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BRIEF REPORT

Heavy alcohol use as a risk factor for severe outcomes among adults hospitalized with laboratory-confirmed influenza, 2005–2012

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Abstract We examined heavy alcohol use as a risk factor for severe influenza (intensive care admission or death) among hospitalized adults. In <65- and ≥65-year-olds, heavy alcohol use increased disease severity [relative risk (RR) 1.34; 95 % confidence interval (CI): 1.04–1.74, and RR 2.47; 95 % CI: 1.69–3.60, respectively]. Influenza vaccination and early, empiric antiviral treatment should be emphasized in this population.

Keywords Influenza · Alcohol abuse · Vaccination

Background

Alcohol is one of the most commonly abused drugs in the United States, with a prevalence of heavy drinking among adults of approximately 6 % [1]. In 2006, approximately 1.2 million emergency room visits were estimated to be due to excessive alcohol use [1]. The relationship between alcohol-related diagnoses and pulmonary infections is well established [1]. Alcohol-related diagnoses are a risk factor for community-acquired pneumonia, and have been associated with increased morbidity and mortality in those with pneumonia [2]. In addition, alcohol has known immunosuppressive effects, which can impair pulmonary immune function [3].

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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Most studies examining the relationship between alcohol and pneumonia focus on bacterial and mycobacterial etiologies [3]. Less is known about the relationship between heavy alcohol use and viral infections, including influenza. Since influenza is preventable and treatable, a better understanding of the association between excessive alcohol use and influenza could strengthen efforts to prevent or treat influenza in this population. We evaluated whether persons with heavy alcohol use were more likely to have severe outcomes among adults hospitalized with laboratory-confirmed influenza.

Methods

We used data collected through the Influenza Hospitalization Surveillance Network (FluSurv-NET). FluSurv-NET conducts population-based surveillance for laboratory-confirmed influenza-associated hospitalizations. The current network represents approximately 9 % of the US population (approximately 28 million people) [4].

For this investigation, case patients are defined as those ≥18 years of age hospitalized for community-onset, laboratory-confirmed influenza virus infection from October to April of the 2005–2006 through 2011–2012 influenza seasons. The 2009 influenza pandemic period includes data from April 2009 through April 2010. Cases were identified by reviewing hospital admission, laboratory, and infection control logs. Testing for influenza was conducted at the discretion of the treating clinician and includes any positive results by viral culture, direct or indirect fluorescent antibody staining, reverse transcription polymerase chain reaction, or rapid diagnostic test, 14 days or less prior to admission or up to 3 days after admission. A standard case-report form was completed for each case patient based on data abstracted from medical records and included demographics, high-risk underlying medical conditions as defined by the Advisory Committee on Immunization Practices (ACIP),[1] clinical outcomes, influenza vaccination history, and International Classification of Diseases, Ninth Revision (ICD9) discharge diagnoses [5].

For these analyses, heavy alcohol use was identified based on the clinician's assessment of heavy alcohol use recorded in the medical records, or if one of the first nine ICD9 hospital discharge diagnoses included (1) Alcohol dependence syndrome (ICD9 303.0–303.9) or (2) Alcohol withdrawal (ICD9 291.81). Alcohol dependence, often referred to as alcohol addiction or alcoholism, is a chronic disease which includes strong cravings for alcohol, continued use despite physical, psychological, or interpersonal problems, and the inability to limit drinking, and is often association with alcohol withdrawal [6].

Patients without these ICD9 codes, but with a discharge diagnosis indicating other forms of alcohol or drug abuse, including acute alcohol intoxication without alcohol dependence, were excluded from the analysis, since we could not interpret the extent of alcohol consumption. We also excluded pregnant women from the analysis, given that their increased risk for severity could be attributed to causes other than heavy alcohol use, and the number of observations were small and would not allow for stratification in the analysis [5]. Other underlying conditions were substantially more common and were considered as potential covariates in our final analysis.

We compared the characteristics of patients with and without heavy alcohol use for those aged <65 and ≥65 years separately. Chi-square and Fisher's exact tests were used to evaluate differences within age stratum. As we detected an interaction effect between age and heavy alcohol use, a regression model was built for each age group (i.e., <65 and ≥65 years) to identify factors independently associated with severe outcome. The outcome variable for the model was severe influenza, defined as death or intensive care unit (ICU) admission given the rare occurrence of death in the cohort. Variables included in each model were chosen based on the results of bivariate analysis and biologic plausibility. Data were analyzed using the SAS version 9.3 statistical software (SAS Institute Inc., Cary, NC).

