

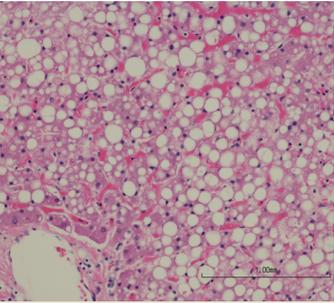


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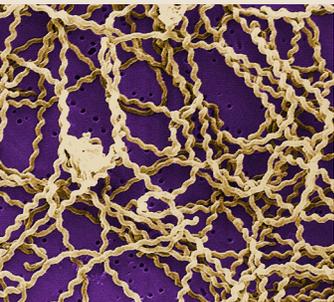
PAGE 2 [Non-alcoholic fatty liver disease \(NAFLD\), active component, U.S. Armed Forces, 2000–2017](#)

Valerie F. Williams, MA, MS; Stephen B. Taubman, PhD; Shauna Stahlman, PhD, MPH



PAGE 12 [Cardiovascular disease-related medical evacuations, active and reserve components, U.S. Armed Forces, 1 October 2001–31 December 2017](#)

Leslie L. Clark, PhD, MS; Gi-Taik Oh, MS; Shauna Stahlman, PhD, MPH



CDC/Rob Weyant

PAGE 17 [Acute flaccid myelitis: Case report](#)

Megan L. Donahue, MD; Shawn S. Clausen, MD, MPH; Allison Malloy, MD, MSc; David H. Dennison, MD; Jennifer Falcon, MD

PAGE 20 [Historical perspective: Leptospirosis outbreaks affecting military forces](#)

Leslie L. Clark, PhD, MS



Non-alcoholic Fatty Liver Disease (NAFLD), Active Component, U.S. Armed Forces, 2000–2017

Valerie F. Williams, MA, MS; Stephen B. Taubman, PhD; Shauna Stahlman, PhD, MPH

During 2000–2017, a total of 19,069 active component service members received incident diagnoses of non-alcoholic fatty liver disease (NAFLD), for a crude overall incidence rate of 77.7 cases per 100,000 person-years. The overall rate of incident NAFLD diagnoses among males was more than 1.5 times the rate among females. Overall incidence rates of NAFLD diagnoses increased with advancing age and were highest among service members aged 50 years or older. Asian/Pacific Islander and Hispanic service members had the highest overall incidence of NAFLD diagnoses compared to those in other race/ethnicity groups. The lowest overall incidence by race/ethnicity was observed among non-Hispanic black service members. Crude annual incidence rates of NAFLD diagnoses increased 12-fold between 2000 and 2017. During this period, annual rates of incident NAFLD diagnoses increased in both sexes and in all age groups. Increases in annual rates were seen over time in all race/ethnicity groups and in all services. More than two-thirds of incident NAFLD cases had one or more diagnosed metabolic comorbidities, with dyslipidemia affecting the greatest percentage of cases, followed by obesity/overweight and hypertension. The percentage of NAFLD cases with 2 or more metabolic comorbidities increased 36.0% during the 18-year surveillance period from 22.2% in 2001 to 30.2% in 2017. Selected recommendations from the American Association for the Study of Liver Diseases 2018 practice guidance document for the diagnosis and management of NAFLD are discussed.

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disorders, beginning as simple non-alcoholic fatty liver (NAFL) which can progress into non-alcoholic steatohepatitis (NASH) and fibrosis, potentially resulting in cirrhosis and even hepatocellular carcinoma.^{1,2} A diagnosis of NAFL requires imaging or histologic evidence of $\geq 5\%$ hepatic steatosis (without inflammation or fibrosis) in the absence of other secondary causes of hepatic fat accumulation such as heavy alcohol consumption, other liver disease, or hepatotoxic medications.^{2,3} In NASH, hepatic steatosis is associated with hepatocellular injury in the form of hepatocyte ballooning and/or lobular inflammation (with or without fibrosis) that may be

histologically indistinguishable from alcoholic steatohepatitis.³ A diagnosis of NASH requires histological evidence of hepatic steatosis through liver biopsy. However, biopsy is expensive, requires expertise for interpretation, and carries some morbidity risk; as such, liver biopsy is generally restricted to more severe cases.³ The global prevalence of NASH in the general population is estimated to be approximately 2% to 7%.⁴

NAFLD is strongly associated with the metabolic syndrome (MetS), a cluster of metabolic abnormalities that directly increases risk of multiple chronic diseases and mortality.^{5,6} MetS is characterized by abdominal obesity, dyslipidemia, elevated fasting plasma glucose level, and

WHAT ARE THE NEW FINDINGS?

This is the first *MSMR* report of the incidence of non-alcoholic fatty liver disease (NAFLD) in the U.S. Armed Forces. This relatively rare disorder was diagnosed in 19,069 service members during 2000–2017 (rate: 77.7 cases per 100,000 person-years). However, incidence of NAFLD increased rapidly, from 12.6 to 152.8 cases per 100,000 person-years between 2000 and 2017.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Service members with severe NAFLD resulting in impaired liver function are unable to perform their military duties and are disqualified from service. There is no cure for NAFLD; instead, treatment is aimed at preventing risk factors and may include physical exercise and low fat diet to reduce body weight.

hypertension.⁶ There is a well-established bidirectional association between NAFLD and components of MetS; features of MetS are highly prevalent in patients with NAFLD and MetS components increase the risk of developing NAFLD.^{4,7,8} A recent large U.S. administrative data-based study demonstrated that the costs associated with the care for NAFLD, independent of its metabolic comorbidities, are very high, especially at first diagnosis.⁹

Many of the studies of NAFLD in the general U.S. population employed imaging or other indirect methods to determine the prevalence of this condition.^{4,10-17} The prevalence of NAFLD in the U.S. diagnosed by ultrasonography was reported to be 24%.¹⁰⁻¹⁷ NAFLD prevalence, as determined by noninvasive methods such as the Fatty Liver Index, serum liver enzyme tests, or ICD diagnostic coding, was estimated at 21%.⁴

Despite an increasing recognition of NAFLD as the most common cause of

chronic liver disease, few studies have systematically examined the incidence of this condition over time in the general U.S. population.³ One recent U.S. administrative data-based study found that the age- and sex-adjusted rate of incident NAFLD diagnoses increased 5-fold, from 62 cases per 100,000 person-years (p-yrs) in 1997 to 329 cases per 100,000 p-yrs in 2014.¹⁸ When stratified by age group, the increase in rates of incident NAFLD diagnoses was highest among young adults aged 18–39 years.¹⁸ A study of NAFLD among a cohort of U.S. veterans during 2003–2011 found that the annual age-adjusted incidence rates of the condition remained stable and ranged from 3.2 cases per 100 persons in 2003 to 2.5 cases per 100 persons in 2011.¹⁷ However, the incidence increased at significantly greater rates among those less than 45 years of age compared to those 45 years or older.¹⁷

At the time of this report, there were no published studies of NAFLD incidence over time among active component U.S. military personnel. Examining the incidence rates of NAFLD and their temporal trends among active component U.S. military members can provide insights into the future burden of NAFLD on the MHS. To address this gap, the current analysis summarizes the overall and annual incidence rates of NAFLD among active component U.S. service members during 2000–2017 by demographic and military characteristics and describes the percentages of NAFLD cases with selected metabolic comorbidities (type 2 diabetes mellitus, hypertension, dyslipidemia, obesity, and the metabolic syndrome) within 1 year of incident NAFLD diagnosis. In addition, trends in the percentages of NAFLD cases with 0, 1, or multiple metabolic comorbidities (not including the metabolic syndrome) within 1 year of incident NAFLD diagnosis are described.

METHODS

The surveillance period was 1 January 2000 through 31 December 2017. The surveillance population included all individuals who served in the active component of

TABLE 1. ICD-9 and ICD-10 diagnostic codes for excluded conditions

Condition	ICD-9 ^a	ICD-10 ^a	
Hepatitis (viral and autoimmune)	070.*	B15.*, B16.*, B17.*, B18.*, B19.*	
	571.4	K73.9	
	571.41	K73.0	
	571.42	K75.4	
	571.49	K73.2, K73.8	
	573.1	K77	
	573.2	K77	
	V02.6*	B18.*	
	Alcoholic liver disease	571	K70.0
		571.1	K70.1*
571.2		K70.3*, K70.2	
571.3		K70.9	
--		K70.4*	
Alcohol-related MH disorders	291.*, 303.*, 305.0*	F10.*	
Other	275.1	E83.01	
	571.6	K74.3, K74.4, K74.5	

^aAn asterisk (*) indicates that any subsequent digit/character is included

the Army, Navy, Air Force, or Marine Corps at any time during the surveillance period. Diagnoses were ascertained from administrative records of all medical encounters of individuals who received care in fixed (i.e., not deployed or at sea) medical facilities of the Military Health System (MHS) or civilian facilities in the purchased care system documented in the Defense Medical Surveillance System (DMSS).

Cases of NAFLD were defined by at least one inpatient or outpatient medical encounter with a qualifying diagnosis in any diagnostic position. Qualifying diagnoses included other chronic non-alcoholic liver disease (ICD-9: 571.8), unspecified chronic liver disease without mention of alcohol (ICD-9: 571.9), other specified inflammatory liver diseases including non-alcoholic steatohepatitis (NASH) (ICD-10: K75.81), other specified inflammatory liver diseases (ICD-10: K75.89), and fatty change of liver not elsewhere classified (ICD-10: K76.0). A similar case definition was employed in several large U.S. administrative data-based studies of NAFLD prevalence and incidence.^{9,19–22} The incident date was the date of the first qualifying medical encounter with a defining diagnosis of NAFLD. An individual could be counted as

an incident case of NAFLD once per lifetime. Service members with case-defining NAFLD diagnoses before the start of the surveillance period (i.e., prevalent cases) were excluded from the analysis.

Consistent with several published studies of NAFLD incidence using data from electronic medical records, individuals with diagnoses of viral or autoimmune hepatitis, alcoholic liver disease, alcohol-related mental health disorders, disorders of copper metabolism (Wilson's disease), or biliary cirrhosis recorded in any diagnostic position of any inpatient or outpatient medical encounter occurring on or prior to the incident NAFLD diagnosis were excluded from the analysis.^{9,18,20,23} A list of ICD codes for these excluded conditions is provided in **Table 1**.

Incidence rates were calculated as incident NAFLD diagnoses per 100,000 p-yrs of active component service. If a service member had more than one case-defining encounter on the same day, a diagnosis of other specified inflammatory liver diseases (including NASH) was prioritized over other diagnoses. After this prioritization, if there were multiple case-defining encounters on the same day, inpatient encounters were prioritized over outpatient

TABLE 2. ICD-9 and ICD-10 codes for comorbidities

Condition	ICD-9 ^a	ICD-10 ^a
Type 2 diabetes mellitus	250.0, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92	E11.*
Hypertension	401.* 402.* 403.* 404.*	I10 I11.* I12.* I13.*
Dyslipidemia	272.*	E78.0*, E78.1-E78.6, E78.70, E78.79, E78.8*, E78.9
Overweight	278.02, V85.2*, V85.53	E66.3, Z68.25-Z68.29
Obese	278.00, 278.03, V85.3*, V85.54	E66.09, E66.1, E66.8, E66.9, Z68.3*
Morbidly obese	278.01, V85.4*	E66.01, E66.2, Z68.4*
Nonspecified overweight/ obesity	278	---
Metabolic syndrome	277.7	E88.81

^aAn asterisk (*) indicates that any subsequent digit/character is included

encounters. Median age at incident NAFLD diagnosis was computed overall, by sex, and by race/ethnicity group. In addition, the proportion of incident NAFLD cases during 2016–2017 who had NASH as the case-defining diagnosis was summarized by demographic characteristics.

Type and frequency of metabolic comorbidities among the incident NAFLD cases were described. Comorbidities were defined by at least one inpatient or outpatient medical encounter with a diagnosis for type 2 diabetes mellitus, hypertension, dyslipidemia, overweight/obesity, or the metabolic syndrome in any diagnostic position in the year before or the year after the incident case diagnosis for NAFLD (**Table 2**). The proportions of total NAFLD cases associated with 0, 1, or multiple metabolic comorbidities during each calendar year also were computed.

