of factors, including changes in diagnosing patterns or increases in the prevalence of risk factors (e.g., diabetes) in this population.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Osteomyelitis is a heterogeneous disease in its pathophysiology, clinical presentation, and management[1]. Osteomyelitis can be due to contiguous spread of infection from adjacent soft tissues and joints, hematogenous seeding, or direct inoculation of bacteria into the bone as a result of trauma or surgery[1,2]. The diagnosis and treatment of osteomyelitis have improved over the previous decades, and a systematic classification and staging system aids in defining treatment plans[3,4]. Along with advances in bone regeneration, the techniques of debridement and reconstruction of infected osseous defects have changed[5-9], and the development of new antibiotics and delivery systems has helped to decrease the medical treatment burden and the length of hospitalizations[10-13]. Additionally, vascular and microvascular surgery has improved soft-tissue management and healing, while internal fixation and advances in implant technology and organized multidisciplinary trauma teams have greatly improved the care of trauma patients[14]. Nevertheless, diabetes mellitus-related infections and infections of the axial or appendicular skeleton remain as devastating complications, often requiring complex multidisciplinary care with mixed outcomes.

As advances are made in the management of osteomyelitis, the epidemiology of the condition appears to have evolved over time. The increased survival following traumatic injury has been accompanied by an increased occurrence of posttraumatic osteomyelitis[15,16]. Similarly, improved life expectancy among elderly patients with diabetes mellitus has resulted in more cases of neuropathy, vascular insufficiency, and the associated local complications of soft-tissue loss, bone destruction, and osteomyelitis[17,18]. To date, however, there are only a handful of epidemiological studies of osteomyelitis in the U.S., and these studies are limited to selected subsets of patients, as defined by age[19], osteomyelitis type[20], anatomical location[21], or infecting organisms[22,23]. To our knowledge, there are no comprehensive epidemiological studies describing the entire spectrum of osteomyelitis in the U.S. With this background, our objective was to examine trends in the age and sex-specific incidence of osteomyelitis over a forty-one-year period from 1969 to 2009. We also compared trends in underlying etiology, disease characteristics at initial presentation, medical outcomes, and patient survival.

Materials and Methods

This population-based historical cohort study was carried out in Olmsted County, Minnesota, using resources of the Rochester Epidemiology Project[24-27]. This is a medical records-linkage system containing medical records from all health-care providers. All medical, surgical, and histologic diagnoses from these health-care providers are entered into computerized indices to facilitate case identification. This population-based data resource ensures virtually complete ascertainment and follow-up of all clinically diagnosed cases of osteomyelitis in a geographically defined community, along with the ability to access original medical records for case validation.

Identification of Incident Osteomyelitis Cases
We identified all potential patients with osteomyelitis by electronically searching the medical diagnostic and surgical procedure indices, the microbiology culture database, and the radiology database. Nursing home residents were included in the study, whereas prisoners residing in the Federal Medical Center were excluded.

Data Collection
Using a standardized data collection form, the medical records of all electronically identified potential patients were reviewed manually by trained registered nurse abstractors for clinical documentation, positive cultures, and/or radiographic diagnoses of osteomyelitis. An orthopaedic surgeon with expertise in osteomyelitis reviewed the records of questionable cases to verify the diagnosis and to determine the incidence date, which was defined as the time of the initial clinical diagnosis (rather than the time of the first biopsy). All patients were classified as having definite, probable, or possible osteomyelitis using criteria similar to those previously used for periprosthetic joint infections[28]. *Definite osteomyelitis* was defined as at least two bone cultures with microbial growth with the same organism, or one positive bone culture combined with the intraoperative findings of purulence, acute inflammation on histologic examination consistent with infection, or a sinus tract communicating to the bone. *Probable osteomyelitis* was defined as at least one bone culture or surgically obtained pathologic specimen revealing acute inflammation on histologic examination consistent with infection, or a sinus tract communicating to the bone. *Possible osteomyelitis* was defined as diagnostic evidence of bone infection on imaging studies, but no available pathologic or microbiologic data. Data analyses included all three groups.