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[1] Persons at higher risk for influenza complications include persons aged ≥65 years; persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle-cell disease), metabolic disorders (including diabetes mellitus), or neurological and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury); and persons with immunosuppression, including that caused by medications or HIV infection. For a complete list, see "Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010" [5].

Data collected were determined by the Centers for Disease Control and Prevention (CDC) to be for routine public health surveillance purposes and were not subject to institutional review board approval for human research protection.

Results

Among 15,676 adults hospitalized with laboratory-confirmed influenza from 2005 through 2012, there were 228 (1.5 %) adults with heavy alcohol use. Among the 190 patients <65 years old with heavy alcohol use, the majority were 40–64 years old (83 vs. 17 %, $p < 0.01$), and among the 38 patients ≥65 years old with heavy alcohol use, the majority were ≥75 years old (55 vs. 45 %, $p = 0.08$). Patients with heavy alcohol use were more likely to be male than female in both age groups ($p < 0.01$), and were less likely to have at least one underlying medical condition (<65 years: 64 vs. 77 %, $p < 0.01$; ≥65 years: 78 vs. 89 %, $p = 0.05$) when compared to those without heavy alcohol use (Table 1).

Patients of any age with heavy alcohol use were more likely to be admitted to the ICU than those without heavy alcohol use, and in patients aged ≥65 years, those with heavy alcohol use were more likely to be mechanically ventilated than those without (19 vs. 8 %, $p = 0.03$).

Vaccination rates varied by age, but were lower in patients with heavy alcohol use. Among patients aged <65 years for whom vaccination data were available, 38/140 (27 %) who had heavy alcohol use and 2,461/7,569 (33 %) who did not have heavy alcohol use received influenza vaccine ($p < 0.01$). Among patients aged ≥65 years for whom vaccination data were available, 19/33 (58 %) who had heavy alcohol use and 3,790/5,819 (65 %) who did not have heavy alcohol use received influenza vaccine ($p = 0.4$).

In the multivariate model, we further controlled for age (18–39, 40–64, 65–74, ≥75 years), presence of chronic lung disease, asthma, cardiovascular disease, chronic metabolic disease, and immunosuppressive condition, and influenza season (to account for differences in seasons). Because further age breakdown did not affect the results, age group was removed from the model and was not considered a potential confounder within age stratum. Among patients aged <65 years, those with heavy alcohol use were 1.3 times as likely to have severe influenza as those without heavy alcohol use [relative risk (RR) 1.34; 95 % confidence interval (CI): 1.04–1.74)]. Chronic lung disease, asthma, cardiovascular disease, chronic metabolic disease, and 2008–2009, 2009 pandemic, and 2010–2011 influenza seasons were also independently associated with severity. Among patients aged ≥65 years, those with heavy alcohol use were 2.5 times as likely to have severe influenza than those without heavy alcohol use (RR 2.47; 95 % CI: 1.69–3.60). Chronic lung disease, cardiovascular disease, and the 2008–2009 and 2009 pandemic influenza seasons were independently associated with severity (Table 2).

Discussion

In this study, heavy alcohol use is a risk factor for severe influenza (ICU admission or death) among those hospitalized with community-acquired influenza, especially in those aged ≥65 years. To our knowledge, this is the only epidemiologic study examining the association between heavy alcohol use and influenza among hospitalized patients. Alcohol is an immunosuppressant, affecting innate, cell-mediated, and humoral immunity, and increasing vulnerability to a variety of pulmonary infections [3]. Our findings are consistent with those demonstrated by Meyerholz et al. [7], who showed increased morbidity, mortality, viral load, and lung pathology, and inhibited immune response among influenza-infected mice exposed to alcohol compared to non-alcohol-exposed infected mice, providing plausible biologic mechanisms whereby alcohol use may directly increase the risk for more severe influenza.

In addition to the direct effects of alcohol exposure on pulmonary immune response, chronic exposure to alcohol is associated with a range of medical conditions that could play a role in severe influenza-related outcomes, including decreased respiratory tract ciliary response, aspiration of oropharyngeal contents, nutritional deficiencies, and decreased bone marrow activation in response to infection [3]. Alcohol-related liver diseases could also contribute to worse outcomes. Cirrhosis, a consequence of chronic liver disease, has been associated with increased risk of influenza complications [8]. Further evaluation of the independent effect of alcohol on influenza outcomes will need to take into account the role of alcohol-induced cirrhosis.