Finally, the annual numbers and rates of abdominal ultrasound testing were calculated to examine the potential impact of screening practices on the ascertainment and diagnosis of NAFLD. Abdominal

FIGURE 1. Annual rates of incident NAFLD diagnoses, active component, U.S. Armed Forces, 2000–2017

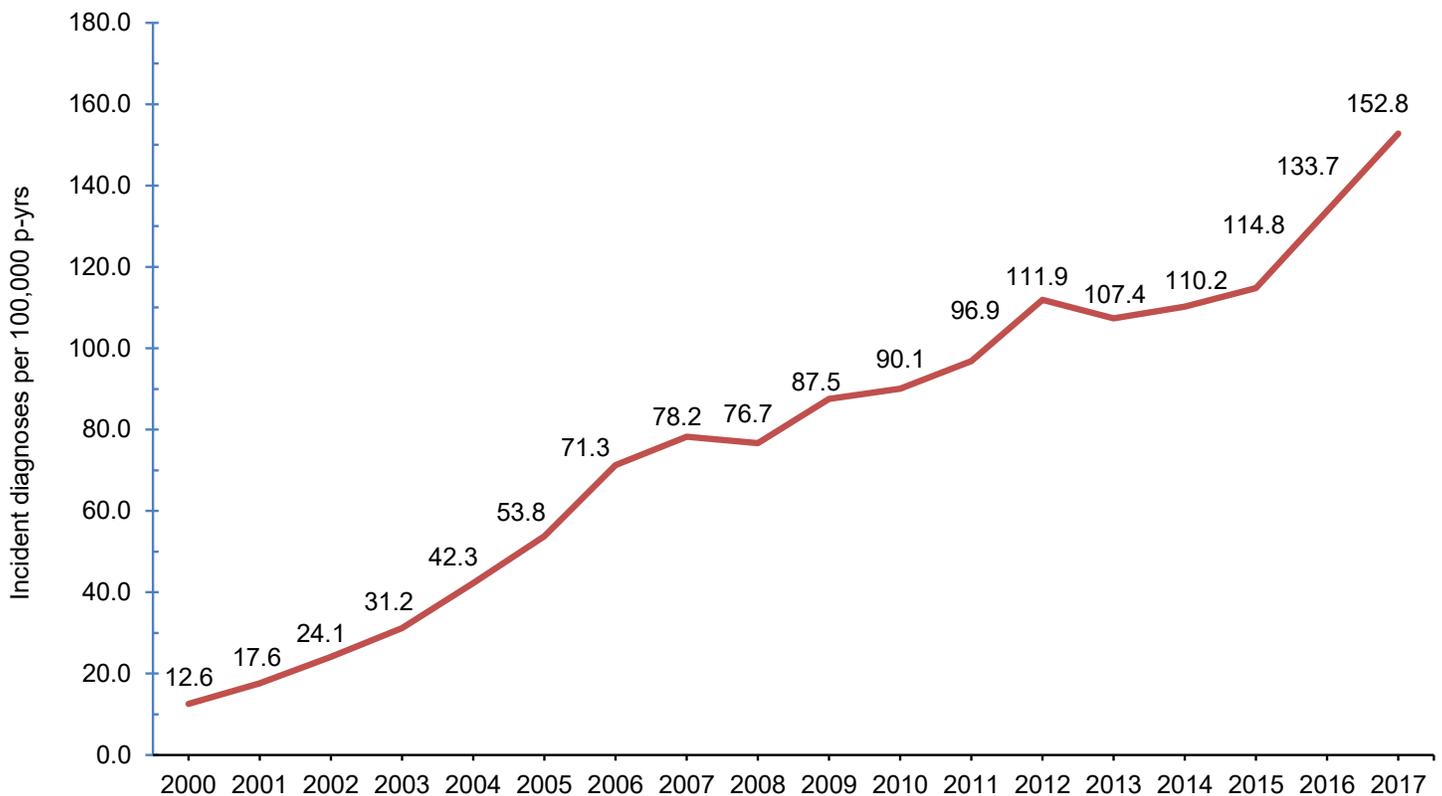


TABLE 3. Incident diagnoses and incidence rates^a of NAFLD by demographic and military characteristics, active component, U.S. Armed Forces, 2000–2017

	Total 2000–2017	
	No.	Rate ^a
Total	19,069	77.7
Inpatient	782	3.2
Outpatient	18,287	74.5
Sex		
Male	17,258	82.6
Female	1,811	49.8
Age group (years)		
≤24	2,010	20.5
25–29	2,860	51.9
30–34	3,284	88.8
35–39	4,318	144.7
40–49	5,822	250.3
50+	775	353.0
Race/ethnicity		
Non-Hispanic white	11,458	76.4
Non-Hispanic black	2,037	48.5
Hispanic	3,197	112.4
Asian/Pacific Islander	1,031	113.8
Other/unknown	1,346	85.0
Service		
Army	7,195	79.2
Navy	4,778	78.6
Air Force	5,998	99.4
Marine Corps	1,098	32.9
Rank/grade		
Junior enlisted (E1–E4)	3,369	31.2
Senior enlisted (E5–E9)	11,985	124.0
Warrant officer (W01–W05)	463	147.6
Junior officer (O1–O3)	1,081	48.1
Senior officer (O4–O10)	2,171	142.6
Military occupation		
Combat-specific ^b	1,783	52.3
Motor transport	408	53.5
Pilot/air crew	569	60.9
Repair/engineering	5,820	80.9
Communications/intelligence	5,073	92.0
Health care	2,110	101.3
Other	3,306	71.2

^aRate per 100,000 person-years

^bInfantry/artillery/combat engineering/armor

ultrasound testing was defined by having a CPT code for real time complete (CPT: 76700) or limited (CPT: 76705) abdominal ultrasound with image documentation, or an inpatient procedure for diagnostic ultrasound of the abdomen and retroperitoneum (ICD-9 PR: 88.76) or ultrasonography of the abdomen (ICD-10 PR: BW40ZZZ). One test per person per day was counted.

RESULTS

During 2000–2017, a total of 19,069 active component service members received incident diagnoses of NAFLD, for a crude overall incidence rate of 77.7 cases per 100,000 p-yrs (Table 3). Affected service members had a total of 37,236 medical encounters that included a diagnosis for NAFLD during the surveillance period (data not shown). The vast majority of NAFLD cases (96%) were diagnosed in an outpatient setting (Table 3).

The overall rate of incident NAFLD diagnoses among males was more than 1.5 times the rate among females (82.6 cases per 100,000 p-yrs and 49.8 per 100,000 p-yrs, respectively) (Table 3). Overall incidence rates of NAFLD diagnoses increased with advancing age and the rate was highest among service members aged 50 years or older (353.0 per 100,000 p-yrs). Asian/Pacific Islander and Hispanic service members had the highest overall rates of NAFLD diagnoses compared to those in other race/ethnicity groups, at 113.8 and 112.4 cases per 100,000 p-yrs, respectively. The lowest overall rate by race/ethnicity was observed among non-Hispanic black service members (48.5 per 100,000 p-yrs).

Across the services, the highest overall rate of incident NAFLD diagnoses was observed among Air Force members (99.4 per 100,000 p-yrs) and lowest among those in the Marine Corps (32.9 per 100,000 p-yrs). The overall incidence rate of NAFLD diagnoses among warrant officers (147.6 per 100,000 p-yrs) and senior officers (142.6 per 100,000 p-yrs) was markedly higher than the overall rates among junior enlisted service members (31.2 per 100,000 p-yrs) and junior officers (48.1 per 100,000 p-yrs). Service members working in

healthcare occupations (101.3 per 100,000 p-yrs) had the highest incidence of NAFLD diagnoses compared to those in other military occupations.

Overall, the median age at case-defining NAFLD diagnosis was 36 years (interquartile range [IQR]=29–41) (data not shown). The median age at NAFLD diagnosis was 37 years (IQR=30–41) for males and 33 (IQR=25–41) years for females (data not shown). Crude comparisons of the age at NAFLD diagnosis by race/ethnicity group showed that Hispanic service members had the youngest median age at diagnosis (median 34 years, IQR=28–40), while Asian/Pacific Islander and non-Hispanic black service members had the oldest median ages at diagnosis (median 38 years, IQR=32–43 for both groups) (data not shown).

Crude annual incidence rates of NAFLD diagnoses increased approximately linearly from 12.6 per 100,000 p-yrs in 2000 to 152.8 per 100,000 p-yrs in 2017 (Figure 1). This increasing trend was observed among both male and female service members, with annual rates of NAFLD among males consistently higher than rates among females (Figure 2). Increases in rates of incident NAFLD diagnoses over time occurred among all age groups, although the most pronounced increases occurred among service members who were 51 years or older and among those aged 41–50 years (data not shown). During the 18-year surveillance period, increases in annual rates of incident NAFLD diagnoses were seen in all race/ethnicity groups; Asian/Pacific Islander and Hispanic service members showed the greatest increases over time and non-Hispanic black service members showed the smallest increase (Figure 3). Annual incidence rates of NAFLD diagnoses increased in each service during the surveillance period (Figure 4). During each year of the period, rates of incident NAFLD diagnoses were highest among Air Force members and lowest among Marine Corps members.

Between 2000 and 2017, more than a third of the 19,069 incident cases of NAFLD had a comorbid diagnosis of dyslipidemia (n=7,954, 41.7%) recorded during a medical encounter in the year before or the year after the case-defining NAFLD diagnosis; most of these dyslipidemia diagnoses

FIGURE 2. Annual rates of incident NAFLD diagnoses, by sex, active component, U.S. Armed Forces, 2000–2017

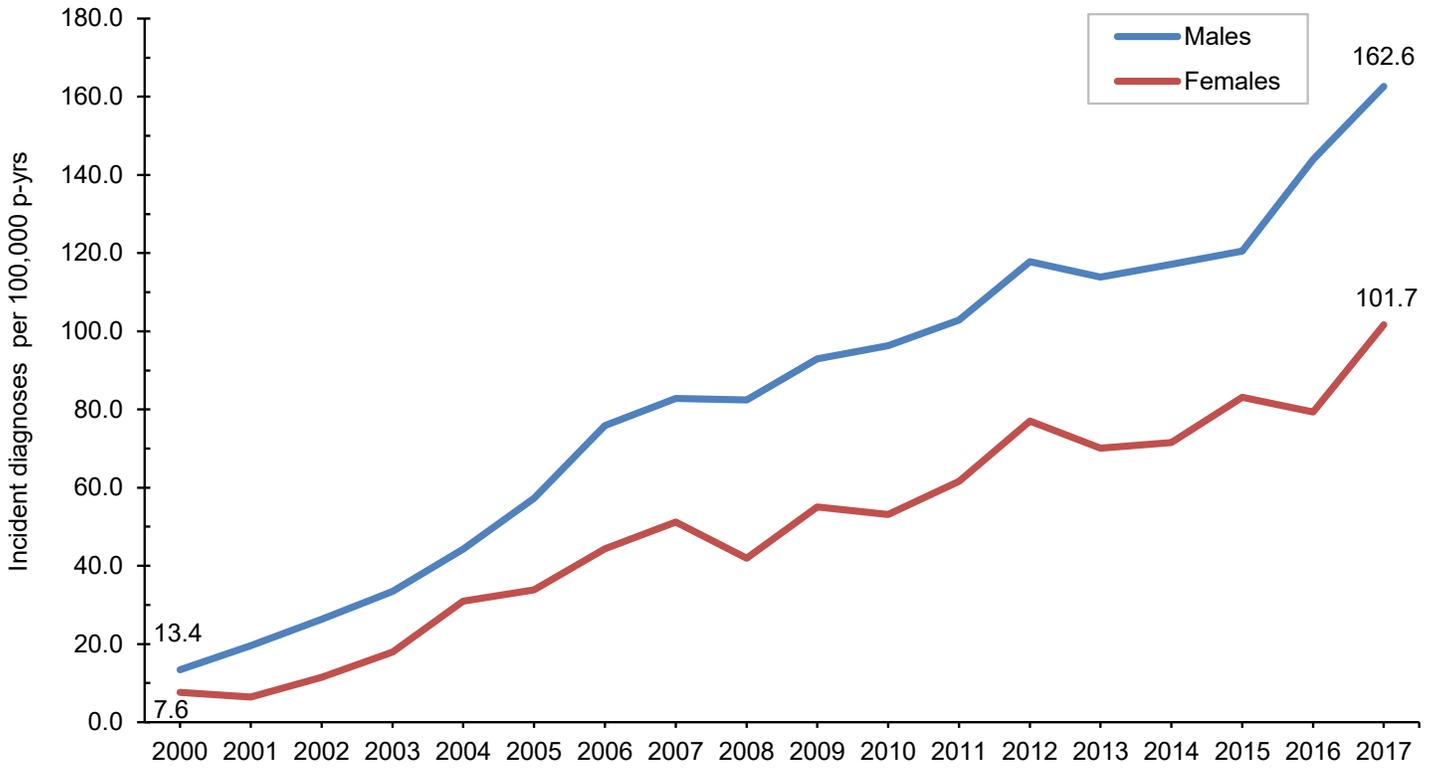


FIGURE 3. Annual rates of incident NAFLD diagnoses, by race/ethnicity, active component, U.S. Armed Forces, 2000–2017