Data elements extracted from the medical records were age, sex, date of first clinic visit for diagnosis and/or treatment of osteomyelitis, anatomical location, laterality (right, left, and axial), method of diagnosis (clinical only, needle biopsy, surgical specimen, and culture), date of first tissue diagnosis, identified organisms if any, clinical classification of etiology (captured under seven categories as diabetes mellitus-related, hematogenous, traumatic, urinary tract infection, septic arthritis, contiguous, and iatrogenic), subsequent amputation(s), date and causes of death if applicable, and the date of last clinical contact.

Statistical Methods
The entire population over the forty-one-year period was considered to be at risk for developing osteomyelitis. Patient demographics were described as the mean and the standard deviation or as the count and the percentage as appropriate. Age and sex-specific and overall age and sex-adjusted incidence rates were calculated for ten-year time periods and overall from 1969 to 2009. Confidence interval (CI) estimates around the incidence estimates were generated from the Poisson distribution. Age and sex-adjusted estimates were calculated by using the 2010 U.S. Census population data. In order to examine whether the characteristics of the patient population changed over time, we similarly examined clinical characteristics in ten-year intervals. The influence of age, sex, time period, etiology, and their possible interactions were assessed using Poisson regression, with the number of cases as the dependent variable and the corresponding population included as an offset. Poisson regression models were generated with the use of generalized additive models, incorporating age and calendar year as smoothed terms, thereby allowing examination of nonlinear trends over time. All crude rates and univariate and multivariable models of incidence were visually assessed. All tables depicting incidence rates were based on the Poisson models. Expected survival was calculated using the Minnesota white population survival estimates as the reference. All significance tests were two-sided, and $p < 0.05$ was considered significant. The analyses were conducted with SAS software (version 9.3; SAS Institute, Cary, North Carolina) and R software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

Source of Funding

Results

Over the forty-one-year time period from January 1, 1969, through December 31, 2009, we identified 760 unique Olmsted County residents with new-onset osteomyelitis. The majority of the patients (59%) were classified as having definite osteomyelitis, but 18% had probable and 23% had possible osteomyelitis. Their mean age was 52 ± 25 years, and 58% of the unique patients were male (Table I). The mean age at incidence was higher among females than males (56 ± 26 versus 49 ± 25 years; $p < 0.001$). The mean age at incidence increased significantly across the four decades, from 38 ± 26 years in the period from 1969 to 1979 to 57 ± 23 years in the period from 2000 to 2009 ($p < 0.001$). Diabetes was the primary contributing factor in 27% of the patients, followed in equal proportion by hematogenous (19%) and trauma-related (19%) infections. The proportion of diabetes-related cases doubled from 13% in the 1970s to 29% in the 2000s.

The majority of the infections (94%) involved only one location, and the most common anatomical sites affected were the tarsal and metatarsal bones and the toes (43%); the long bones of the lower extremities (20%); and the spine, sternum,

