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Report No. 00-28

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MILITARY MEDICINE, 166, 9:759, 2001

Prospective Study of Respiratory Infections at the U.S. Naval Academy

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Midshipmen at the U.S. Naval Academy have recently suffered epidemics of upper respiratory tract infections. Seeking to determine cause, in June 1998 we enrolled 1,243 (99.5%) of 1,249 new midshipmen (plebes) and followed them during their first 11 months of training. Eighty-five plebes sought medical attention for acute respiratory disease. Using culture, serologic studies, and polymerase chain reaction, considerable evidence for respiratory pathogen infection was found among the ill subjects: *Chlamydia pneumoniae* in 41 (52.6%), *Mycoplasma pneumoniae* in 19 (25.3%), influenza in 11 (14.2%), *Streptococcus pneumoniae* in 6 (7.3%), and adenovirus in 1 (1.2%). Additionally, 873 (81%) the 1,077 plebes who completed an end-of-year questionnaire complained of having one or more respiratory symptoms (>12 hours) during their first year of school. Of these, 132 (15%) reported that the symptoms significantly affected their performance. Study results suggest that respiratory infections were frequent, had a significant adverse impact on training, and were often attributable to bacterial pathogens.

Introduction

Epidemics of acute respiratory disease are common among military populations, especially those undergoing introductory training.[1] The cause of the epidemics vary with season and geographic site and often include adenoviruses,[2] influenza viruses,[3] *Mycoplasma pneumoniae*,[4,5] *Chlamydia pneumoniae*,[6,7] *Streptococcus pneumoniae*,[1,8] *Bordetella pertussis*,[9] and *Streptococcus pyogenes*.[10] Preventive and control measures are tailored for training sites based on the most prevalent agents.[1,11] Although respiratory disease has often been studied among U.S. enlisted trainees,[12-14] data are sparse regarding U.S. officer trainees. After approximately 400 midshipmen sought medical attention for acute respiratory disease in the autumn of 1997, the Navy Surgeon General invited us to design a study to investigate the causes of respiratory disease at the U.S. Naval Academy in Annapolis, Maryland. This report documents our subsequent study. This is the first prospective study of acute respiratory disease at a U.S. service academy.

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This work has been presented at the following professional meetings: 40th Navy Occupational and Preventive Medicine Workshop, January 29 to February 4, 2000, Norfolk, VA; 6th Annual Uniformed Services Recruit and Trainee Healthcare Symposium, April 24-28, 2000, Chicago, IL; and International Conference on Emerging Infectious Diseases 2000, July 16-19, 2000, Atlanta, GA.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the U.S. Government. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

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This manuscript was received for review in December 2000. The revised manuscript was accepted for publication in April 2001.

Methods

Study Population

Midshipmen receive appointments from all 50 states, U.S. protectorates, and several foreign countries. Newly enrolled midshipmen (plebes) range in age from 17 to 23 years. A typical class is approximately 1,200 in size and composed of approximately 16% women and 19% representatives from various minority groups.

During their first year, plebes are closely monitored by upperclassmen and faculty. If they have no documentation of previous recent vaccination, plebes receive a number of immunizations, including influenza, measles/rubella, tetanus/diphtheria, polio, meningococcus, and varicella. Typically, two or three midshipmen share a small dormitory room. The midshipmen study and train in close contact with their peers in groups or companies of approximately 70 persons. Although individuals spend most of their time within their company, they mix with other companies in dining facilities, athletic areas, classrooms, and other common areas.

Since its establishment, the U.S. Naval Academy has experienced a number of respiratory disease epidemics, particularly during U.S. influenza pandemics.[15] These outbreaks have not been well documented, and until we approached Academy officials, no comprehensive evaluation of the cause of respiratory disease had ever been performed.

Data and Specimen Collection

On June 30 and July 1, 1998, we explained the study to new midshipmen candidates within 24 hours of their arrival at the Academy. After they granted informed consent and completed a one-page questionnaire, we collected throat swabs for streptococcal carriage studies and sera for possible future study.

Clinical data were gathered each time a study participant presented to the outpatient clinic or sick call with a fever of ≥38.0°C and symptoms of acute respiratory infection, such as cough, sore throat, runny nose, wheezing, or chest tightness. Plebes who met the case definition were asked if they would allow medical staff to obtain four throat swabs for microbiologic study and a blood sample for serologic study. Each ill study

subject was also asked to donate a convalescent serum specimen approximately 4 weeks after their acute respiratory infection was first evaluated. Subjects were reevaluated if a subsequent acute episode of acute respiratory infection occurred.

