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Incidence and Effects of Seasonality on Nonpurulent Lower Extremity Cellulitis After the Emergence of Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

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Abstract

Nonpurulent lower extremity cellulitis (NLEC) is a common clinical diagnosis, with β-hemolytic streptococci and *Staphylococcus aureus* considered to be the most frequent causes. In 1999, the US Public Health Service alerted clinicians to the presence of community-acquired methicillin-resistant *S aureus* (CA-MRSA) infections in 4 children in the upper Midwest. Since then, it has become a well-recognized cause of skin and soft-tissue infections, in particular, skin abscess. A previous population-based study of NLEC in Olmsted County, Minnesota, reported an unadjusted incidence rate of 199 per 100,000 person-years in 1999, but it is unknown whether CA-MRSA subsequently has affected NLEC incidence. We, therefore, sought to determine the population-based incidence of NLEC since the emergence of CA-MRSA. Age- and sex-adjusted incidence (per 100,000 persons) of NLEC was 176.6 (95% CI, 151.5-201.7). Incidence differed significantly between sexes with age-adjusted sex-specific rates of 133.3 (95% CI, 104.1-162.5) and 225.8 (95% CI, 183.5-268.0) in females and males, respectively. Seasonal incidence differed, with rates of 224.6 (95% CI, 180.9-268.4) in warmer months (May-September) compared with 142.3 (95% CI, 112.8-171.9) in colder months (January-April and October-December). Despite emergence and nationwide spread of CA-MRSA since 1999 in the United States, the incidence of NLEC in Olmsted County was lower in 2013 than in 1999, particularly in females. This suggests that CA-MRSA is not a significant cause of NLEC and that NLEC cases are seasonally distributed. These findings may be important in formulation of empirical therapy for NLEC and in patient education because many patients with NLEC are prone to recurrent bouts of this infection.

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Nonpurulent lower extremity cellulitis (NLEC) is one of the most common skin/soft-tissue infections (SSTIs) encountered by clinicians.[1,2] Despite its frequency in clinical practice, few studies describe the incidence of NLEC, which has ranged from 19 to 2740 per 100,000 person-years.[3-6] Most of these studies did not include individual medical record review, and by using only *International Classification of Diseases, Ninth Revision* (ICD-9) codes, their incidence figures included patients with purulent SSTIs because cellulitis and skin abscess share a common *ICD-9* code (681.x). To our knowledge, only 1 study has described the incidence of NLEC in a population-based cohort in the United States (199 per 100,000 person-years in 1999) and included individuals from Olmsted County, Minnesota.[7]

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has been described as early as the 1980s as a cause of bacterial endocarditis in intravenous drug abusers.[8] The first cases of CA-MRSA causing purulent SSTIs were seen in the 1990s in the United States.[9,10] In response to an increase in infections due to CA-MRSA, the US Public Health Service began monitoring the prevalence of CA-MRSA infections in this country. Changes in the prevalence of CA-MRSA in Minnesota have been prospectively monitored by 12 sentinel hospital-based laboratories

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throughout the state.[11] In 2000, the prevalence of CA-MRSA infections among all MRSA infections in Minnesota was 11% and had significantly increased to 33% by the end of 2005.[12] Most CA-MRSA infections were SSTIs, increasing from 75% to 87% between 2000 and 2005.[12]

Whether CA-MRSA has caused a similar increase in NLEC cases, however, remained undefined. Establishing or refuting a causal link between CA-MRSA and NLEC is difficult because microbiologic data are not obtained in the bulk of NLEC cases. Due to the overall increase in SSTI prevalence since the emergence of CA-MRSA, there may be an understandable inference that CA-MRSA may play a role in NLEC. Such inferences may lead to empirical antimicrobial prescribing practices that include unnecessary coverage for CA-MRSA. Therefore, if one could demonstrate that despite the increase in incidence of SSTIs caused by CA-MRSA, the incidence of NLEC had remained unchanged, then this could justify the selection of empirical antibiotic drug therapy for NLEC that does not include coverage for CA-MRSA. In this regard, no studies have evaluated the influence of CA-MRSA on the incidence of NLEC. In the present study, we, therefore, define the incidence of NLEC after the emergence of CA-MRSA in the United States by using the same population-based cohort evaluated by our group in 1999.[7]

METHODS

This retrospective, population-based study was conducted in Olmsted County in adult residents with NLEC from January 1 through December 31, 2013. Medical records were accessible through the Rochester Epidemiology Project (REP), a medical records linkage system for all county-based medical facilities.[13] The initial set of potential cases was identified using the same *ICD-9* codes for cellulitis and abscess as were used in the 1999 study[7] (Supplemental Table 1, available online at http://www.mayoclinicproceedings. org). *Current Procedural Terminology* codes were applied to exclude patients with purulent SSTIs requiring procedural drainage (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

Medical records were reviewed and cases were initially included or excluded by trained nurse abstractors. One of us (J.R.M.) rereviewed cases to confirm that they met the case definition or were appropriately excluded. Another one of us (L.M.B.) independently randomly reviewed 5% of all medical records (n=93); agreement was 96% on medical record classification. Without laboratory gold standards for NLEC diagnosis, previous studies have accepted the evaluating clinician's diagnosis. Our case definition is consistent with that used in recent studies[7,14,15]: a clinician's clinical diagnosis with documentation of acute onset of warmth, erythema, and edema on the lower extremities. Excluded patients had purulent or necrotizing SSTIs, osteomyelitis, secondary skin infections, burn wounds, infected prosthetic material, or infected human or animal bite wounds. Warmer months (May-September) and colder months (January-April and October-December) were predetermined according to seasonal periods identified in the 1999 study.[7]

Statistical Analyses

To examine the incidence of NLEC, count data for cases and total person-time were generated for subsets of the local population defined by sex and age (in single years from age 18-100 years). Numbers of persons in Olmsted County were ascertained via linkage with data sources from the REP, which provide a reliable means for enumerating population estimates.[16] Unadjusted incidence rates were derived using counts of cases in the numerator and the corresponding counts of the county population in the denominator. Age- and sex-adjusted rates were computed based on direct standardization against the 2010 US white population,[17] with 95% CIs estimated using the Poisson distribution.

All incidence rates are presented per 100,000 person-years; calculations of monthly and seasonal incidence rates required correcting the population counts to compensate for an observation period shorter than 1 year (eg, for monthly incidence, counts were multiplied by a constant of 1/12). Smoothing techniques based on the nonparametric loess method were used to illustrate the relation of age, sex, and calendar time with incidence rate, and multivariable Poisson regression