TABLE I Characteristics of Incident Osteomyelitis Infections in 760 Olmsted County Residents (1969-2009)					
	1969-1979 (N = 91)	1980-1989 (N = 145)	1990-1999 (N = 247)	2000-2009 (N = 277)	Total (N = 760)
Age* (yr)	38 ± 26	43 ± 25	56 ± 24	57 ± 23	52 ± 25
Male (no. [%])	55 (60)	86 (59)	136 (55)	164 (59)	441 (58)
Osteomyelitis diagnosis (no. [%])					
Definite	58 (64)	96 (66)	146 (59)	149 (54)	449 (59)
Probable	22 (24)	29 (20)	52 (21)	32 (11)	135 (18)
Possible	11 (12)	20 (14)	49 (20)	96 (35)	176 (23)
Method of diagnosis (no. [%])					
Clinical only	36 (40)	89 (62)	82 (33)	121 (44)	328 (43)
Needle biopsy	15 (16)	12 (8)	15 (6)	28 (10)	70 (9)
Surgical specimen	40 (44)	44 (30)	150 (61)	128 (46)	362 (48)
Etiology (no. [%])					
Diabetes mellitus-related	12 (13)	31 (21)	83 (34)	80 (29)	206 (27)†
Hematogenous	16 (18)	39 (27)	38 (15)	50 (18)	143 (19)
Urinary tract	0 (0)	1 (1)	3 (1)	4 (1)	8 (1)
Contiguous	50 (55)	55 (38)	86 (35)	107 (39)	298 (39)
Traumatic	29 (32)	27 (19)	29 (12)	58 (21)	143 (19)
Septic arthritis	4 (4)	3 (2)	13 (5)	6 (2)	26 (3)
Iatrogenic	13 (14)	20 (14)	40 (16)	40 (14)	113 (15)
Osteomyelitis location (no. [%])					
One location	87 (96)	133 (92)	241 (98)	256 (92)	717 (94)
More than one location	4 (4)	12 (8)	6 (2)	21 (8)	43 (6)
Upper extremities‡	4 (4)	8 (6)	15 (6)	8 (3)	35 (5)
Lower extremities‡	29 (32)	35 (24)	46 (19)	42 (15)	152 (20)
Feet and/or toes	29 (32)	51 (35)	131 (53)	115 (42)	326 (43)
Hand and/or fingers	14 (15)	17 (12)	11 (4)	19 (7)	61 (8)
Craniofacial	6 (7)	13 (9)	11 (4)	11 (4)	41 (5)
Spine, sternum, and/or pelvis	9 (10)	21 (14)	33 (13)	82 (30)	145 (19)
Laterality (no. [%])					
Right	41 (45)	58 (40)	116 (47)	117 (42)	332 (44)
Left	38 (42)	54 (37)	89 (36)	84 (30)	265 (35)
Axial	12 (13)	33 (23)	42 (17)	76 (28)	163 (21)†
Organisms identified (no. [%])					
None	18 (20)	14 (10)	55 (22)	102 (37)	189 (25)†
Monomicrobial	38 (42)	72 (50)	122 (49)	105 (38)	337 (44)
Polymicrobial	35 (38)	59 (41)	70 (28)	70 (25)	234 (31)
Microbiology (no. [%])					
Staphylococcus aureus	43 (47)	86 (59)	113 (46)	95 (34)	337 (44)†
Staphylococcus epidermidis	22 (24)	31 (21)	42 (17)	32 (12)	127 (17)
Streptococci species	14 (15)	31 (21)	45 (18)	28 (10)	118 (16)
Pseudomonas species	6 (7)	12 (8)	23 (9)	11 (4)	52 (7)
Anaerobes	4 (4)	8 (6)	10 (4)	11 (4)	33 (4)
Escherichia coli	6 (4)	6 (4)	7 (3)	7 (3)	26 (3)
Amputation (no. [%])	18 (20)	29 (20)	87 (35)	83 (30)	217 (29)

*The values are given as the mean and the standard deviation. †P < 0.001 for trend. ‡These numbers refer to long bones of the upper and lower extremities and exclude hand, fingers, feet, and toes.

TABLE II Age and Sex-Specific Annual Incidence of Osteomyelitis in Olmsted County (1969-2009)

Age Group (yr)	No. of Cases			Incidence Rate* (per 100,000 person-years)		
	Female	Male	Total	Female	Male	Total
<18	41	71	112	6.6	10.9	8.8
18-29	22	42	64	5.0	10.9	7.8
30-39	20	46	66	5.7	13.2	9.4
40-49	20	40	60	6.8	14.0	10.4
50-59	46	71	117	20.8	33.5	27.0
60-69	52	67	119	33.4	49.2	40.8
70-79	57	54	111	49.4	66.7	56.5
≥80	61	50	111	70.3	128.4	88.3
Total	319	441	760	16.7 (14.8, 18.6)	27.7 (24.9, 30.5)	21.8 (20.2, 23.4)

*Values in parentheses are the 95% CI.

Skull (0%)
Clavicle (0%)
Jaw (1%)
Scapula (0%)
Sternum (0%)
Humerus (0%)
Radius (0%)
Spine (6%)
Ulna (0%)
Pelvis (2%)
Carpal (0%)
Metacarpal (0%)
Fingers (2%)
Femur (0%)
Tibia (4%)
Fibula (1%)
Tarsal (8%)
Metatarsal (29%)
Toes (56%)

Mean age, years	64 (±16)
Male sex (%)	55
Laterality (%)	
Right	56
Left	36
Axial	8
Amputation (%)	60
Polymicrobial (%)	40

