Pathogen-specific Risk of Reactive Arthritis from Bacterial Causes of Foodborne Illness

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ABSTRACT. ***Objective.*** Reactive arthritis (ReA) is a sequelae of common bacterial infections of acute gastroenteritis. We assessed incidence of ReA following *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* infection utilizing a US Department of Defense medical database.

Methods. Subjects with acute gastroenteritis attributed to these pathogens were matched with ≥ 4 unexposed subjects. Medical history was analyzed for 6 months postinfection to assess for incident ReA.

Results. A total of 1753 cases of gastroenteritis were identified. ReA incidence ranged from 0 to 4 per 100,000 person-years.

Conclusion. These data are consistent with prior studies and highlight the need for continued primary prevention efforts. (First Release April 1 2013; J Rheumatol 2013;40:712–14; doi:10.3899/jrheum.121254)

Key Indexing Terms:
PATHOGEN REACTIVE ARTHRITIS FOODBORNE ILLNESS

Roughly 47.8 million cases of illness related to foodborne pathogens occur annually in the United States, with acute affects alone costing billions of dollars[1,2,3]. The major bacterial enteropathogens responsible for morbidity and mortality include nontyphoidal *Salmonella*, *Campylobacter*, *Shigella*, and *Yersinia enterocolitica*[2]. Each of these pathogens has been linked with subsequent development of reactive arthritis (ReA)[4]. ReA is typified as an asymmetric, additive, aseptic arthritis, and the most common antecedent infection associated with ReA is infectious gastroenteritis attributable to one of several bacterial etiologies[5,6].

We assessed incidence of ReA following *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* infection using a US Department of Defense medical database.

MATERIALS AND METHODS

This was a retrospective cohort study in which the medical records of subjects diagnosed with nontyphoidal *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., or *Y. enterocolitica* between 1998 and 2009 were assessed for incident ReA. Data were obtained from the Armed Forces Health Surveillance Center, which oversees the data repository for all medical encounters of active duty US military personnel.

History of medical encounter was obtained for all subjects with an inpatient or outpatient visit in which one of the following (*International Classification of Diseases*, 9th Revision) ICD-9 codes was assigned: non-typhoidal *Salmonella* spp. (003.0 and 003.9), *Shigella* spp. (004), *Campylobacter* spp. (008.43), and *Y. enterocolitica* (008.44). Diagnosis was made by positive cultures of these organisms reported through the electronic database. These subjects were matched by age (± 1 year), sex, number of deployments, medical treatment facility, encounter type (inpatient, outpatient), and time (± 1 year), to up to 4 subjects without documented gastrointestinal infection.

Incident ReA was identified in the 6 months following infection using medical encounters (minimum of 2 separate encounters) with specific ICD-9 codes in any diagnostic position, as follows: Reiter's disease (ICD-9 099.3 and 711.1) and postdysenteric arthritis (ICD-9 711.3). Additionally, the incidence of the following non-ReA rheumatological findings was assessed using nonspecific ICD-9 codes as described[7]. Other covariates recorded included race, military rank, and socioeconomic factors (level of education, marital status).

Incidence was estimated using the number of incident ReA cases by person-time of followup truncated at 6 months postinfection. Modified Poisson regression analyses were used to compare the incidence of ReA or nonreactive rheumatological outcomes across exposure[8]. Two-tailed significance was evaluated using $\alpha = 0.05$. All analyses were performed using SAS 9.2 (SAS Institute).

The sample size for our study was limited by the number of documented cases of *Campylobacter*, *Salmonella*, *Shigella*, and *Yersinia* in this population between 1998 and 2009 and all cases were included in the analysis. A conservative estimate of the number of these subjects was made using the maximum number of events identified in the Defense Medical Epidemiologic Database. This query identified roughly 1500 exposures of interest. Using a 4:1 matching strategy and an estimate of 5 ReA cases/100,000 bacterial infections (0.005%) and a presumed OR of 4.5, a 2-group continuity-adjusted chi-square of equal proportions yielded a 75% power ($1 - \beta$) to detect a significant difference in the proportion of infectious gastroenteritis-exposed individuals developing ReA in the 6-month followup period compared to unexposed subjects[5,6,7].