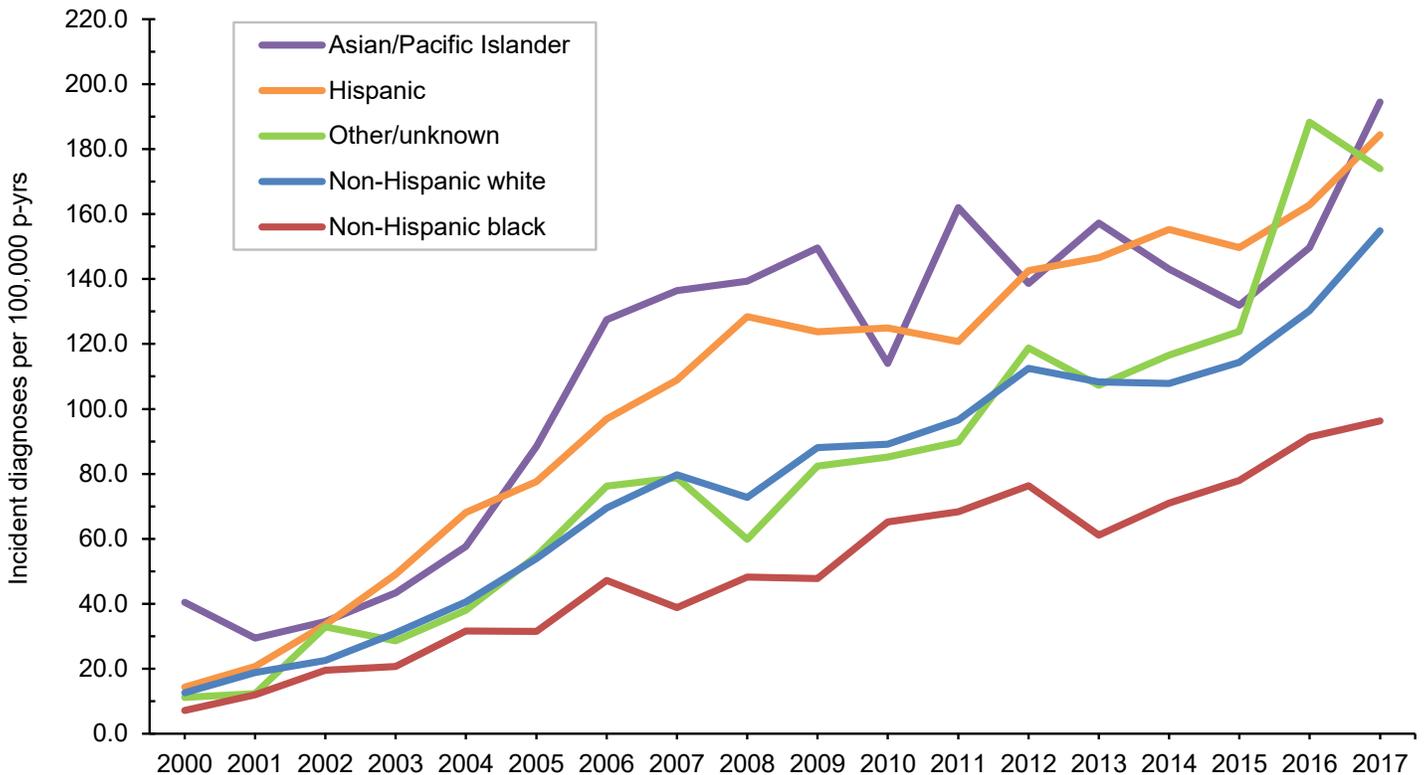


FIGURE 4. Annual rates of incident NAFLD diagnoses, by service, active component, U.S. Armed Forces, 2000–2017

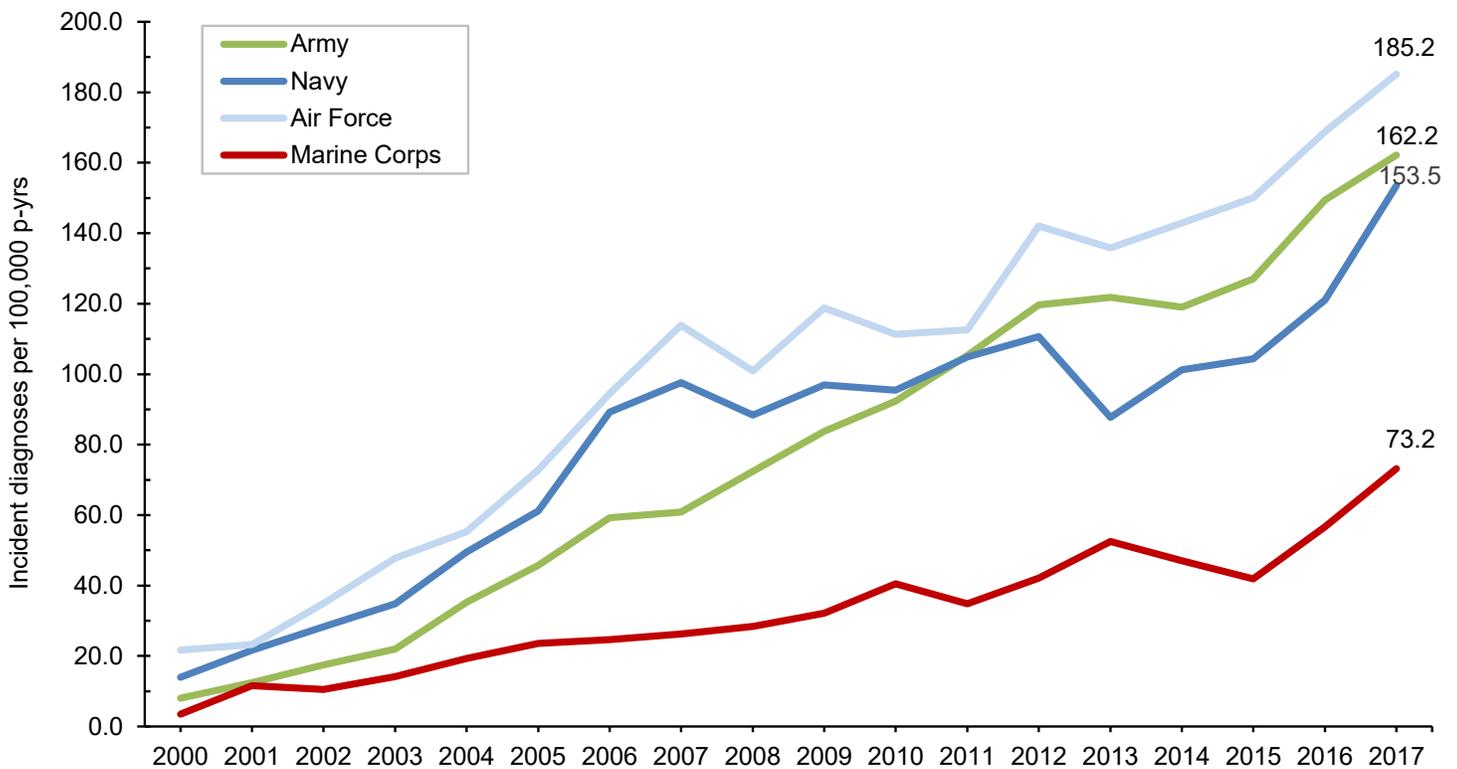


TABLE 4. Number and percentage^a of NAFLD cases with selected comorbidities within 1 year of incident NAFLD diagnosis

Condition	1 year before or 1 year after		1 year before	
	No.	%	No.	%
Type 2 diabetes mellitus	909	4.77	567	2.97
Hypertension	7,136	37.42	5,845	30.65
Dyslipidemia	7,954	41.71	6,316	33.12
Obese or overweight	7,540	39.54	5,393	28.28
Overweight	2,875	15.08	1,883	9.87
Obese	6,028	31.61	4,244	22.26
Morbidly obese	624	3.27	387	2.03
Nonspecific overweight/obesity	3	0.02	1	0.01
Metabolic syndrome	348	1.82	197	1.03

^aCases may have more than one comorbidity

occurred in the year prior to the incident NAFLD diagnosis (n=6,316, 33.1%) (Table 4). Obesity/overweight (n=7,540, 39.5%) and hypertension (n=7,136, 37.4%) were the next most frequently diagnosed comorbidities, with the majority of these diagnoses preceding the case-defining diagnosis of NAFLD (n=5,393, 28.3% and n=5,845,

30.7%, respectively). Type 2 diabetes was diagnosed within a year of the case-defining NAFLD diagnosis among 4.8% (n=909) of cases and metabolic syndrome was diagnosed among 1.8% (n=348).

More than two-thirds (n=13,474, 70.7%) of incident NAFLD cases had one or more diagnosed metabolic comorbidities

including hypertension, dyslipidemia, obesity, or type 2 diabetes. Among all incident NAFLD cases during 2000–2017, the proportions affected by 1, 2, 3, or 4 metabolic comorbidities were 32.9%, 24.6%, 11.3%, and 1.9%, respectively (Table 5). Most cases of NAFLD had at least one metabolic comorbidity diagnosed within the year prior to their incident NAFLD diagnoses (n=11,318, 59.4%). From 2000 through 2017, the percentage of incident NAFLD cases with at least one metabolic comorbidity fluctuated between 55.4% in 2001 and 74.8% in 2012. The percentage of NAFLD cases with 2 or more metabolic comorbidities increased 36.0% during the 18-year period from 22.2% in 2001 to 30.2% in 2017 (Figure 5). The percentage of NAFLD cases with 3 or more metabolic comorbidities increased from 5.3% in 2000 to 11.2% in 2017.

Of the 3,622 incident NAFLD cases diagnosed during 2016–2017, 278 (7.7%) had NASH (ICD-10: 75.8) as the case-defining diagnosis (data not shown). More than half (56.8%) of these cases were 35 years or older at NASH diagnosis. The

TABLE 5. Percentage of NAFLD cases with zero, one, two, three or four comorbidities^a within 1 year of the incident NAFLD diagnosis

	1 year before/after		1 year before	
	No.	%	No.	%
0 comorbidities	5,595	29.34	7,751	40.65
1 comorbidity	6,276	32.91	6,144	32.22
2 comorbidities	4,684	24.56	3,702	19.41
3 comorbidities	2,161	11.33	1,315	6.90
4 comorbidities	353	1.85	157	0.82

^aNot including the metabolic syndrome

majority of NAFLD cases with NASH as the case-defining diagnosis were non-Hispanic white (56.1%) and over one-fifth were Hispanic (21.9%) (data not shown).

The incidence rate of abdominal ultrasound testing more than doubled from 217.8 tests per 100,000 p-yrs in 2000 to a peak of 591.7 tests per 100,000 p-yrs in 2015. This peak in rates was followed by a marked decrease to 391.1 tests per 100,000 p-yrs in 2017 (Figure 6).

EDITORIAL COMMENT

In this large and demographically diverse population of active component U.S. service members, crude annual rates of incident NAFLD diagnoses increased 12-fold between 2000 and 2017. During this period, annual rates of NAFLD increased in both sexes and in all age groups. Increases in annual rates were seen over time in all race/

ethnicity groups, with the greatest increases seen among Asian/Pacific Islander and Hispanic service members and the smallest increases seen in non-Hispanic black service members. The findings by sex and race/ethnicity mirror the results of NAFLD incidence studies in the general U.S. population.¹²⁻¹⁸ As in the general population, the increase in NAFLD incidence among active component service members may be due, at least in part, to an increase in median BMI and increasing rates of clinical overweight.^{18,24} However, given the increasing trend in abdominal ultrasound testing seen in the MHS during 2000–2015, increased use of such imaging may also be a contributor to the increasing trend in NAFLD diagnosis rates observed among active component service members in the current study.