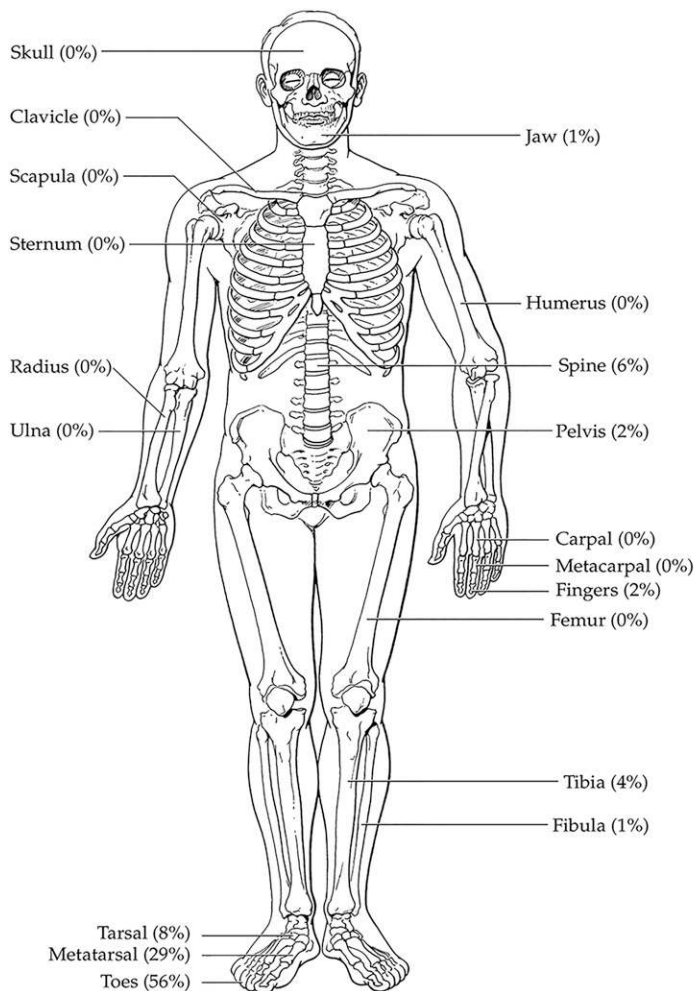| Organisms	%
Staphylococcus aureus	42
Staphylococcus epidermidis	22
Streptococci species	25
Pseudomonas species	8
Anaerobes	5
Escherichia coli	6
Enterobacteriaceae	1
Proteus species	3

Fig. 1-A

Figs. 1-A, 1-B, and 1-C Clinical characteristics according to osteomyelitis etiology. (By permission of the Mayo Foundation for Medical Education and Research. All rights reserved.) **Fig. 1-A** Diabetes mellitus-related osteomyelitis.

Skull (0%)
Clavicle (3%)
Scapula (0%)
Sternum (2%)
Radius (2%)
Ulna (0%)
Jaw (1%)
Humerus (3%)
Spine (35%)
Pelvis (6%)
Carpal (1%)
Metacarpal (1%)
Fingers (1%)
Femur (8%)
Tibia (24%)
Fibula (6%)
Tarsal (6%)
Metatarsal (3%)
Toes (5%)

Fig. 1-B
Hematogenous osteomyelitis.