Chronic lung disease, cardiovascular disease, and chronic metabolic disease were independently associated with severe influenza. These findings are consistent with the seasonal and pandemic influenza literature [8]. In our analysis, asthma was associated with less severe disease. It could be that patients with asthma may be hospitalized due to asthma exacerbation or concern of severe complications, not necessarily due to a more severe influenza presentation. If that is the case, in our data, asthma may be a marker of less severe disease. This has been described in previous studies of hospitalized patients [9].

There are several limitations to this analysis. Categorizing alcohol use based on ICD9-coded discharge

Table 1 Demographics, chronic medical conditions, and outcomes associated with heavy alcohol use among adults <65 years and ≥65 years hospitalized with laboratory-confirmed influenza, 2005–2012

	Bivariate analysis					
	<65 years (n = 9,092)			≥65 years (n = 6,584)		
	Heavy alcohol use (n = 190)	No heavy alcohol use (n = 8,902)	p-value	Heavy alcohol use (n = 38)	No heavy alcohol use (n = 6,546)	p-value
Age (years)						
18–39	33 (17 %)	2,989 (34 %)	**<0.01**	–	–	0.08
40–64	157 (83 %)	5,913 (66 %)		–	–	
65–74	–	–		17 (45 %)	2,074 (32 %)	
≥75	–	–		21 (55 %)	4,472 (68 %)	
Sex						
Female	43 (23 %)	4,798 (54 %)	**<0.01**	8 (21 %)	3,738 (57 %)	**<0.01**
Male	147 (77 %)	4,104 (46 %)		30 (79 %)	2,807 (43 %)	
Influenza season						
2005–2006	7 (4 %)	332 (4 %)	**<0.01**	2 (5 %)	601 (9 %)	**<0.01**
2006–2007	9 (5 %)	282 (3 %)		1 (3 %)	293 (4 %)	
2007–2008	22 (12 %)	1,011 (11 %)		6 (16 %)	1,578 (24 %)	
2008–2009	6 (3 %)	455 (5 %)		2 (5 %)	311 (5 %)	
2009 pandemic	54 (28 %)	3,840 (43 %)		6 (16 %)	773 (12 %)	
2010–2011	40 (21 %)	2,209 (25 %)		5 (13 %)	2,059 (31 %)	
2011–2012	52 (27 %)	773 (9 %)		16 (42 %)	931 (14 %)	
Medical condition[a,b]	122 (64 %)	6,831 (77 %)	**<0.01**	30 (78 %)	5,832 (89 %)	0.05
Chronic lung disease[c]	47 (25 %)	1,622 (18 %)	**0.02**	21 (55 %)	2,062 (32 %)	**<0.01**
Asthma	40 (21 %)	2,611 (29 %)	**0.01**	5 (13 %)	790 (12 %)	0.8
Cardiovascular disease[d]	20 (14 %)	1,612 (19 %)	0.07	16 (52 %)	3,547 (58 %)	0.5
Chronic metabolic disease	41 (22 %)	2,665 (30 %)	**0.01**	15 (39 %)	2,737 (42 %)	0.8
Renal disease	16 (8 %)	978 (11 %)	0.3	8 (21 %)	1,311 (20 %)	0.9
Hemoglobinopathy	2 (1 %)	161 (2 %)	0.4	2 (5 %)	73 (1 %)	**0.02**
Neuromuscular disorder	0 (0 %)	477 (5 %)	**<0.01**	0 (0 %)	420 (6 %)	0.1
Cognitive dysfunction	2 (1 %)	428 (5 %)	**0.02**	4 (11 %)	939 (14 %)	0.5
Immunosuppressive condition	18 (9 %)	1,490 (17 %)	**0.01**	2 (5 %)	573 (9 %)	0.4
Morbid obesity	5 (3 %)	437 (5 %)	0.4	0 (0 %)	152 (2 %)	1.0
Discharge diagnosis						
Pneumonia	65 (34 %)	3,223 (36 %)	0.6	18 (47 %)	2,461 (38 %)	0.2
Encephalitis	4 (2 %)	89 (1 %)	0.1	0 (0 %)	87 (1 %)	1.0
Hospital outcome[e]						
Death	6 (3 %)	305 (3 %)	0.8	3 (8 %)	331 (5 %)	0.4
ICU	54 (28 %)	1,901 (21 %)	**0.02**	15 (39 %)	1,072 (16 %)	**<0.01**
Mechanical ventilation	31 (16 %)	1,067 (12 %)	0.1	7 (19 %)	518 (8 %)	**0.03**

[a] If no medical condition was noted in the medical chart, it was assumed that there was no underlying medical condition