In May 1999, at the end of their first academic year, study subjects completed a one-page questionnaire regarding respiratory disease infections.

Laboratory Studies

Enrollment throat swabs were cultured for streptococcal carriage. Acute respiratory infection specimens were evaluated more comprehensively for the pathogens listed below. With the exception of streptococcal culture and identification, all laboratory analyses were conducted at the Navy Respiratory Disease Laboratory of the Naval Health Research Center in San Diego, California.

Streptococcal Culture and Susceptibility Testing

Throat swabs for streptococci were plated on tryptic soy agar supplemented with 5% sheep blood agar (BAP) and incubated at 37°C in 5% CO_2 for 24 hours under the same conditions. β-Hemolytic streptococci were identified and subcultured to a new BAP. A bacitracin disk was placed onto the medium, and the agar medium was reincubated for an additional 24 hours. Latex agglutination was used to confirm group A streptococcal identification. Colonies resembling *S. pneumoniae* were subcultured onto BAP with an Optochin disk and incubated at 37°C in 5% CO_2 for 24 hours. Optochin sensitivity and bile solubility were used to confirm identification. The antibiotic susceptibility of streptococcal isolates was determined by the standard E-test susceptibility method (AB Biodisk, Piscataway, New Jersey) at the Naval Health Research Center.[16] The minimum inhibitory concentration was defined as the lowest concentration of the antimicrobial agent that prevented visible growth.

Viral Culture

Viral specimens were obtained from the patients' posterior pharynx using a sterile Dacron swab. The swab was placed in viral transport medium, frozen, and stored at −70°C until thawed for viral culture. After culture in rhesus monkey kidney and A549 cells, adenovirus, influenza, parainfluenza, and respiratory syncytial virus were identified using virus-specific fluorescently labeled monoclonal antibodies (Chemicon International, Temecula, California).

M. pneumoniae Culture

Throat cultures were collected using Dacron swabs. Swabs were placed into SP-4 broth[17] and held at −70°C until transport to the Naval Health Research Center. *M. pneumoniae* cultures were performed using standard culture techniques.[18] Briefly, specimens in SP-4 broth were serially diluted and one drop of the concentrated specimen was placed onto an SP-4 agar plate. The SP-4 broth was incubated at 37°C in a non-CO_2 incubator, whereas the SP-4 agar was incubated at 37°C in a CO_2 incubator. Both the SP-4 broth and agar were inspected weekly for a color change or the presence of typical *M. pneumoniae* colonies. Cultures were incubated for 6 weeks before cultures were considered negative.

Serologic Testing

Sera were studied for evidence of infection with *M. pneumoniae* and *C. pneumoniae* as described previously.[19] Indirect fluorescence antibody tests for immunoglobulins (IgM and IgG, Zeus Scientific, Inc., Raritan, NJ) on the paired sera were performed for evidence of *M. pneumoniae* infection. Similarly, the presence of *C. pneumoniae* antibody in sera was determined by an enzyme immunoassay (EIA) detection kit (Labsystems, Franklin, Massachusetts). Positive specimens were then studied with microimmunofluorescence technique (MRL Diagnostics, Cypress, California) to determine antibody titer. For either *M. pneumoniae* or *C. pneumoniae*, a 4-fold increase in IgG or IgM titer or a change in IgM titer from negative to positive was considered serologic evidence of acute infection.[20,21]

S. pneumoniae Polymerase Chain Reaction/EIA

All polymerase chain reaction (PCR) testing was accompanied by use of positive and negative controls. Acute serum samples were extracted using the QIAmp DNA Blood Mini kit (Qiagen, Valencia, California). The extracted samples were subjected to PCR using a similar method described by Dagan et al.[22] and amplified using the two primers (5′-GTGATATTTCTGTAACAGCTACC-3′ and 5′-GAGAATTCCCTGTCTTTTCAAAG-3′) directed against the pneumolysin gene. After amplification, specimens were placed into a 96-well EIA tray, and the manufacturer's instructions for setup and interpretation were followed (Diasorin, Stillwater, Minnesota). A positive test for pneumococcal pneumolysin PCR/EIA was considered evidence of recent infection by *S. pneumoniae*.