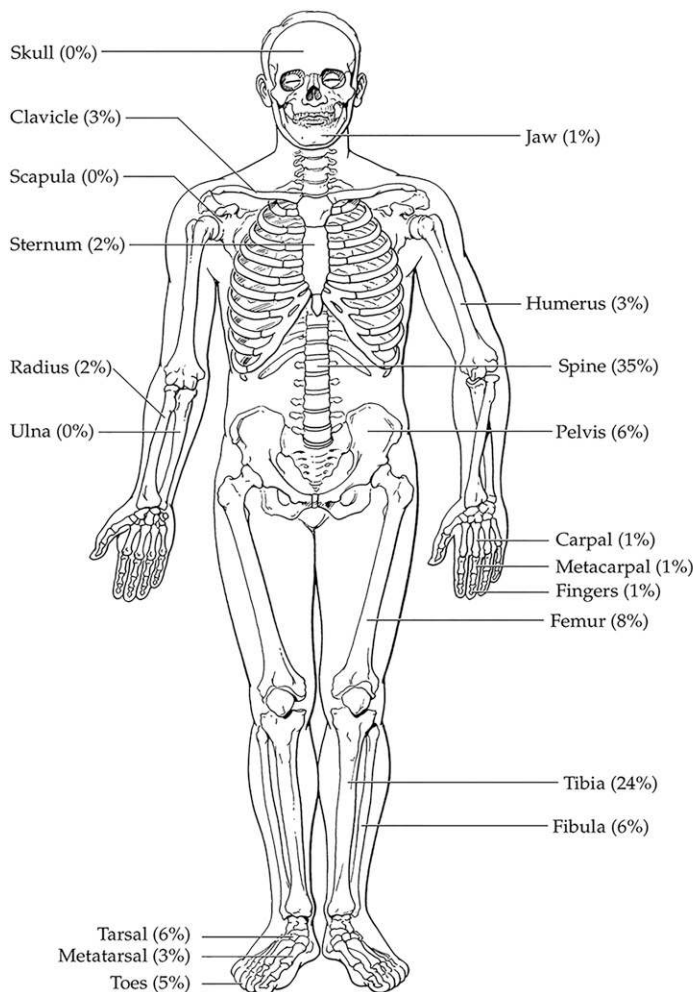| Mean age, years	39±29
Male sex (%)	60
Laterality (%)	
Right	29
Left	29
Axial	42
Amputation (%)	6
Polymicrobial (%)	13
Organisms	**%**
Staphylococcus aureus	48
Staphylococcus epidermidis	7
Streptococci species	8
Pseudomonas species	3
Anaerobes	3
Escherichia coli	1
Proteus species	1

and/or pelvis (19%). Consistent with temporal trends in the distribution of cases by underlying etiology, there was an increase in patients with osteomyelitis of the feet and/or toes and axial locations, but a decline in lower-extremity osteomyelitis of the long bones. In the latest time period, 42% of the cases involved the feet and toes, and 28% involved the axial locations, mostly hematogenous infections of the spine. A small number of patients (6%) had infections in more than one location. In these patients, each location was identified as a primary location.

Staphylococcus aureus infections were responsible for 44% of the cases, followed by Staphylococcus epidermidis (17%) and Streptococcus infections (16%). We observed a decline in the proportion of patients with Staphylococcus infections and an increase in the proportion of patients with culture-negative cases over time. In a total of 217 patients (29%), osteomyelitis resulted in amputations at various levels of the extremity.

Clinical characteristics according to osteomyelitis etiology are illustrated in Figures 1-A, 1-B, and 1-C. We observed notable differences in demographics, location, and affecting organisms according to etiology. For example, the mean age was significantly lower in patients with hematogenous osteomyelitis than

in those with diabetes-related osteomyelitis (thirty-nine versus sixty-four years; p < 0.001). An axial location (mainly the spine) was more common in patients with hematogenous osteomyelitis (42%) than in those with diabetes-related (8%) or contiguous osteomyelitis (16%). Polymicrobial etiology was uncommon in patients with hematogenous osteomyelitis (13%) compared with those with diabetes-related osteomyelitis (40%) and those with contiguous osteomyelitis (35%). Although S. aureus, S. epidermidis, and Streptococcus species were the most common organisms, S. epidermidis, streptococci species, and anaerobes were less common in hematogenous osteomyelitis. Finally, 60% of the diabetes-related osteomyelitis cases resulted in amputations compared with 6% of the hematogenous infections and 24% of the contiguous infections, mostly involving the toes and the tarsal and metatarsal bones.

Age and Sex-Specific Incidence
The overall age and sex-adjusted annual incidence of osteomyelitis over the entire forty-one-year time period was 21.8 cases (95% CI, 20.2 to 23.4) per 100,000 person-years (Table II). The annual incidence was higher in men than in women (27.7 versus 16.7 cases per 100,000 person-years; p < 0.001) and increased with age

TABLE III Trends in Age-Specific Incidence of Osteomyelitis in Olmsted County (1969-2009)								
	Time Period							
	1969-1979		1980-1989		1990-1999		2000-2009	
Age Group (yr)	No.	Incidence Rate	No.	Incidence Rate	No.	Incidence Rate	No.	Incidence Rate
<18	26	7.9	28	9.9	30	9.6	28	8.0
18-29	15	7.3	20	9.4	14	7.1	15	7.2
30-39	8	6.0	23	13.8	19	9.4	16	8.0
40-49	9	9.3	11	9.6	13	7.9	27	13.4
50-59	10	12.8	17	20.6	39	35.8	51	31.2
60-69	11	18.9	16	26.6	48	65.8	44	43.8
70-79	5	12.9	19	45.7	45	88.4	42	64.6
≥80	7	35.0	11	43.4	39	113.5	54	117.3
Total*	91	11.4 (8.8, 13.9)	145	17.5 (14.4, 20.6)	247	28.6 (24.9, 32.4)	277	24.4 (21.5, 27.3)