The overall incidence of NAFLD diagnoses increased with advancing age and was higher among males than females. The age-related rise of NAFLD incidence observed in many other studies has been attributed to increasing prevalence of MetS components with increasing age in the general population.^{25,26} However, some recent administrative

FIGURE 5. Percentage of NAFLD cases with 0, 1, 2, or 3+ comorbidities within 1 year of incident NAFLD diagnosis, active component, 2000-2017

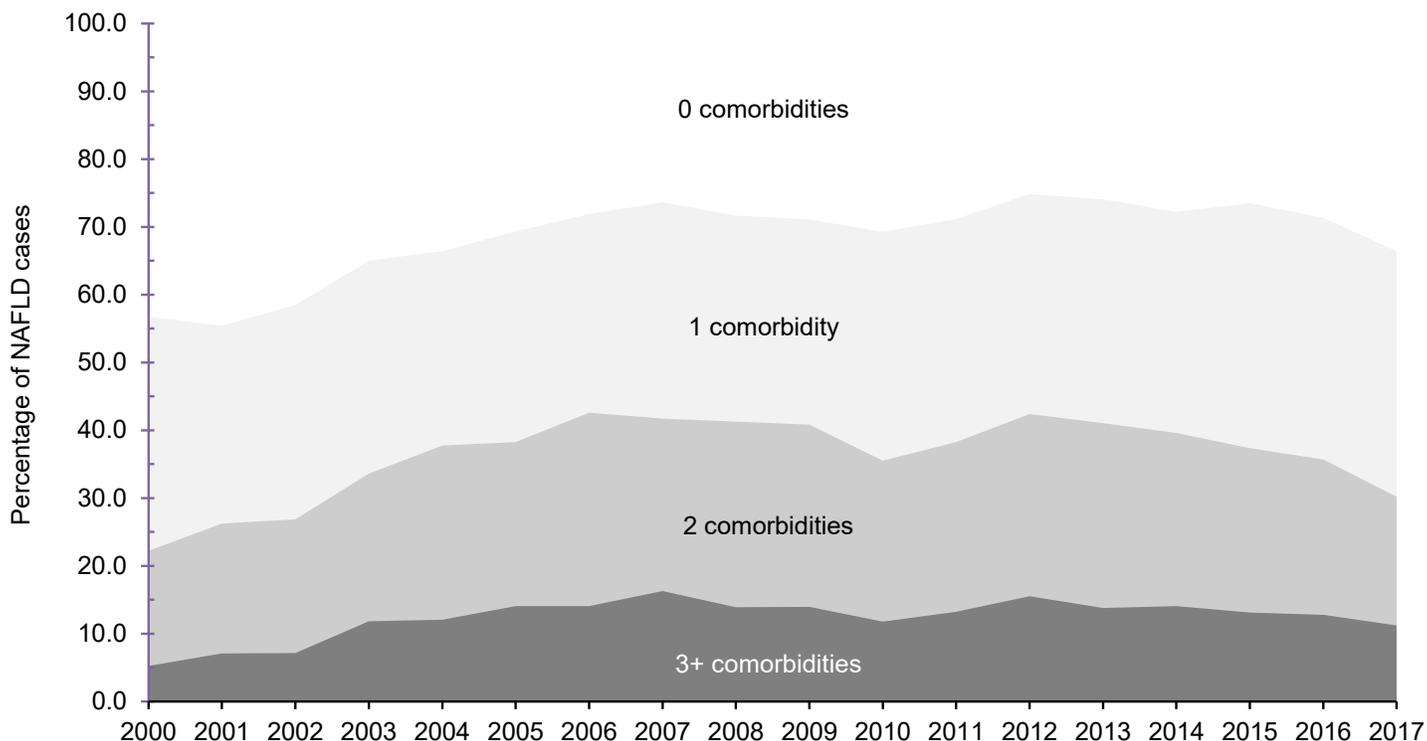
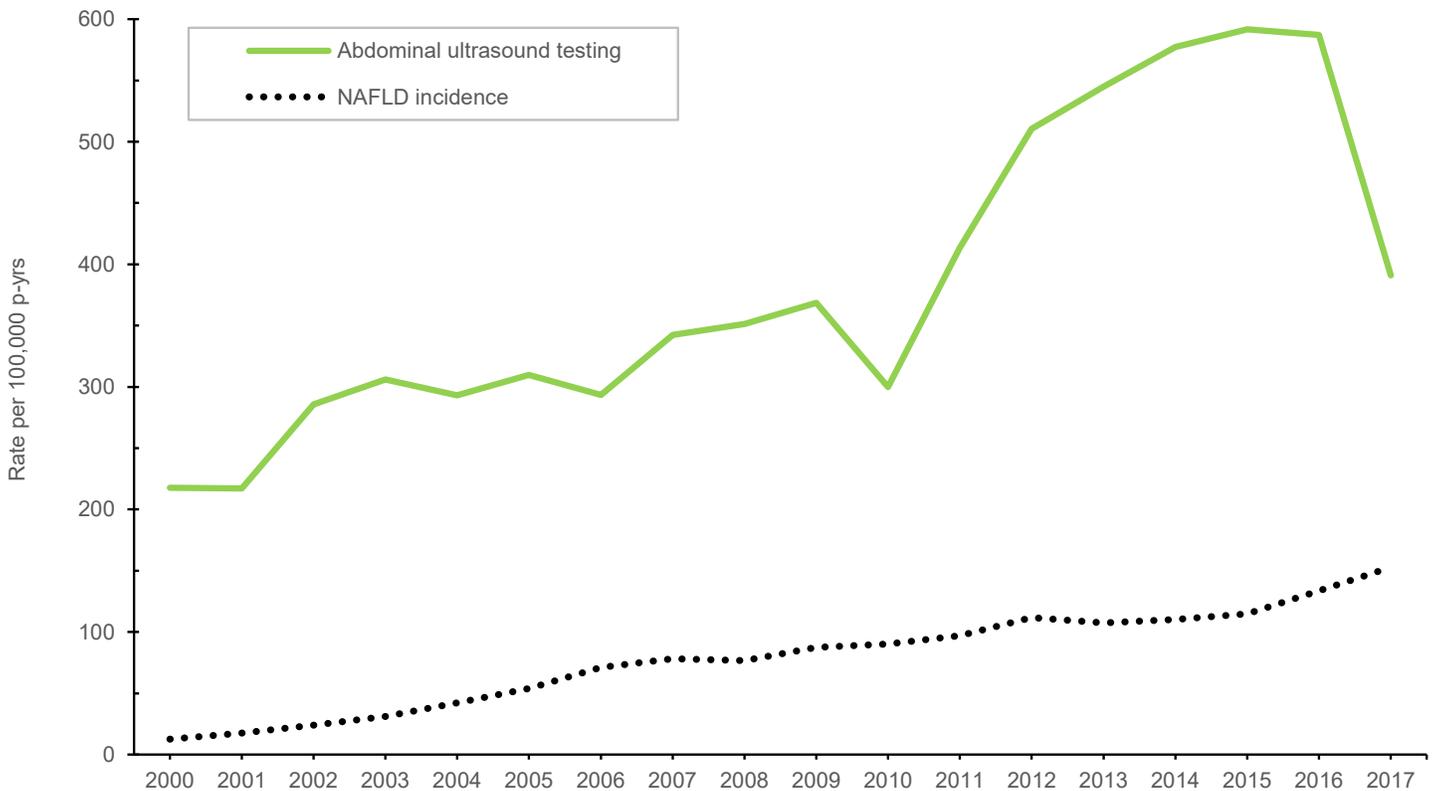


FIGURE 6. Annual rates of abdominal ultrasound testing^a, active component, 2000–2017



^aCPT codes: 76700 (abdominal complete), 76705 (abdomen limited); ICD-9 procedure code 88.76 (diagnostic ultrasound of abdomen and retroperitoneum), ICD-10 procedure code BW40ZZZ (ultrasonography of abdomen)

data-based studies of the general U.S. population show that the greatest increases in incidence of NAFLD occur among adults 45 years of age or younger.^{17,18} Results of population-based studies carried out in the U.S. indicate that NAFLD is more common among men than among women.^{4,10-13,27} The effect of sex hormones as well as sex-based differences in lifestyle and physiology (e.g., body fat distribution) have consistently been proposed to account for sex differences in NAFLD prevalence.^{11,28} Results of longitudinal studies indicate that women tend to develop NAFLD up to 10 years later than men, due to the putative protective effect of estrogens.²⁸ In the current study, however, the median age at NAFLD diagnosis among male active component service members was 4 years older than among females.

The overall incidence rates of NAFLD were highest among Asian/Pacific Islanders and Hispanics, intermediate among non-Hispanic whites, and lowest among non-Hispanic blacks. U.S. population-based studies have found similar differences among race/

ethnicity groups in the risk of NAFLD.^{4,10-13,17,27} A high prevalence of a polymorphism in the gene that encodes patatin-like phospholipase domain-containing 3 (*PNPLA3*) in Hispanics has been posited as a contributing factor to the higher prevalence of NAFLD observed in this group.²⁹ Moreover, results of several studies indicate that Hispanics are more susceptible to advanced NAFLD disease than non-Hispanic whites with the lowest susceptibility observed among non-Hispanic blacks.³⁰⁻³² Genetic differences in lipid metabolism (i.e., lower serum triglyceride levels and higher serum HDL cholesterol levels) are leading explanations for the lowest incidence and prevalence of both NAFLD and NASH among non-Hispanic blacks compared to those in other race/ethnicity groups.³² Other possible explanations for these risk differences include differences in dietary habits (increased consumption of low-nutrient, high sodium and high-fat foods—especially meat-derived fats and lower amounts of fresh fruit) and physical activity levels.^{12,33-35}

The pattern of higher overall rates of NAFLD observed among warrant officers and senior officers compared to junior enlisted service members and junior officers is likely highly associated with and confounded by age. The finding that overall incidence of NAFLD was lowest among Marine Corps members may be related to differences in the age and overweight/obesity distributions of the services.^{36,37} In addition, the finding that the highest overall incidence rate of NAFLD was observed among service members in healthcare occupations is likely due, at least in part, to heightened medical awareness and easier access to care compared to their respective counterparts in other occupations. It is important to note that results of a recent *MSMR* analysis of the incidence of MetS among active component service members during 2002–2017 showed that the highest overall incidence of MetS (as indicated by ICD diagnostic codes for MetS) was observed among Asian/Pacific Islanders, Air Force members, warrant officers, and those in healthcare occupations;

the lowest overall incidence rates were seen among Marine Corps members and junior enlisted personnel and officers.³⁸

More than two-thirds of incident NAFLD cases had one or more diagnosed metabolic comorbidities, with dyslipidemia affecting the greatest percentage of cases, followed by obesity/overweight and hypertension. Moreover, the percentage of NAFLD cases with 2 or more metabolic comorbidities increased 36.0% during the 18-year surveillance period from 22.2% in 2001 to 30.2% in 2017. A similar trend in metabolic comorbidities over time has been noted in at least one large administrative data-based U.S. study; however, the magnitude of the increase over time seen in the general population was greater (21% to 53%).¹⁸ This difference in magnitude is likely due to differences between the populations in terms of age and overall health status. Regardless of this difference, the slight trend of increasing dysmetabolic burden over time observed among incident NAFLD cases in the current study suggests that the clinical profile of those with NAFLD is becoming more complex, because of the presence of more metabolic comorbidities near the time of NAFLD diagnosis.