M. pneumoniae PCR

A Dacron throat swab was placed into 2.0 mL of 1× Tris-ethylene-diamine tetraacetic acid buffer, and the sample was used in a direct PCR method as described by Ieven et al.[23] The American Type Culture Collection *M. pneumoniae* strain 15537 was used as the positive control, and PCR-grade water was used as the negative control. Briefly, specimens stored at −70°C were thawed and DNA was extracted and amplified using the two primers (5′-GCCACCCTCGGGGGCAGTCAG-3′ and 5′-GAGTCGGGATTCCCCGCGGAGG-3′) directed against the P1 adhesion gene. After amplification, samples were run in a 1.5% agarose gel and visualized after electrophoresis for 2 hours using ethidium bromide dye. The expected DNA fragment was 209 bp. The PCR bands were distinguished using Gel Doc 2000 (Perkin Elmer Biosystems, Foster City, California).

C. pneumoniae PCR

Using the original specimen for *M. pneumoniae* PCR, the sample was subjected to PCR using the method by Madico et al.[24] The American Type Culture Collection *C. pneumoniae* strain VR-1355 was used as the positive control, and PCR-grade water was used as the negative control. Briefly, specimens stored at −70°C were thawed and DNA was extracted and amplified using the two primers CPN90 (5′-GGTCTCAACCCCATCCGTGTC-3′ and CPN91 5′-CGGAAAGCTGTATTTCTACAGTT-3′). After amplification, specimens were run in a 1.5% agarose gel and visualized after electrophoresis for 2 hours using ethidium bromide dye. The expected DNA fragment for *C. pneumoniae* PCR was 196 bp. The PCR bands were distinguished using Gel Doc 2000.

Results

Subject Data Collection

Within 24 hours of arriving at the Academy, 1,243 (99.5%) of the 1,249 plebes granted informed consent and completed enrollment questionnaires. Study subjects reported a mean age of 19 years (range, 17–23 years). Among the 1,243 subjects, 15% were female, 82% were white, 6.1% were black, and 11.1% had other self-reported ethnicities.

Working closely with clinicians, research staff collected specimens from 77 (90.6%) of 85 study subjects who sought medical attention for acute respiratory infection during the 11 months of the study. The weekly incidence of acute respiratory infection demonstrated a peak soon after the plebes arrived at the Academy (Fig. 1). After this small spike, and in contrast to the previous 3 years, no large epidemic of acute respiratory infection was detected during the 11 months of observation.

The 85 ill plebes had an average oral temperature of 38.6°C and missed an average of 2.9 days of training. Seven (58%) of the 12 subjects who received chest radiographs had evidence of an infiltrate. Antibiotics were prescribed for 26 (36%) of the 85 subjects. Upon clinical evaluation, 82.4% complained of sore throat, 78.8% reported cough, 51% had rhinorrhea, 31.8% complained of difficulty breathing, and 27.1% complained of wheezing.

In May 1999, 149 (11.9%) of the original 1,249 plebes had separated from the Academy for various nonmedical reasons. Among the remaining 1,100 plebes, 1,078 (98%) completed an end-of-year questionnaire.

Laboratory Findings

Enrollment throat cultures revealed that plebes had a low prevalence of asymptomatic carriage of streptococci: 0.4% with *S. pneumoniae* and 0.2% with *S. pyogenes*. Among the five *S. pneumoniae* isolates, 100% met resistant or intermediate resistance criteria to penicillin. The two *S. pyogenes* isolates were both sensitive to penicillin, erythromycin, ceftriaxone, levofloxacin, and vancomycin.

Laboratory findings among the 77 plebes who were evaluated for acute respiratory infection revealed that with the exception of 11.5% whose throat cultures grew influenza, few had evidence of viral infection (Table I). In contrast, 48.0% of ill plebes had evidence of *C. pneumoniae* (chiefly by PCR) and/or *M. pneumoniae* (chiefly by serology) infections. Sixteen of the 77 ill plebes had evidence of multiple pathogen infections, with 5 having evidence of acute infections with both *C. pneumoniae* and *M. pneumoniae*. Considering culture, PCR, and serologic tests together, bacterial pathogens explained most of the acute respiratory infections. There was evidence of *C. pneumoniae* in 52.6%, *M. pneumoniae* in 25.3%, and *S. pneumoniae* in 7.3%.

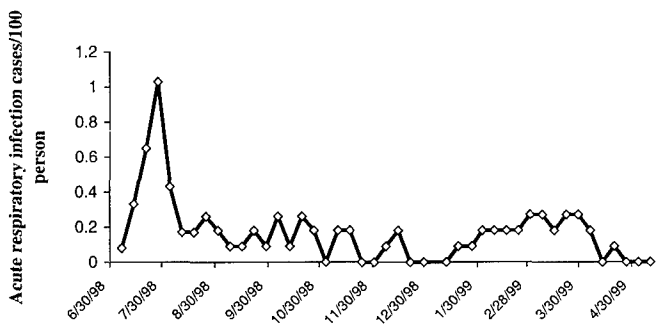

Fig. 1. Incidence of study subjects seeking medical attention for acute respiratory infection.