*The values are given as the age and sex-adjusted incidence rates per 100,000 person-years; values in parentheses are the 95% CI.
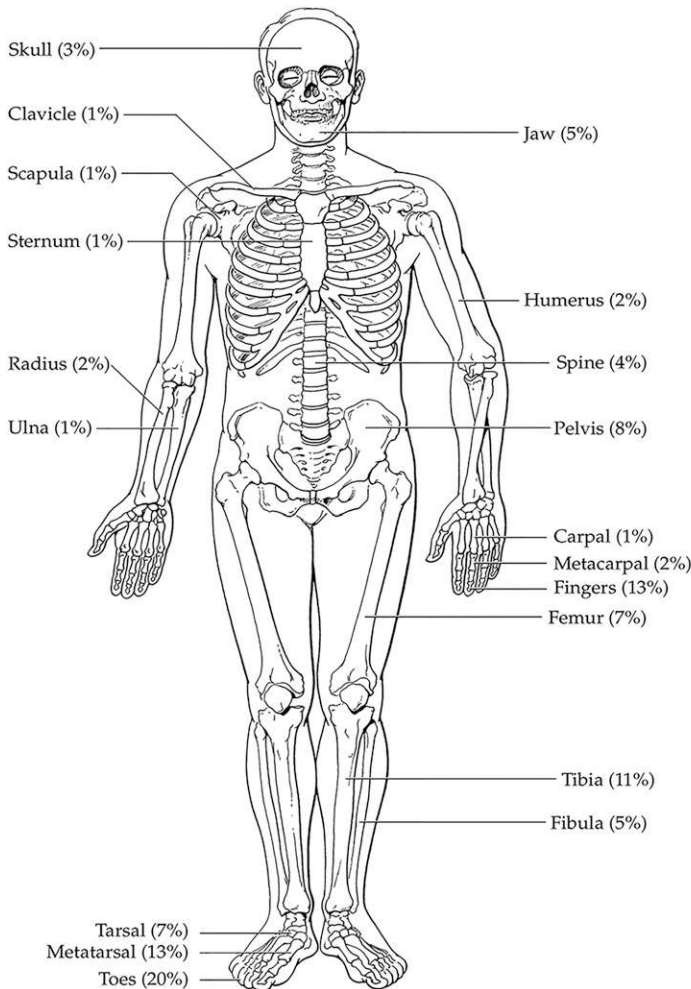

| Skull (3%) |
| Clavicle (1%) |
| Jaw (5%) |
| Scapula (1%) |
| Sternum (1%) |
| Humerus (2%) |
| Spine (4%) |
| Radius (2%) |
| Ulna (1%) |
| Pelvis (8%) |
| Carpal (1%) |
| Metacarpal (2%) |
| Fingers (13%) |
| Femur (7%) |
| Tibia (11%) |
| Fibula (5%) |
| Tarsal (7%) |
| Metatarsal (13%) |
| Toes (20%) |

Mean age, years	49±26
Male sex (%)	60
Laterality (%)	
Right	45
Left	39
Axial	16
Amputation (%)	24
Polymicrobial (%)	35

Organisms	%
Staphylococcus aureus	45
Staphylococcus epidermidis	17
Streptococci species	14
Pseudomonas species	8
Anaerobes	5
Escherichia coli	3
Enterobacteriaceae	3
Proteus species	3

Fig. 1-C
Contiguous osteomyelitis.