The American Association for the Study of Liver Diseases (AASLD) 2018 practice guidance document for the diagnosis and management of NAFLD recommends that the management of this condition consist of treating liver disease as well as the associated metabolic comorbidities. However, pharmacological treatments aimed mainly at improving liver disease should generally be restricted to those cases with biopsy-proven NASH and fibrosis.³ Lifestyle modification including diet, exercise, and weight loss is advocated to treat patients with NAFLD. Weight loss of at least 3% – 5% of body weight seems necessary to improve steatosis, but loss of 7% – 10% of body weight is required to improve most of the histopathological features of NASH.³ It is further recommended that aggressive modification of cardiovascular disease risk factors be considered in all patients with NAFLD.³ Because patients with NAFLD or NASH are not at higher risk for serious liver injury from statins, these medications can be used to treat dyslipidemia in individuals with these conditions.³

Results of the current study must be interpreted in the context of several

limitations. First, it is important to note that the use of diagnostic codes for case ascertainment can limit disease specificity, especially with a diagnosis of exclusion such as NAFLD. To address this limitation, the current analysis refined the case definition by excluding individuals with alternative liver diseases and those with diagnoses of alcohol-related mental health disorders. Using a similar case definition and exclusion list as the current study, Allen and colleagues found that 85% of incident NAFLD cases identified using ICD-9 codes were true cases of NAFLD based on chart review; the remaining 15% were determined to be cases of alternative liver diseases.¹⁸ Chart review also showed that, of the cases that were excluded based on codes for alternative liver diseases and/or alcohol-related mental health disorders, 87% were true non-NAFLD liver disease and 13% were NAFLD. It is important to note, however, that a large proportion of outpatient incident cases (approximately 58%) identified in this study were single outpatient visits without any follow-up encounters during the surveillance period. It is possible that many of these are miscoded screening visits, in which case the analysis would overestimate the true incidence of NAFLD. At the time of this report, there were no U.S. population-based studies of NAFLD incidence using other indirect methods (e.g., ultrasonography, serum liver enzyme tests) available for comparison.

Another limitation of the current analysis is related to the implementation of MHS GENESIS, the new electronic health record for the Military Health System. For 2017, medical data from sites that were using MHS GENESIS are not available in DMSS. These sites include Naval Hospital Oak Harbor, Naval Hospital Bremerton, Air Force Medical Services Fairchild, and Madigan Army Medical Center. Therefore, medical encounter and person-time data for individuals seeking care at one of these facilities during 2017 were not included in the analysis.

As one of the few published U.S. studies of NAFLD incidence among a large demographically diverse population, this study makes a useful contribution to the literature on temporal changes in the incidence of NAFLD by sex and race/ethnicity. Observed differences in incidence rates of NAFLD diagnoses by race/ethnicity and service warrant further analysis to examine adjusted

(e.g., by age, sex) incidence rates among service members within these groups. Results indicating that Asian/Pacific Islanders and Hispanics have higher incidence of NAFLD diagnoses than those in other race/ethnicity groups underscore the importance of effective prevention and management programs targeting these higher risk groups. Moreover, the substantial rise in rates of incident NAFLD diagnoses coupled with cases who may present with an increasing number of comorbid dysmetabolic conditions, suggests the need for heightened efforts toward awareness, early intervention, and multidisciplinary management.

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Cardiovascular Disease-related Medical Evacuations, Active and Reserve Components, U.S. Armed Forces, 1 October 2001–31 December 2017

Leslie L. Clark, PhD, MS; Gi-Taik Oh, MS; Shauna Stahlman, PhD, MPH

From 1 October 2001 through 31 December 2017, a total of 697 medical evacuations of service members from the U.S. Central Command (CENTCOM) area of responsibility were followed by at least one medical encounter in a fixed medical facility outside the operational theater with a diagnosis of a cardiovascular disease (CVD). The vast majority of those (n=660; 94.7%) evacuated were males. More than a third of CVD-related evacuations (n=278, 39.9%) occurred in service members 45 years of age or older; slightly more than half (n=369; 52.9%) occurred in reserve or guard members. The most common CVD risk factors which had been diagnosed among evacuated service members prior to their deployment were hypertension (n=236; 33.9%) and hyperlipidemia (n=241; 34.9%). Much lower percentages had been previously diagnosed with obesity (n=74, 10.6%) or diabetes (n=21, 3.0%). More than 1 in 4 service members with a CVD-related medical evacuation had been diagnosed with more than one risk factor (n=182, 26.1%). Both limitations to the data available and strategies to reduce CVD morbidity in theater are discussed.

WHAT ARE THE NEW FINDINGS?

This is the first *MSMR* summary of cardiovascular-related medical evacuations from the CENTCOM AOR. The highest rates of evacuation occurred in males, those 45 years of age or older, senior officers and warrant officers, and members of the reserve or guard. A third of evacuees had pre-deployment diagnoses of the modifiable risk factors hypertension or hyperlipidemia.

WHAT IS THE IMPACT ON READINESS AND FORCE HEALTH PROTECTION?

Pre-deployment medical screening should continue to ensure that service members meet the minimal standards of fitness for deployment to CENTCOM AOR. Service members with hypertension or hyperlipidemia controlled on a medication regimen should be stable for at least 90 days prior to deployment.

Since the beginning of military operations in the U.S. Central Command (CENTCOM) area of operation (AOR) in 2001, there have been over 50,000 medical evacuations from the CENTCOM AOR. Throughout this period, disease and non-battle injury (DNBI) have accounted for at least three quarters of medical evacuations. During periods of limited combat operations, over 90% of medical evacuations have been due to DNBI.¹⁻³

Medical evacuations have a significant impact on military readiness due to loss of personnel and the resultant effects on unit cohesion and mission effectiveness. The costs of medical evacuation related to DNBI are also considerable; one estimate of the cost of medical evacuations from the CENTCOM AOR between 2008 and 2013 was in excess of \$300 million dollars.⁴

The U.S. military has developed policy related to deployment standards which

are applied during the pre-deployment screening process to determine medical and psychological fitness to deploy. As part of this process, potential deployers complete DD Form 2795 (Pre-Deployment Health Assessment or Pre-DHA) which is reviewed by a health care provider to help identify and address medical issues which might impact deployment medical readiness. During pre-deployment screening, a service member can receive a referral to a primary or specialty care provider for further evaluation of a specific condition if necessary. If a service member is determined to be unfit for deployment or non-deployable, he or she can request a medical deployment waiver which (if approved) will permit deployment of the service member.^{5,6}

A recent retrospective cohort study in Army personnel evaluated the impact of receiving a medical deployment waiver on

the subsequent probability of being medically evacuated for DNBI causes from the CENTCOM AOR. This study reported that soldiers receiving a waiver were more than twice as likely to be medically evacuated for DNBI as matched controls without waivers (relative risk[RR]:2.03; 95% CI: 1.74–2.36). Notably, the greatest number of waivers granted to soldiers during the study period (2008–2013) were for cardiology/pulmonary conditions.⁴

Some additional insight into the prevalence of cardiovascular disease (CVD) in deployed personnel can be gleaned from published literature. A prior *MSMR* report on deaths attributed to cardiovascular causes occurring in the CENTCOM AOR documented 62 such deaths between October 2001 and December 2012.⁷ An analysis evaluating the burden of disease in theater reported that more than 7,800 medical encounters in male service members

in 2017 were attributable to CVDs; this represents 5.5% of all medical encounters in deployed servicemen during the year.⁸ Published reports from cardiology consultants at combat support hospitals provide limited data on the extent of cardiac disease requiring medical evacuation. Two studies conducted in Iraq between 2004 and 2005 and Afghanistan between 2010 and 2013 reported evacuation rates of 14% and 15%, respectively, for military members referred for cardiac symptoms.^{9,10} However, a paucity of literature exists providing a comprehensive summary of medical evacuations from the CENTCOM AOR related to cardiovascular diagnoses.

This descriptive analysis summarizes the demographic characteristics, counts, rates and temporal trends for CVD-related medical evacuations from the CENTCOM AOR. In addition, the percentage of those evacuated who had received pre-deployment diagnoses indicating cardiovascular risk is summarized. Responses to questions regarding health status and physician referrals on the DD2795 are also summarized.

METHODS

The surveillance period was 1 October 2001 through 31 December 2017. The surveillance population included all members of the active and reserve components of the U.S. Army, Navy, Air Force and Marine Corps who were deployed as part of operations in the CENTCOM AOR in Southwest Asia. Medical evacuations were included in the analysis if the evacuated service member was evacuated from CENTCOM to a medical treatment facility outside the CENTCOM AOR and if the service member had at least one outpatient or inpatient medical encounter during the time period from 5 days before to 10 days after the reported evacuation date. Evacuations were included only if they occurred after the start date of a service member's deployment and within 90 days after the end of the deployment.

Deployment records were available from the Defense Manpower Data Center Contingency Tracking System and are archived in the Defense Medical

Surveillance System (DMSS). Records of all medical evacuations conducted by the U.S. Transportation Command (TRANSCOM) and maintained in the TRANSCOM Regulating and Command System (TRAC2ES) were used as the source of evacuation data. Medical encounter data and data from the Pre-Deployment Health Assessment form (DD2795) are provided for health surveillance purposes to the Armed Forces Health Surveillance Branch and archived in DMSS.

Evacuations were classified as CVD-related based on International Classification of Disease diagnostic codes (ICD-9/ICD-10) reported in the first recorded hospitalization or outpatient medical encounter outside the CENTCOM AOR during the time period outlined above. These codes are listed in **Table 1**. Diagnoses for CVD were considered the reason for the subject evacuation if they were documented in the first or second diagnostic position. For this analysis, one medical evacuation per deployment was counted.

Denominators for rates of medical evacuations were calculated by determining the length of each individual's deployment and summing the person-time of all deployers. If the deployment end date was missing, the end date was imputed based on average deployment times per service.

All pre-deployment Health Assessment Forms (DD2795s) completed within

120 days of start date of the linked deployment were identified for each case. If multiple forms were identified during this step, the form completed on a date closest to the start of the deployment was retained.

The presence or absence of pre-deployment cardiovascular risk factors were ascertained for all service members identified as a "case" of CVD-related medical evacuation. The specific cardiovascular risk factors evaluated were hypertension, hyperlipidemia, obesity, abnormal blood glucose, and diabetes. Each risk factor was defined with a specific set of ICD-9 and ICD-10 codes as outlined in **Table 1**. If any of the specific diagnostic codes was identified in any diagnostic position of a record of an ambulatory medical encounter or hospitalization at any point before the start date of the relevant deployment, the risk factor was classified as being present pre-deployment (i.e., prior to deployment).

RESULTS

During the surveillance period, a total of 697 medical evacuations of service members from CENTCOM AOR were related to CVD. The overall rate of CVD-related evacuations was 0.3 per 1,000 deployed person-years (dp-yrs). (**Table 2**)

TABLE 1. ICD-9 and ICD-10 codes used for identification of cardiovascular disease and risk factors

Cardiovascular diseases	ICD-9 ^a	ICD-10 ^a
Hypertensive heart and/or kidney disease	402.*, 403.*, 404.*	I11.*, I12.*, I13.*
Ischemic heart disease	410.*, 411.*, 412, 413.*, 414.*	I20.*-I25.*
Cerebrovascular diseases	430, 431, 432.*, 433.*, 434.*, 435.*, 436, 437.0-437.2	I60.*-I66.*, I67.2
Risk factors		
Essential hypertension	401.*	I10, I16.*
Hyperlipidemia	272.0-272.4	E78.0*-E78.5
Obesity	278.00, 278.01, 278.03, V85.3*-V85.4*, V85.54	E66.0*-E66.2, E66.8-E66.9
Abnormal glucose level	790.2*	R73.*
Diabetes mellitus	250.**	E10.*, E11.*

^aAn asterisk (*) indicates that any subsequent digit/character is included

Overall, more than 17 times as many males (n=660) as females (n=37) were medically evacuated for cardiovascular diagnoses and the rate of evacuations in males (0.32 per 1,000 dp-years) was twice that in females (0.16 per 1,000 dp-yrs). (Table 2) The diagnoses most frequently associated with CVD-related medical evacuations were coronary atherosclerosis, acute myocardial infarction, and cerebral artery occlusion (data not shown).

The rates of CVD-related medical evacuation increased with age and the highest rate of evacuation occurred in those 45 years of age or older (2.6 per 1,000 dp-yrs). Rates in this age category were more than twice that of those in the 40-44 year old age category (1.0 per 1,000 dp-yrs). Rates in service members under 30 years of age were relatively low (0.1 per 1,000 dp-yrs).

Overall, CVD-related medical evacuation rates were highest among black, non-Hispanic service members (0.4 per 1,000 dp-yrs) and lowest among service members of "other" or unknown race/ethnicity (0.2 per 1,000 dp-yrs). Compared to their respective counterparts, rates of CVD-related evacuation were higher among deployers in the Army and in armor/motor transport or healthcare occupations. Notably, the reserve component service member rate of CVD-related evacuation (0.6 per 1,000 dp-yrs) was three times that of members of the active component (0.2 per 1,000 dp-yrs). Senior officers and warrant officers had the highest overall rates of CVD-related medical evacuations (0.7 per 1,000 dp-yrs) although they comprised only 9.9% and 4.5% of all CVD-related evacuations, respectively.