[b] If the patient had at least one of the listed medical conditions, they were included as having a medical condition

[c] Chronic lung disease excludes asthma

[d] Cardiovascular disease excludes patients with hypertension only

[e] The denominator varies depending on the data available for each outcome. Outcomes are not mutually exclusive

diagnoses may lead to misclassification. If a patient had a history of heavy alcohol use which was not listed as one of the first nine discharge diagnoses, they could be misclassified as non-heavy alcohol users, which would bias our results towards the null, underestimating the association between alcohol and influenza severity. It is worth noting that the overall prevalence of heavy alcohol use in our cohort was substantially lower than that in the

Table 2 Multivariate regression for the association of heavy alcohol use with severe disease among adults aged <65 years and ≥65 years hospitalized with laboratory-confirmed influenza, 2005–2012

Variables	Multivariate regression			
	<65 years old		≥65 years old	
	Adjusted relative risk[a] (95 % CI)	*p*-value	Adjusted relative risk[a] (95 % CI)	*p*-value
Heavy alcohol use	1.34 (1.04–1.74)	**0.02**	2.47 (1.69–3.60)	**<0.01**
Chronic lung disease	1.35 (1.23–1.48)	**<0.01**	1.51 (1.36–1.68)	**<0.01**
Asthma	0.85 (0.77–0.93)	**<0.01**	–	–
Cardiovascular disease[b]	1.12 (1.02–1.24)	**0.02**	1.41 (1.26–1.57)	**<0.01**
Chronic metabolic disease	1.29 (1.19–1.40)	**<0.01**	–	–
Immunosuppressive condition	1.07 (0.97–1.12)	0.2	–	–
Influenza season 2005–2006	Ref	Ref	Ref	Ref
Influenza season 2006–2007	1.16 (0.82–1.64)	0.4	1.15 (0.86–1.52)	0.4
Influenza season 2007–2008	0.96 (0.72–1.28)	0.8	0.84 (0.68–1.04)	0.1
Influenza season 2008–2009	1.46 (1.08–1.97)	**0.01**	1.36 (1.05–1.77)	**0.02**
2009 pandemic	1.68 (1.30–2.17)	**<0.01**	1.45 (1.18–1.79)	**<0.01**
Influenza season 2010–2011	1.38 (1.06–1.79)	**0.02**	1.08 (0.89–1.31)	0.5
Influenza season 2011–2012	1.23 (0.85–1.77)	0.3	0.87 (0.67–1.11)	0.3

Outcome is combined death or intensive care unit (ICU) admission. Model A includes patients aged <65 years and Model B includes patients aged ≥65 years. Variables were chosen from each model based on the underlying medical conditions that were significant in the bivariate analysis, as well as those which may be confounders based on biologic plausibility

[a] Neuromuscular disorder was not included as a variable in the model for patients aged <65 years since it was not recorded in any patient who abused alcohol. Asthma, chronic metabolic disease, and immunosuppression were not included in the model for patients aged ≥65 years since they were not significant in the bivariate analysis

[b] Cardiovascular disease excludes patients with hypertension only

general US population (1.5 vs. 6 %, respectively). Second, we did not collect information on smoking status throughout the study period. Alcohol use is associated with smoking, and being a smoker could partially explain the increased risk for influenza severity in this group, even though we controlled for the presence of chronic lung disease and cardiovascular disorders. Finally, we had a small number of patients with heavy alcohol use, with limited range of age and vaccination status. This did not allow us to include vaccination status in the multivariable analysis or explore further the potential effect of age on severity.

Our analysis shows an increased risk of severe disease among hospitalized patients with laboratory-confirmed influenza and heavy alcohol use, especially among those aged ≥65 years. These findings indicate that alcohol use is likely a risk factor for severe influenza. Corroboration of these findings with additional studies is important to establish alcohol use as a risk factor for severe influenza outcomes. Universal influenza vaccination is currently recommended in the United States, and vaccination is the best means of preventing influenza and its complications [5]. However, given the challenges in providing primary care to those with alcohol abuse, this population may be less likely to receive influenza vaccine [10]. Providers should consider ensuring vaccination among this potentially high-risk population and use any medical encounter, including emergency department visits, as an opportunity to offer vaccination to this population. When patients with a history of heavy alcohol use present with influenza-like illness during the influenza season, providers should be aware that they are potentially at high risk of influenza-related complications, and may consider prompt empiric antiviral treatment to improve outcomes in this vulnerable population.

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Conflict of interest No potential conflict of interest.

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