TABLE IV Trends in Incidence of Osteomyelitis by Underlying Etiology or Location in Olmsted County (1969-2009)								
	Time Period							
	1969-1979		1980-1989		1990-1999		2000-2009	
Etiology or Location	No.	Incidence Rate*	No.	Incidence Rate*	No.	Incidence Rate*	No.	Incidence Rate*
Diabetes mellitus-related	12	2.3 (1.0, 3.6)	31	4.4 (2.8, 6.0)	83	10.5 (8.2, 12.9)	80	7.6 (5.9, 9.2)
Hematogenous	16	1.4 (0.7, 2.2)	39	4.4 (2.9, 5.9)	38	3.6 (2.4, 4.8)	50	4.2 (3.0, 5.4)
Contiguous	50	6.0 (4.2, 7.8)	55	6.6 (4.7, 8.4)	86	9.7 (7.5, 11.8)	107	9.1 (7.4, 10.9)
Vertebral	3	0.5 (0, 1.0)	10	1.5 (0.5, 2.6)	21	2.5 (1.4, 3.6)	51	4.7 (3.4, 6.0)

*Age and sex-adjusted incidence rates per 100,000 person-years; values in parentheses are the 95% CI.

($p < 0.001$). The male preponderance was evident in all age groups. The annual incidence of osteomyelitis was less than eleven cases per 100,000 person-years until the sixth decade of life. Thereafter, incidence rates increased steeply with age, corresponding to a roughly 50% increase in incidence per decade of life. The highest incidence was among elderly men (128 cases per 100,000 person-years for those at least eighty years old).

Time Trends in Incidence

Incidence rates increased significantly ($p < 0.001$) over time (Table III). The overall age and sex-adjusted incidence was 11.4 cases per 100,000 person-years in the period from 1969 to 1979 and increased to 24.4 cases per 100,000 person-years in the period from 2000 to 2009. These trends were similar for both males and females. Consistent with trends by etiology, incidence rates remained relatively stable among children and young adults (less than fifty years old) but almost tripled among individuals at least sixty years of age.

We observed an increase in incidence in all categories of osteomyelitis over time but most notably in diabetes-related cases and vertebral osteomyelitis (Table IV). The age and sex-adjusted incidence of diabetes-related osteomyelitis increased significantly from 2.3 cases per 100,000 person-years in the period from 1969 to 1979 to 10.5 cases per 100,000 person-years in the period from 1990 to 1999 and then declined to 7.6 cases per 100,000 person-years in the period from 2000 to 2009 ($p < 0.001$). The age and sex-adjusted incidence of vertebral osteomyelitis increased from 0.5 case per 100,000 person-years in the period from 1969 to 1979 to 4.7 cases per 100,000 person-years in the period from 2000 to 2009.

Survival

During follow-up of the entire osteomyelitis cohort, we observed 386 deaths when 141.2 deaths were expected on the basis of age, sex, and calendar year-specific death rates in the Minnesota population. This difference corresponded to a standardized mortality ratio of 2.73 (95% CI, 2.46 to 3.00), indicating that the risk of death is increased at least 2.5-fold.

Discussion

In this population-based study, we describe trends in the incidence of osteomyelitis over time and demonstrate that the epidemiology of osteomyelitis changed substantially over the four decades between 1969 and 2009. Although the published literature provides some information for selected subgroups and subtypes of osteomyelitis (e.g., pediatric patients, methicillin-resistant S. aureus [MRSA]-related disease, and vertebral involvement)[29-31], this study is the first, as far as we know, to describe the population burden of osteomyelitis in the U.S. Our findings corroborate clinical observations and indicate that the incidence has increased over time, and is generally higher in males than in females. We further demonstrate that incidence rates remained relatively stable among children and young adults (less than fifty years old) but almost tripled among the elderly, mostly driven by a secular increase in diabetes-related cases. These intriguing findings underscore the importance of time trends and natural history studies in generating important etiological clues about the condition. Further research is needed to replicate these findings in other populations and to address potential preventive measures to curb the burden of osteomyelitis.

Age is an important factor in determining the etiology of osteomyelitis. The most common etiology in children is hematogenous infections. Previous studies from Norway[32,33] and Lithuania[34] have noted an annual incidence of approximately ten to fourteen cases of hematogenous osteomyelitis per 100,000 children. On the other hand, a lower incidence of acute hematogenous osteomyelitis has been reported in Scotland in two separate studies of the Glasgow population between 1970 and 1997, with an annual incidence of 2.9 new cases per 100,000 population[35,36]. These rates from Europe were much lower than the rates among Maori children, with a crude annual incidence as high as forty-three per 100,000 population[37,38]. In our study, about half (48%) of pediatric osteomyelitis cases were hematogenous infections, 38% were mostly trauma-related contiguous infections, and 14% were iatrogenic or diabetes-related infections. The overall incidence of osteomyelitis in children remained relatively stable over time (eight to ten cases per 100,000 person-years), as did the incidence by etiology. Although S. aureus infections comprised 65% of the pediatric hematogenous osteomyelitis cases in our cohort, we were unable to observe temporal trends with respect to MRSA infections since we did not collect information on methicillin sensitivity[39]. This is the subject of our ongoing analyses.