Almost 1 in 4 of the service members who were evacuated for a CVD diagnosis endorsed having either a medical problem (n=107; 15.4%) or a health concern (n=57; 8.2%) when completing the pre-deployment health assessment form (DD275). Relatively few were given a cardiac (n=2; 0.3%), primary care (n=1; 0.1%), or other referral (n=10; 1.4%). Twenty-two service members (3.2%) were determined to be "non-deployable". Almost 1 in 5 of the evacuated service members (n=135; 19.4%) did not have a DD2795 available at the time of analysis (Table 3).

In the separate examination of cardiovascular risk factors diagnosed in the pre-deployment period, of the 697 service members medically evacuated for cardiovascular reasons, more than a third had been diagnosed with hypertension (n=236; 33.9%) or hyperlipidemia (n=241; 34.6%). About 1 in 10 service members had an obesity related diagnosis prior to deployment (n=74, 10.6%). Relatively few service members had been previously diagnosed with diabetes (n=21; 3.0%). More than a quarter of all service members with a CVD-related medical evacuation had been diagnosed with more than one cardiovascular risk factor (n=182; 26.1%).

EDITORIAL COMMENT

This analysis found that 697 medical evacuations from CENTCOM related to cardiovascular diagnoses occurred between October 2001 and December 2017. Service members with a CVD-related medical evacuation were more likely to be male and 45 years of age or older. These findings are not surprising because it is well documented that the incidence of CVD is higher in men than women of comparable age.¹¹ Likewise, increasing age is also a well-known, traditional, and non-modifiable risk factor for CVD.¹²

As documented in a recent *MSMR* analysis, rates of diagnosed CVD in active component service members are low. During the ten-year period between 2007-2016, less than 1% of active component service members received a CVD diagnosis.¹³ This low prevalence of CVD may explain, in part, the paucity of referrals identified via DD2795 data in CVD-related medical evacuees in this analysis. Relatively few service members with overt CVD are likely to have undergone pre-deployment screening.

Notably, more than a third of evacuees had modifiable CVD risk factors (hypertension, dyslipidemia) and about 1 in 10 had received a diagnosis of obesity prior to their deployment. A significant limitation of this analysis is the lack of data on medical management or treatment of these risk factors which may have ameliorated these conditions.

TABLE 2. Demographic characteristics of service members with cardiovascular disease-related medical evacuations, October 2001–December 2017

	Medical evacuations		
	No.	%	Rate ^a
Total	697	100	0.3
Sex			
Male	660	94.7	0.3
Female	37	5.3	0.2
Age group (years)			
<20	4	0.6	0.1
20–24	50	7.2	0.1
25–29	43	6.1	0.1
30–34	58	8.3	0.2
35–39	105	15.1	0.4
40–44	159	22.8	1.0
45+	278	39.9	2.6
Race/ethnicity			
Non-Hispanic white	461	66.1	0.3
Non-Hispanic black	131	18.8	0.4
Hispanic	64	9.2	0.3
Other	41	5.9	0.2
Grade			
Junior enlisted (E1–E4)	120	17.2	0.1
Senior enlisted (E5–E9)	445	63.8	0.5
Junior officer (O1–O3)	32	4.6	0.2
Senior officer (O4–O10)	69	9.9	0.7
Warrant officer (W1–W5)	31	4.5	0.7
Component			
Active	328	47.1	0.2
Reserve/guard	369	52.9	0.6
Service			
Army	549	78.8	0.4
Navy	44	6.3	0.3
Air Force	67	9.6	0.2
Marine Corps	37	5.3	0.1
Occupation			
Combat-specific ^b	140	20.1	0.3
Armor/motor transport	65	9.3	0.4
Pilot/air crew	16	2.3	0.2
Repair/engineering	161	23.1	0.3
Communications/intelligence	153	22	0.3
Health care	47	6.7	0.4
Other	115	16.5	0.3

^aRate per 1,000 deployed person-years

^bInfantry/artillery/combat engineering

TABLE 3. Risk characteristics of service members with cardiovascular disease-related medical evacuations, October 2001-December 2017

	Medical Evacuations	
	No.	%
Total	697	100.0
Risk-related responses on forms DD2795 (Pre-deployment health assessment)		
No DD2795 form available	135	19.4
Reported fair or poor health (HEALTH_ASSESSMENT=F or P)	21	3.0
Endorsed medical problems (MED_PROBLEMS=Y)	107	15.4
Endorsed health concerns (HEALTH_CONCERNS=Y)	57	8.2
Provider gave cardiac referral (REF_CARDIAC=Y)	2	0.3
Provider gave primary care referral (REF_PRIMARY=Y)	1	0.1
Provider gave other referral (REF_OTHER=Y or REF_SPEC_OTHER=Y or REF_OTHER_SPEC=Y)	10	1.4
Determined non-deployable (MED_DISP=N in DD2795_199905 or MED_DISP=3 or 4 in DD2795_201209)	22	3.2
With pre-deployment diagnoses of cardiovascular disease risk factors		
Hypertension	236	33.9
Hyperlipidemia	241	34.6
Obesity	74	10.6
Abnormal glucose level	22	3.2
Diabetes	21	3.0
More than 1 risk factor	182	26.1

This analysis appears to indicate that despite robust pre-deployment screening policies, some service members will present in theater with significant cardiovascular issues. One step that has been taken to mitigate the severity of the consequences for these patients is the deployment of cardiology consultants to the CENTCOM AOR.¹⁰

Watts et al. reported on the impact of deploying a dedicated theater cardiology consultant to Bagram Air Field in Afghanistan in an attempt to mitigate morbidity and mortality related to cardiovascular complaints and to increase rates of return to duty. This study reported an 85% return to duty rate for military members and a corresponding 15% evacuation rate for those referred for cardiology evaluations between 2010-2013.¹⁰ A similar study conducted in Iraq between 2004-2005 demonstrated an 86% return-to-duty rate (and a 14% evacuation rate) for troops referred to a cardiology consultant for evaluation of cardiac symptoms.⁹ It is notable that these

evacuation rates following cardiology evaluations were remarkably similar during two different time periods and in two different locations. These studies seem to indicate that a certain percentage of deployers will require evacuation for cardiovascular reasons regardless of pre-deployment medical screening processes.

In this analysis, the “cause” of a medical evacuation was estimated from diagnoses that were recorded during hospitalizations or outpatient encounters occurring in fixed medical facilities after evacuation from theater. Therefore, classification of an evacuation as CVD-related relied on a diagnosis given in a fixed medical treatment facility after evacuation. This methodology reflects the standard *MSMR* approach utilized in previous analyses of the causes of medical evacuations.¹⁻³ These diagnoses may differ from the original diagnoses given in the medical evacuation record as provided by TRA2CES. As a result, the estimates of the frequency of CVD-related medical evacuations might differ from estimates derived

from diagnoses recorded in the medical evacuation record.

There are several limitations to this analysis that should be considered when interpreting results. The availability of data on the cardiovascular health status of reserve and guard members is limited. Thus, the estimation of pre-deployment diagnoses of cardiovascular conditions in reserve and guard members is likely significantly underestimated.

Data about waivers for cardiovascular conditions were unavailable for this analysis. These data would have provided useful information on the relationship between waived cardiovascular conditions and subsequent medical evacuation. Conrath et al. determined that soldiers granted a cardiology/pulmonary waiver were significantly more likely to be medically evacuated while deployed than matched controls not granted a waiver (RR: 1.80; 95% CI: 1.40-2.30).⁴ However, the exposure in Conrath and colleagues’ analysis was not limited to cardiovascular conditions (i.e., waivers for pulmonary conditions were also included) and the outcome was not specifically CVD-related. Analysis evaluating this specific question could provide useful insights to guide future policy.

Another limitation to this analysis is the lack of data on use of nutritional and sports supplements during deployment. The use of nutritional supplements is well documented in deployed populations, as are adverse effects related to these supplements.¹⁴⁻¹⁶ Young, healthy military personnel with no prior history of CVD may present with cardiac symptoms in theater as a result of nutritional supplement use. A report summarizing the experiences of internal medicine physicians at a combat support hospital in Kandahar, Afghanistan documented multiple cases of patients presenting with serious cardiac manifestations after use of 1,3-dimethylamine (DMAA)-containing supplements. These manifestations ranged from chest pain to ST-elevation myocardial infarction requiring medical evacuation.¹⁷ DMAA use is now prohibited by the military. However, supplement use continues to be an issue. Increased efforts to educate military members about the risks and benefits of nutritional supplements are warranted and

should continue to be a focus of prevention efforts.¹⁸

This analysis was also unable to evaluate the presence of several other important cardiovascular risk factors due to the unavailability of accurate individual-level data. The factors include levels of physical activity, diet, and, most importantly, tobacco use. Previous surveys of military personnel have reported that approximately 25% of service members are current cigarette smokers. It is likely that a similar proportion of service members requiring medical evacuation in this analysis were current tobacco users. Analyses conducted in the future will likely benefit from the implementation of the standardized periodic health assessment which collects more comprehensive data on tobacco use and other lifestyle-related cardiovascular risk factors.

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Acute Flaccid Myelitis: Case Report

Megan L. Donahue, MD (CPT, USA); Shawn S. Clausen, MD, MPH (CDR, USN); Allison Malloy, MD, MSc; David H. Dennison, MD (COL, USA); Jennifer Falcon, MD (CPT, USA)

In August 2018, the U.S. Centers for Disease Control and Prevention (CDC) noted an increased number of reports of patients in the U.S. having symptoms clinically compatible with acute flaccid myelitis (AFM). AFM is characterized by rapid onset of flaccid weakness in one or more limbs and distinct abnormalities of the spinal cord gray matter on magnetic resonance imaging (MRI). Clinical and laboratory data suggest that AFM is associated with an antecedent viral infection. AFM may be difficult to differentiate from other causes of paralysis and, given that it is rare, has the potential to be overlooked. This case highlights important clinical characteristics of AFM and emphasizes the importance of including AFM in the differential diagnosis when evaluating active duty service members and Military Health System (MHS) beneficiaries presenting with paralysis.

CASE REPORT

On 23 September 2018, the previously healthy 9-year-old daughter of an active duty service member presented to the Fort Belvoir Community Hospital (FBCH) emergency department with sore throat, left earache, headache, neck pain, and history of fever to 101.0°F.

Symptoms of cough and congestion started approximately two weeks prior, on 10 September 2018. Unlike her younger brother, who had similar symptoms and improved, the patient's symptoms worsened such that she missed school on Friday, 14 September 2018 and Monday, 17 September 2018. The patient attempted to resume normal activities but nearly fainted on 19 September 2018 while testing for her Purple Belt in Tae Kwon Do. On 20 September 2018, the patient developed nausea, anorexia, malaise, dizziness, and fever to 100.5°F. By 23 September 2018, her temperature had increased to 101.0°F and her symptoms progressed to include symptoms that led to her emergency room visit.

When the patient presented to the emergency department on 23 September 2018, her temperature was 98.8°F. Her left tympanic membrane appeared erythematous. Her neck was tender and lymphadenopathy was noted; Kernig and Brudzinski signs could not be elicited. The patient was diagnosed with left otitis media and neck strain. She was treated with ibuprofen 400 mg and dexamethasone 10 mg by mouth. She was discharged home on amoxicillin and ibuprofen.

By 25 September 2018, day 16 of illness, the patient had difficulty turning on the bathroom light due to weakness in her upper extremities. She also had weakness in her neck and imbalance such that she had difficulty ambulating. The patient presented to the pediatric clinic in a wheelchair with headache, neck pain, imbalance, and generalized weakness. Her examination was remarkable for left facial weakness and neck pain radiating to the lower back with neck flexion. She was directed to the emergency department for further evaluation and treatment.