The study protocol was approved by the Naval Medical Research Center Institutional Review Board in compliance with all applicable US

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The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

Supported by the Military Infectious Disease Research Program.

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Accepted for publication January 7, 2013.

Federal Government regulations governing the protection of human subjects.

RESULTS

We identified 1753 active-duty US military personnel diagnosed with 1 of the 4 pathogens of interest (*Campylobacter* 738; *Salmonella* 624; *Shigella* 376; *Y. enterocolitica* 17). A total of 6765 subjects were included in the referent cohort for a total of 4259 person-years. In general, the demographic data of the study population were representative of the active-duty military population in terms of race (68.5% white), education (62% with high school education), branch of service, rank, and marital status (69% married).

Six of the 1753 (0.3%) active-duty personnel were diagnosed with Reiter's disease (*Shigella* 2, *Salmonella* 3, *Campylobacter* 1) within 6 months of infection [median 22 days; interquartile range (IQR) 0 days, 48 days], yielding the following pathogen-specific incidence rates [per 100,000 person-years (p-y)]: *Shigella* 4.4, *Salmonella* 2.6, *Campylobacter* 0.7, *Yersinia* 0.0. Subjects with pathogen-attributable ReA reported for ReA-related medical care a median of 10 times (IQR: 3, 22) during their active duty service. Care persisted beyond 1 year for the majority (67%) of exposed cases with a median duration of 414 days (IQR 258, 1550 days). One additional case of ReA was noted in the exposed cohort beyond the 6-month window (Day 603). One subject (0.01%) in the reference cohort met the Reiter's disease case definition ($p = 0.002$) 213 days after initiation of surveillance with no documented infectious event. The incidence of non-ReA rheumatological findings over the same time period was similar among exposed and unexposed populations (2.2 and 1.7 per 100,000 p-y, respectively; $p = 0.6$). The rates of all rheumatological findings were similar across all the demographic characteristics assessed (data not shown).

DISCUSSION

We found ReA incidence of 2.2 per 100,000 p-y following infectious gastroenteritis attributable to 1 of 4 bacterial enteropathogens, similar to previous estimates[5,6]. One complication of studies of ReA is terminology[9]. The most common ICD-9 ReA diagnosis used for medical billing purposes is "Reiter's disease" (ICD-9 codes 099.3 and 711.1). However, this diagnosis necessitates the classic triad of symptoms of arthritis, urethritis, and conjunctivitis. An alternative diagnosis of postdysenteric arthritis (ICD-9 code 711.3) is also rarely used. As proposed elsewhere, we attempted to assess a myriad of nonspecific arthralgias and arthropathies that may have been used to characterize ReA lacking a known antecedent infection or the characteristic profile of ReA[7,9]. While incident non-ReA rheumatologic findings were identified, they were diagnosed at a rate similar to that of the unexposed reference cohort. Detailed clinical investigations on these cases were not available; however, such reports may have provided discriminatory information that distinguished postinfective outcomes.

The median duration of ReA-related medical care persisted beyond 1 year, with numerous medical encounters per subject. Previous studies similarly indicated longterm care associated with ReA. Thomson, *et al* reported that 66% of post-*Salmonella* ReA cases had persistent symptoms 5 years postinfection[10]; Curry, *et al* reported over 30% receiving ReA-related medical care 7 years following infectious gastroenteritis[7]. This highlights the potential of significant cost associated with this postinfectious sequela. For example, calculating direct and indirect costs for new-onset ReA cases in Sweden, Söderlin, *et al* reported a median cost per patient of US$4085 (year 2000 dollars)[11].

Limitations are inherent in studies using medical encounter data to assess the incidence of ReA, as reviewed[12,13,14]. Nonetheless, if recent estimates of cases of *Campylobacter*, *Salmonella*, and *Shigella* in the United States[2] are accurate and the incidence estimates reported here and elsewhere reflect the general US population, one can presume that these 3 pathogens are responsible for over 1 million new ReA cases annually. While the morbidity associated with the acute illness attributable to these pathogens is significant, recognition of the longterm health outcomes to include ReA, functional and organic bowel disorders, and neurologic disorders further magnifies the importance of food and water safety and primary prevention efforts to reduce infectious gastroenteritis.

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