Older adults are prone to osteomyelitis because they experience a higher frequency of disorders that lead to infection, such as orthopaedic surgeries and diabetes mellitus. Therefore, the higher incidence of osteomyelitis among older individuals in Olmsted County agrees with general clinical observations[2,40]. In particular, vertebral osteomyelitis is a rare condition with a reported incidence of approximately 2.2 to 2.4 cases per 100,000 person-years and a male-to-female ratio of 1.5[21,31,41,42]. We observed a significant increase ($p < 0.001$) in the incidence of vertebral osteomyelitis over time (from 0.5 to 4.7 cases per 100,000 person-years), and the incidence was slightly higher in males than in females. S. aureus is the primary causative organism in the majority of vertebral cases, and some recent studies have described an increase in culture-negative cases as a result of early antibiotic administration[43]. We also observed a similar trend in our cohort, in which half of the vertebral osteomyelitis cases after 2000 were culture-negative.

The largest driver of the increase in osteomyelitis incidence over time in our study was diabetes. The incidence of diabetes-related osteomyelitis quadrupled from 2.3 to 10.5 cases per 100,000 person-years from the 1970s to the 1990s, but we observed a leveling off of the incidence at 7.6 cases per 100,000 person-years in the 2000s. Despite the large number of studies describing diabetic foot ulcers and lower-extremity amputations[44-46], there are few studies specifically on the incidence and outcomes of osteomyelitis in this population. The incidence of foot osteomyelitis among patients with diabetes mellitus is estimated to be approximately 0.3% per year, with a lifetime risk of 4%[47,48]. In our study, 68% of patients with diabetes-related foot osteomyelitis had an amputation. This proportion is similar to those in other studies and remained relatively stable over the forty-one-year time period of our study, indicating that amputation is still relatively common once osteomyelitis develops. These findings are consistent with national data that indicate that forefoot or toe amputations have remained relatively stable over the previous decades[49]. Therefore, efforts should focus on effective prevention and treatment of diabetic foot disease since prognosis is poor once osteomyelitis develops.

The results of this study should be interpreted in light of some potential limitations. Although this is the first population-based report of overall osteomyelitis incidence in the United States that we are aware of, the demographics of Olmsted County may not be representative of some ethnic and racial groups who may have a higher incidence of osteomyelitis[25]. A large proportion of osteomyelitis cases (43%) were based on clinical diagnosis only without surgical sampling or needle aspiration biopsy. Otherwise, all cases were clinically and/or surgically managed as osteomyelitis. A notable strength of this study is the unique ability to review the original medical records to confirm the osteomyelitis diagnosis and collect detailed information on disease characteristics, medical management, and surgical interventions. This is rarely possible in other settings. S. aureus is well known as a leading cause of osteomyelitis and was present as the primary organism in about half of the cases in our cohort. The commonness of S. aureus is also important, given the present-day existence of MRSA strains. Unfortunately, we lack data on methicillin sensitivity and are unable to examine trends in the proportion of MRSA infections. We also did not collect details on tobacco use or the level of amputations. Despite these limitations, the present study documents the population burden of all types of clinically recognized osteomyelitis over four decades using a consistent case validation methodology. Published studies to date have tended to be mostly small retrospective case series focusing on a subset of patients or age groups. As part of our ongoing studies, we are monitoring additional aspects of osteomyelitis, including MRSA infections, the risk and predictors of amputations, and the presence and type of comorbidities.

In conclusion, this comprehensive review of all cases of osteomyelitis in a population-based setting over four decades indicates that osteomyelitis continues to be a substantial burden to patients, providers, and the health-care system. Despite notable changes in the epidemiology of the disease, the overall incidence of osteomyelitis increased over time and this was mostly driven by an increase in diabetes-related cases and vertebral osteomyelitis in recent years. Further research is warranted to replicate these findings in other populations and to address potential preventive measures to curb the increase in the burden of osteomyelitis. ∎

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