On examination in the emergency department, the patient's vital signs were

stable; her temperature was 99.6°F. Examination of her head, eyes, ears, nose and throat revealed dull tympanic membranes, pharyngeal erythema, and left facial weakness consistent with Bell's palsy. Upper extremity weakness and nuchal rigidity were also noted. The patient's chest x-ray was clear and computed tomography (CT) of the head was normal. Her rapid strep test was negative. A monospot was ordered (results not reported). Her white blood cell count (WBC) was 6,600 cells/ μ L with neutrophilic predominance (81.6%); hematocrit and platelets were normal. Her basic metabolic panel was also normal. A lumbar puncture was performed revealing clear, colorless cerebrospinal fluid (CSF) with a white blood count of 77 cells/ μ L (normal 0-5 cells/ μ L) (neutrophils 19%; lymphocytes 64%; monocytes 17%), red blood count 0 cells/ μ L; protein 49 mg/dl (normal 15-45 mg/dl); glucose 64 mg/dl (normal 60-80 mg/dl). Gram stain of the CSF was negative. A rapid multiplex CSF PCR panel was negative for *Escherichia coli* Ag; *Hemophilus influenzae* rRNA; *Listeria Monocytogenes* rRNA; *Neisseria meningitidis* rRNA; *Streptococcus agalactiae* Ag; *Streptococcus pneumoniae* rRNA; Cytomegalovirus DNA; Herpes Simplex Virus 1 DNA; Herpes Simplex Virus DNA; Human Herpesvirus 6 DNA; Parechovirus RNA; Varicella Zoster Virus DNA; Enterovirus RNA; and *Cryptococcus neoformans* rRNA. Blood and CSF cultures were sent.

The patient was treated presumptively for meningitis with intravenous ceftriaxone in the emergency room and she was admitted to the hospital. Additional history revealed that the patient had a bull's-eye rash while living in Utah 16 months prior, and that she was treated presumptively for Lyme disease at the time. Her history also revealed that she had complained of knee and ankle pain since August 2018. Although the patient lived and vacationed in wooded areas where Lyme disease is prevalent, she had no history of a tick bite.

The patient developed a rash after her first dose of ceftriaxone and was switched to meropenem. She was also treated with doxycycline for presumed Lyme disease. CSF and blood cultures were negative at 48-hours and meropenem was discontinued. Lyme serology and Lyme CSF PCR were negative on 28 September 2018. Doxycycline was continued due to high suspicion for Lyme disease.

On 29 September 2018, magnetic resonance imaging (MRI) of the brain (without contrast) was normal. MRI of the cervical spine revealed abnormal central T2 signal within the spinal cord with expansion extending from the level of cervical vertebrae C2–C3 to C6–C7 consistent with myelitis. Given the clinical presentation, MRI findings, and CSF pleocytosis, the patient was diagnosed with acute flaccid myelitis (AFM). She was treated with methylprednisolone 1 gram IV daily for 3 days.

Repeat MRI of the brain (with contrast) and MRI of the internal auditory canals were performed on 1 October 2018 and were normal. MRI of the thoracic spine was normal on 2 October 2018. Additional testing included a respiratory virus culture which was negative for influenza A/B, parainfluenza, adenovirus, and respiratory syncytial virus. Tests for *Mycoplasma pneumoniae* IgM, *Bartonella*, West Nile Virus, and *Ehrlichia* were negative. Myelin-associated Glycoprotein-Sulfated Glucuronic Paragloboside IgM was less than 1:10 (negative) and Neuromyelitis Optica Antibody IgG was less than 1.5 U/ml (negative).

The patient's weakness worsened during the first 2 days following admission then improved over the course of her hospitalization. Weakness was limited to the face, neck, and upper extremities. Her facial weakness was associated with transient left facial numbness and arm weakness was associated with reduced tendon reflexes. The patient did not experience lower extremity weakness, dysphagia, or respiratory compromise. Joint pain involving the knees, ankles, wrists and elbows was noted. Gabapentin provided partial relief.

The patient was discharged home in stable condition on 3 October 2018. In spite of her diagnosis, doxycycline was continued for the unlikely possibility of Lyme disease. Follow-up with primary care,

pediatric neurology, pediatric infectious disease, and occupational and physical therapy was scheduled.

EDITORIAL COMMENT

The incidence of acute flaccid paralysis (AFP) in the U.S. decreased dramatically following the introduction of inactivated polio vaccine (IPV) in 1955 and oral polio vaccine (OPV) in 1961. However, cases of AFP attributable to oral trivalent attenuated polio vaccine¹ and other viruses (including enterovirus [EV-A71],² enterovirus D68 [EV-D68],³ Epstein-Barr virus,⁴ and West Nile virus⁵) continue to occur. The estimated incidence of AFP in the U.S. among those under 15 years of age is 1.4 per 100,000 person-years.⁶

In August 2012, the California Department of Public Health (CDPH) was notified of 3 cases of AFP associated with anterior myelitis. In spite of laboratory testing, a causative agent could not be found. Following these reports, CDPH posted alerts requesting early reporting of cases and collection of clinical samples. A case was defined as flaccid paralysis in at least one limb consistent with anterior myelitis as indicated by neuroimaging of the spine or electrodiagnostic studies (e.g., nerve conduction studies and electromyography) and with no known alternative etiology. Between June 2012 and June 2014, 23 cases of AFP with anterior myelitis were identified. Common features included an upper respiratory or gastrointestinal prodrome less than 10 days before AFP onset and CSF pleocytosis. The median age of patients was 10 years (range=1–73 years). The etiology of AFP among reported cases was unclear; poliovirus was determined to be an unlikely cause.⁷

On 3 October 2014, CDC posted a Morbidity and Mortality Weekly Report (MMWR) Early Release describing a cluster of 9 children evaluated at Children's Hospital Colorado for acute neurologic illness characterized by extremity weakness or cranial nerve dysfunction (or both) following a febrile illness. Among the 8 children who had magnetic resonance imaging of the spinal cord, 7 had lesions of the gray

matter spanning multiple levels, and 8 had mild to moderate CSF pleocytosis. Based on reported clinical and anatomic characteristics, the illness was referred to as acute flaccid myelitis (AFM), to distinguish it from other forms of AFP.⁸ Given that the cases occurred during a national outbreak of EV-D68 and laboratory testing among some cases suggested recent EV-D68 infection, EV-D68 was identified as a potential cause.⁹ However, a definitive cause of the illness cluster could not be determined.¹⁰

From August through December 2014, 120 AFM cases from 34 states were reported to CDC. A case was defined as any person aged 21 years of age or younger, with acute onset of limb weakness and a spinal MRI revealing lesions predominantly of the gray matter. During the 5-month period, the crude nationwide AFM incidence among persons 21 years of age or younger was 0.32 cases/100,000 population/year. The most common site of involvement on MRI was the cervical spinal cord. CSF pleocytosis was present in 81% of cases. The median age was 7.1 years (range=0.4–20.8 years). Most affected individuals experienced a respiratory or febrile illness prior to the onset of limb weakness.¹¹

In 2015, the Council of State and Territorial Epidemiologists (CSTE) and CDC updated the case definition for AFM to include CSF-based criteria. The current case definition for AFM is a person with onset of acute flaccid limb weakness, AND a magnetic resonance image showing a spinal cord lesion largely restricted to gray matter, and spanning one or more vertebral segments (confirmatory evidence), OR cerebrospinal fluid (CSF) with pleocytosis (CSF white blood cell count >5 cells/ μ L); CSF protein may or may not be elevated (supportive evidence).¹² In spite of the broadened case definition, the number of cases reported to CDC dropped to 22 confirmed cases in 2015. The count increased again in 2016 to 149 confirmed cases, then dropped in 2017 to 33 confirmed cases.

In August 2018, CDC noted an increase in the number of reports of patients with potential AFM.¹³ On 23 August 2018, CDC issued a notice via the Epidemic Information Exchange (Epi-X) to increase clinician awareness and provide guidance for case

reporting. An *MMWR* Early Release dated 13 November 2018 reported 106 confirmed cases of AFM. This number increased to 165 confirmed cases among 320 reported cases on 14 December 2018.¹⁴

The case described in this report meets the CSTE and CDC case definition for AFM. Similar to other confirmed cases, limb weakness was accompanied by decreased deep tendon reflexes and preceded by a febrile illness. Of note, in the case reported here, the interval between onset of respiratory symptoms and onset of neurological symptoms (16 days) was longer than the median interval of 7 days (range=1–12 days) reported by CDC in 2017.¹⁵ The patient's history of a bull's eye rash and residence in a wooded area where Lyme is prevalent introduced a distracting clue into diagnostic deliberations. It also highlights the ambiguity and challenges clinicians face when they encounter rare conditions that have significant clinical overlap, an undefined etiology, and an evolving case definition.

Rapid identification of potential cases and early reporting have the potential to expedite identification of the etiologic agent or agents responsible for AFM, progressive characterization of clinical features, detection of risk factors, and identification of preventive measures.

Clinicians caring for patients with limb weakness should maintain a wide differential diagnosis, inquire about recent fever, respiratory and gastrointestinal symptoms, and perform MRI promptly. While AFM is not a reportable disease, potential cases of AFM should be referred to military Preventive Medicine departments and reported in the Disease Reporting System Internet

(DRSi) under "Any Other Unusual Condition, Not Otherwise Specified." Clinicians should also report potential cases of AFM to their state or local health departments, and to the CDC. In addition, specimens (i.e., cerebrospinal fluid, serum, stool, and respiratory samples) should be sent to CDC for standardized testing and expanded testing protocols. Information related to specimen collection and shipping is available at <https://www.cdc.gov/acute-flaccid-myelitis/hcp/instructions.html>.

Author affiliations: Walter Reed National Military Medical Center, Bethesda, MD (CPT Donahue); Armed Forces Health Surveillance Branch, Silver Spring, MD (CDR Clausen); Uniformed Services University of the Health Sciences, Bethesda, MD (Dr. Malloy); Defense Health Agency National Capital Region Medical Directorate (COL Dennison); Fort Belvoir Community Hospital, VA (CPT Falcon).

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Historical Perspective: Leptospirosis Outbreaks Affecting Military Forces

Leslie L. Clark, PhD, MS

Leptospirosis is a widespread and highly prevalent bacterial zoonotic disease that is caused by pathogenic spirochetes of the genus *Leptospira*. It is transmitted to humans primarily through contact of abraded skin or mucous membranes with water or wet soil that has been contaminated with infected animal urine. Many wild and domestic animals are susceptible to infection by pathogenic *Leptospira* bacteria including rats, dogs, cattle, goats, sheep, and swine. Once chronically infected, a carrier animal can shed *Leptospira* bacteria in urine for long periods of time and *Leptospira* bacteria can survive in water or soil for weeks to months.¹

Leptospirosis has a global distribution with an estimated 1.03 million cases and 58,900 deaths attributed to the disease annually.² Leptospirosis incidence is highest in tropical regions. Leptospirosis also demonstrates seasonal variation in incidence. Cases in temperate regions occur predominantly in the summer and fall and cases in tropical regions increase during the rainy season.¹ In the U.S., between 100–150 cases are reported each year; Puerto Rico and Hawaii consistently account for the majority of U.S. leptospirosis cases.³ Both global and national incidence are likely significantly underestimated due to underreporting, misdiagnosis, and lack of laboratory confirmation.²

Occupational exposures are a significant source of infection and occupations involving contact with animals or infected water or soil confer increased risk (e.g., veterinarians, farmers, sewer workers).¹ Increasingly, recreational activities involving fresh water, foreign travel, or a combination of the two have been implicated in leptospirosis outbreaks. Notable examples include triathlons⁴⁻⁶ and adventure travel activities like white water rafting and caving.⁷ Transmission can also occur during periods of extensive flooding and high seasonal rainfall, both of which increase the risk of exposure to water contaminated with pathogenic leptospires.⁸

The spectrum of disease caused by leptospirosis can be highly variable ranging from mild and self-limiting to potentially

fatal. A significant proportion of cases are asymptomatic or subclinical. When symptoms occur, the average incubation period is between 7 and 12 days, although onset can range between 3 and 30 days after exposure. Initial symptoms often include fever, chills, myalgias (i.e., muscle pain), and headache and overlap considerably with the symptoms of many other acute febrile illnesses (e.g., dengue fever, influenza, malaria). Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) occur in about half of cases. Other, less common signs and symptoms include non-productive cough, hepatosplenomegaly (enlargement of the liver and spleen), lymphadenopathy (lymph node enlargement), pharyngitis, and rash. The presence of conjunctival suffusion (redness of the conjunctiva of the eye without discharge) can help distinguish leptospirosis from other infectious diseases. In approximately 90% of cases, the disease follows a biphasic course in which an initial acute symptomatic phase lasting 5-7 days is followed by “immune” phase during which antibodies develop and symptom improvement can occur. A more severe illness, known as icteric leptospirosis or Weil’s disease, occurs in about 10% of cases. Weil’s disease is severe and rapidly progressive and the classic presentation of this form of leptospirosis includes fever, jaundice, renal failure, and hemorrhage. Frequently, other organ systems (i.e., lungs, heart, central nervous system) are also involved.^{1,9}