TABLE I

LABORATORY FINDINGS FROM PLEBES WHO SOUGHT MEDICAL ATTENTION WITH ACUTE RESPIRATORY INFECTIONS, JULY 1998 TO MAY 1999

Laboratory Test	Positive/ No. Tested	Percentage
Culture		
Adenovirus	1/80	1.2
Influenza A	9/78	11.5
Influenza B	2/78	2.6
Respiratory syncytial virus	0/78	0.0
Parainfluenza 1	0/78	0.0
Parainfluenza 2	1/78	1.3
Parainfluenza 3	1/78	1.3
S. pyogenes	0/82	0.0
S. pneumoniae	0/82	0.0
M. pneumoniae	0/81	0.0
PCR		
M. pneumoniae	7/82	8.5
C. pneumoniae	40/82	48.8
S. pneumoniae	6/82	7.3
Serology		
M. pneumoniae	15/78	19.2
C. pneumoniae	2/74	2.7
Overall (at least one positive: culture, PCR, or serology)		
C. pneumoniae	41/78	52.6
M. pneumoniae	19/75	25.3
Influenza A	9/78	11.5
S. pneumoniae	6/82	7.3
Influenza B	2/78	2.6
Parainfluenza	2/78	2.6
Adenovirus	1/80	1.2%

Estimating Acute Respiratory Infection Risk and Morbidity

Enrollment questionnaire data were examined for predictors of acute respiratory tract infection. No difference in risk was observed considering age, gender, race/ethnicity, home of record, previous history of asthma, smoking, bronchitis, pneumonia, or whooping cough (data not shown). However, plebes who had a history of allergies before entering the Academy had a higher risk of developing acute respiratory infection (relative risk = 2.67; 95% confidence interval, 1.64–4.35).

The end-of-year questionnaire revealed that many study subjects had prolonged symptoms consistent with acute respiratory disease infection during their plebe year, but they did not seek medical attention (Table II). Overall, 873 (81%) of the 1,077 midshipmen who completed the end-of-year questionnaire complained of one or more respiratory illness symptoms during their 11 months at the Academy. Among the 873, 132 (15%) self-reported that these symptoms moderately or greatly affected their performance. The most frequently reported symptoms (present for 12 or more hours) were runny nose (69.5%), cough (66.4%), sore throat (58.5%), fever (40.2%), and difficulty breathing (11.8%).

TABLE II

END-OF-YEAR QUESTIONNAIRE FINDINGS AMONG STUDY RESPONDENTS

Question	No. of Respondents	Percent Reporting Yes
Did you experience runny nose for 12 or more hours during this school year?	1,077	69.5
Did you experience cough for 12 or more hours during this school year?	1,076	66.4
Did you experience sore or inflamed throat for 12 or more hours during this school year?	1,077	58.5
Did you experience feverish feeling for 12 or more hours during this school year?	1,071	40.2
Did you experience wheezing for 12 or more hours during this school year?	1,075	16.0
Did you experience difficulty or rapid breathing for 12 or more hours during this school year?	1,076	11.8

Discussion

Although a recent outbreak investigation had been conducted at a U.S. military academy,[5] ours was the first prospective study of acute respiratory disease at a service academy. Although an outbreak did not occur as in the three previous winters, study findings were significant in demonstrating infection cause and the large portion of trainees who were affected by respiratory disease symptoms some time during their first year in training.

Knowing the cause of acute respiratory infections was important because Academy officials were considering whether adenovirus vaccines should be used in this population. Surprisingly, adenovirus explained few infections, and at present the vaccines do not appear to be indicated. In contrast, when adenovirus vaccines are not available, adenovirus often explains up to 90% of acute respiratory disease at enlisted training camps in the United States.[1,25] It was also surprising that jointly *C. pneumoniae* and *M. pneumoniae* accounted for 48.0% of infections. These findings will aid medical providers in selecting empirical antibiotics for the treatment of acute respiratory tract infections.

It is not surprising that a high proportion of plebes reported prolonged respiratory symptoms during training and yet failed to seek medical care. A midshipman's success depends largely on effective time management, and a visit to the medical clinic can be viewed as counterproductive. In studies of Marine trainees in southern California, only 36% sought medical attention despite having a prolonged sore throat and serologic evidence of *S. pyogenes* infection.[10] When stratified by development of acute respiratory infection, end-of-year data suggest that the most symptomatic midshipmen had two to three times the odds of reporting medical respiratory symptoms for more than 12 hours (data not shown).

This study has a number of limitations. The viral culture methods were not optimal for detecting respiratory syncytial virus, and accordingly we may have missed some respiratory syncytial virus infections. We relied on self-referral for evaluation of acute respiratory disease. As indicated by our high proportion of plebes who never sought medical attention but who had prolonged respiratory symptoms, we likely underestimated the true incidence of disease. However, it was not possible to periodically collect specimens from all trainees, and it is likely, as shown by our cases having more symptoms, that we have captured data from the most symptomatic subjects. One might argue that our findings have the most practical implications for therapeutic decisions, so perhaps our sampling limitations do not significantly detract from the study's value. Finally, we did not collect laboratory specimens from asymptomatic trainees, and we are thus unable to determine how different the laboratory findings of our symptomatic trainees were from those of asymptomatic trainees.

This study has a number of strengths. This is the first time a class of U.S. military academy trainees has been prospectively followed for respiratory disease. We had high study enrollment (99.5%), high capture of clinical specimens from subjects with acute respiratory illness (90.6%), and high response to end-of-year questionnaires (98%).

We conclude that during this prospective study of acute respiratory infections among first-year officer trainees at the U.S. Naval Academy, many trainees had symptoms consistent with acute respiratory disease infection, viral causes were uncommon, and *C. pneumoniae* and *M. pneumoniae* were leading causes of clinical respiratory morbidity.

Acknowledgments

We thank the following individuals who assisted us in conducting the study at the U.S. Naval Academy: Tomoko Hooper, MD MPH; Richard J. Thomas, MD MPH; Patricia Petitt, DO; Norman West, Margaret Camarca, Kim Sylvester, and Julia Takafuji of the Uniformed Services University of Health Science (Bethesda, Maryland); Kevin S. Winstead, John R. Daye, Claxton Whiteside, and Pamela Hinton of the Naval Medical Clinic (Annapolis, Maryland); Mark Malakooti, MD MPH, of the Navy Environmental and Preventive Medicine Unit No. 2 (Norfolk, Virginia); Carolyn Fisher, DVM MPH, of the Walter Reed Army Institute of Research (Washington, DC); and Pulak R. Goswami, Debbie Kamens, Pamela Poblete, and Katia Hiliopoulos of the Naval Health Research Center (San Diego, California). This represents report 00-28 supported by the Department of Defense Global Emerging Infections System, under work unit No. 61102A0101.BKX.6425.

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REPORT DOCUMENTATION PAGE

1. Report Date (DD MM YY)	2. Report Type	3. DATES COVERED (from - to)
27/ 07/ 00	New	1998-1999

4. TITLE AND SUBTITLE
Prospective Study of Respiratory Infections at the United States Naval Academy

5a. Contract Number: DoD/HA
5b. Grant Number: Reimbursable
5c. Program Element:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 6609

6. AUTHORS
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Naval Health Research Center
P.O. Box 85122
San Diego, CA 92186-5122

9. PERFORMING ORGANIZATION REPORT NUMBER
Report No. 00-28

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
Chief, Bureau of Medicine and Surgery
MED-02
2600 E St NW
Washington, DC 20372-5300

10. Sponsor/Monitor's Acronyms(s)
BUMED

11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT (maximum 200 words)

During the winters of 1995 through 1997, college students (midshipmen) at the US Naval Academy suffered epidemics of upper respiratory tract infections of unknown causes. We sought to determine to measure the impact of respiratory diseases and to determine etiology. Over the 11 months of active surveillance, 85 midshipmen sought medical attention for acute respiratory disease and were evaluated with PCR, serologic studies, and culture for acute respiratory disease etiology. Among these 85, there was considerable evidence for respiratory pathogen infection: *Chlamydia pneumoniae* in 52.6%, *Mycoplasma pneumoniae* in 33.3%, influenza in 14.2%, *Streptococcus pneumoniae* in 7.3%, and adenovirus in 1.2%, Twenty-two percent of the cases had more than one pathogen identified and 18.8% were negative for all pathogens under study. The ill plebes had an average oral temperature of 38.6°C and missed an average of 2.9 days of training. 873 (81%) the 1077 plebes who completed a end-of-training questionnaire complained of having 1 or more respiratory symptoms (>12 hours) during their first year of training. Of these, 132 (15%) reported that the symptoms moderately or greatly affected their performance. Study data suggested that respiratory infections were frequent, had significant impact upon training, and were often due to bacterial pathogens.

15. SUBJECT TERMS
Respiratory Infection, Naval Academy, bacterial pathogens

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b.ABSTRACT	c. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	5	19b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429