There are several diagnostic tests available to screen for and confirm a diagnosis of leptospirosis although the value and accuracy of each test depends on the stage of disease. Tests that detect the presence of bacteria include polymerase chain reaction (PCR) and culture and will yield positive results only in the acute phase. Tests that detect antibodies specific for the *Leptospira* bacteria include the immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) and microscopic agglutination test (MAT) which will produce positive results later in the disease process. IgM ELISA detects early production of antibodies

and therefore can become positive earlier than the MAT but may produce false positive or false negative results. Direct culture of leptospires from urine or serum takes time and is very difficult with a low success rate. Although it is a complex test to control and perform, MAT is the “gold standard” test for a confirmatory leptospirosis diagnosis. A single titer of 1:100 or a 4-fold rise in titer between acute and convalescent sera is considered confirmatory.^{1,9,10}

The Centers for Disease Control and Prevention (CDC) recommends initiation of antibiotic therapy early (before confirmation via laboratory testing) as it may prevent patients from progressing to more severe disease or may reduce the duration of disease.¹⁰ Doxycycline (100 mg orally, twice daily) is the recommended regimen for adults with mild leptospirosis who are not pregnant. Ampicillin and amoxicillin are also potential treatment options for mild cases. Severe disease requires supportive therapy (e.g., intravenous (IV) hydration, electrolyte supplementation) and both IV penicillin and ceftriaxone have been demonstrated to be equally effective for treatment.^{9,10}

Pre-exposure prophylaxis with doxycycline (200 mg orally once per week) was effective in a double-blind trial conducted in deployed military personnel undergoing jungle training in Panama.¹¹ This regimen is also the current standard for leptospirosis prophylaxis for U.S. military personnel experiencing short term high-risk exposure.¹² In contrast, a 2009 systematic review of antibiotic prophylaxis for leptospirosis concluded that there was an unclear benefit with this regimen and it increased the odds of nausea and vomiting in those receiving prophylaxis.¹³

Leptospirosis in military forces

Leptospirosis has been the cause of significant morbidity in military forces throughout history. During World War I, outbreaks confirmed in French, German, and British troops were likely due, in part, to

the favorable conditions conferred by trench warfare including standing water and rat infestation. Leptospirosis outbreaks during World War II were linked to troops bathing in rivers and streams.¹⁴

The term “Fort Bragg Fever” came into existence due to a leptospirosis outbreak which hospitalized 40 soldiers at Ft. Bragg in North Carolina in the summer of 1942. Similar outbreaks occurred during the summers of 1943 and 1944. Despite an extensive epidemiologic investigation, leptospirosis (specifically *Leptospira autumnalis*) was not

determined to be the causative agent in these outbreaks until 1951.¹⁵

In 1961, a leptospirosis outbreak among U.S. Army troops occurred in the Panama Canal Zone and subsequent serological testing identified multiple serotypes of *Leptospira* as potential etiologic agents.¹⁶ Throughout the remainder of that decade, leptospirosis also caused significant disease in U.S. military personnel during the Vietnam War. One study estimated that leptospirosis accounted for 20% of acute febrile illnesses among service members in South Vietnam.¹⁷

Leptospirosis continued to have a significant impact on U.S. military members in Panama, especially on troops training at the Jungle Operations Training Center (JOTC). Between 1977-1982, surveillance on U.S. Army units undergoing the 3 week training course at the JOTC identified 91 confirmed and probable cases of leptospirosis. This translates to an annualized incidence of 41% (41,000 cases per 100,000 p-yrs).¹⁸

In 1987, a waterborne outbreak of leptospirosis in Okinawa, Japan in U.S. military personnel included two distinct case clusters

TABLE 1. Summary of leptospirosis outbreaks affecting U.S. and foreign military personnel, 1990 to present

Month/year of outbreak onset	Setting	Attack rate/ Number of leptospirosis cases	Description of outbreak	Reference
September 2014	Cases diagnosed in U.S. military personnel after recreational running event in Guam	Attack rate not reported; 8 lab-confirmed cases	All cases seroconverted to leptospirosis in convalescent blood samples. All cases experienced symptom resolution within 4 days after treatment with intravenous (IV) normal saline, antiemetics and empirical treatment with doxycycline 100 mg twice daily. No hospitalizations were reported.	20
August 2014	Endurance course training for U.S. Marines at the Jungle Warfare Training Center (JWTC) in Okinawa, Japan	Overall attack rate ^a : 33.9%; 81 cases/ 239 personnel. Group A attack rate: 21.9%; 21 cases/96 personnel. Group B attack rate: 42%; 60 cases/143 personnel	Laboratory confirmation used qualitative immunoblot (or Dot Blot) testing; only 35.3% of samples returned positive or borderline results. One member of Group A was hospitalized with acute cholecystitis (a known complication of leptospirosis) and 47 members of Group B were hospitalized due to symptom severity.	12
November 2011	Field training for Malaysian "commando recruits" in and around the west coast of Malaysia	Attack rate not reported; 24 cases reported	24 trainee commandos were hospitalized for suspected leptospirosis infection. The method of laboratory confirmation was not reported.	21
June 2011	Canyon-rescue training exercises for gendarmes (members of the French Armed Forces) in and near the Absalon River in Martinique	Attack rate: 20%; 8 suspected cases (7 lab-confirmed)/41 personnel	Seven cases were confirmed by at least one of the following: i) positive qPCR; (ii) culture isolation of <i>Leptospira</i> ; or (iii) positive MAT. Beta-lactam antibiotics were prescribed for all eight cases; two were hospitalized for three days.	22
November 2009	Field training exercises for Brazilian recruits in and around the Paraiba do Sul river valley in southeastern Brazil	Attack rate not reported; 2 lab-confirmed cases	Both cases tested positive for multiple <i>Leptospira</i> serovars via microscopic agglutination test (MAT). Both cases were hospitalized and empirically treated with doxycycline beginning on day 9 (case 1) and day 10 (case 2). Both cases recovered fully.	23
June 2002	Military exercise for Israeli Defense Force (IDF) troops near the Jordan River in northern Israel	Attack rate: 25.9%; 7 lab-confirmed cases/ 27 personnel	Method of lab confirmation was not reported. The first case was administered empirical doxycycline (100mg per day for 7 days) and one additional case was treated with empirical amoxicillin (500 mg three times a day for seven days). The duration of illness ranged from five to eight days and all cases recovered fully.	24
May 1999	Field training for Peruvian military recruits in the high jungle region of eastern Andes Mountains	Attack rate: 37.3%; 72 lab-confirmed cases/193 personnel	72 cases (of 78 hospitalized) were positive via MAT for acute leptospirosis.	25
December 1992	Recreational exposure in Oahu, Hawaii	Attack rate not reported; 2 lab-confirmed cases in U.S. military personnel	Leptospirosis diagnoses were confirmed via culture. Both cases were hospitalized.	26

^aThis outbreak affected two separate units (Group A and Group B). 239 exposed personnel were interviewed and 19 were not interviewed due to deployment away from Okinawa.

MAT, microscopic agglutination test

which differed by time and place of exposure. Attack rates were higher in the case cluster designated as recreational swimmers (47%) than among those in the cluster undergoing training at the Jungle Warfare Training Center (JWTC) (18%).¹⁹ This outbreak prompted the initiation of doxycycline prophylaxis at the JWTC.¹²

Leptospirosis outbreaks affecting both U.S. and foreign military personnel since 1990 are summarized in **Table 1**.

EDITORIAL COMMENT

This summary of leptospirosis outbreaks in U.S. and foreign military members demonstrates that leptospirosis poses a significant risk to military members through both occupational and recreational exposures.

Several of the reported outbreaks occurred during military training exercises conducted in endemic regions or in environments likely to pose a high risk of exposure. While the best way to avoid infection is to avoid contact with potentially contaminated bodies of water, operational and military needs may not allow for exposure avoidance. In these cases, preventive efforts should focus on chemoprophylaxis, the use of protective clothing and footwear, and covering cuts and abrasions with occlusive dressings.

The highest reported attack rates in military personnel (41% in Panama¹⁸ and 42% in Okinawa¹²) have occurred in troops undergoing jungle warfare training. Attack rates of this magnitude underscore that intense and concentrated exposure to contaminated environments can have a significant impact on unit capabilities.¹⁸

Although the standard doxycycline prophylaxis protocol was employed for personnel undergoing training in the 2014 Okinawa outbreak, Dierks et al. noted the apparent failure of doxycycline prophylaxis in this case and recommended further study into an ideal prophylaxis regimen with special emphasis on the evaluation of dosing frequency.¹² In addition, measures to increase adherence with any prophylaxis regimen are warranted.

Participation in recreational and water sport-related activities also pose a risk for military personnel as demonstrated by the

outbreaks in Guam in 2014 and Oahu in 1992. Military personnel should be educated to increase awareness of how the disease is contracted and to avoid contact with high risk bodies of water. High risk behaviors such as swallowing water and swimming with cuts or abrasions should be minimized. Any exposure to contaminated bodies of water should be avoided, especially in cases where posted warnings are located.

Although no outbreak in military personnel has yet been documented as a result of participation in a humanitarian or relief mission, these activities can also be a source of risk. U.S. military personnel are frequently deployed in support of disaster relief and after extreme weather events, especially in regions where leptospirosis is endemic and where conditions (e.g., flooding) increase risk for leptospirosis transmission. Threat briefings to military members engaged in these missions can emphasize measures to reduce exposure. Preventing future leptospirosis outbreaks requires vigilance on the part of line officers and preventive medicine staff to ensure that military personnel have been informed of both exposure risks and any and all available means of risk reduction.

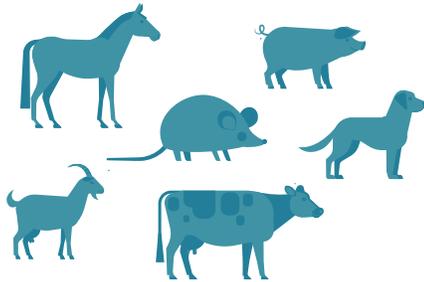
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Protect Yourself from Leptospirosis

After the Storm

Leptospirosis is a bacterial disease that can increase after hurricanes or floods when people may have to wade through contaminated water or use it for drinking or bathing.



People can get leptospirosis when they have contact with:

- urine from infected animals, which can include rodents, dogs, livestock, pigs, and wildlife.
- floodwater, freshwater like rivers or streams, unsafe tap water, wet soil, or food contaminated with the urine of infected animals.

The bacteria can enter the body through cuts or scratches or through the eyes, nose, or mouth.

Prevent It



Do not wade, swim, bathe, or put your head in, or swallow floodwater or any fresh water source that may be contaminated by floodwater or animal urine.



Cover cuts or scratches with waterproof bandages or other coverings that seal out water.



Do not walk outside barefoot. Wear waterproof protective clothing, gloves, closed shoes, or boots near water or wet soil that may be contaminated by animal urine or floodwater.



Treat potentially contaminated water to make it safe for drinking by boiling or chemically treating.



Prevent rodent infestation by keeping food and trash in closed containers and trapping rodents.

Learn the Symptoms

Flu-like symptoms



Get Treatment



If you have symptoms of leptospirosis, see a doctor as soon as possible. Early treatment with antibiotics may help prevent more severe illness and decrease how long you are sick. Without treatment, leptospirosis symptoms can get worse. People can develop kidney and liver failure, meningitis, difficulty breathing, bleeding, and, in some cases, people may die from their infection.



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Centers for Disease Control and Prevention

www.cdc.gov/leptospirosis

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Chief, Armed Forces Health Surveillance Branch

COL Douglas A. Badzik, MD, MPH (USA)

Editor

Francis L. O'Donnell, MD, MPH

Contributing Editors

Leslie L. Clark, PhD, MS

Shuana Stahlman, PhD, MPH

Writer/Editor

Valerie F. Williams, MA, MS

Managing/Production Editor

Valerie F. Williams, MA, MS

Layout/Design

Darrell Olson

Editorial Oversight

COL James D. Mancuso, MD, MPH, DrPH (USA)

CDR Shawn S. Clausen, MD, MPH (USN)

Mark V. Rubertone, MD, MPH

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