REVIEW

CME MOC

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Pneumonia and alcohol use disorder: Implications for treatment

ABSTRACT

Patients with alcohol use disorder (AUD) are at higher risk of pneumonia and of poor outcomes. This article reviews the etiology of pneumonia in patients with AUD, its impact on mortality and resource utilization, and its implications for treatment.

KEY POINTS

Contrary to common belief, pneumonia due to *Klebsiella pneumoniae* or other gram-negative organisms is not more common among patients with AUD than in the general population.

Pneumonia patients with AUD have a higher prevalence of *Streptococcus pneumoniae* infection than other pneumonia patients.

Broad-spectrum antibiotics to empirically cover gram-negative organisms are not necessary for patients with AUD unless other risk factors are present, such as hospitalization in the past 90 days or previous infection with a resistant gram-negative organism.

Hospitalized patients should be monitored for signs of alcohol withdrawal syndrome, which is a key contributor to increased morbidity and mortality.

All adults with AUD should be given pneumococcal vaccine.

Dr. Deshpande has disclosed membership on advisory committees or review panels for Ferring Pharmaceuticals.

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Alcohol consumption is a risk factor for community-acquired pneumonia and for poorer outcomes of community-acquired pneumonia. In theory and according to conventional wisdom, patients with community-acquired pneumonia who are heavy drinkers should be at greater risk of infection with gram-negative organisms such as *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* than nondrinkers, but clinical studies do not bear this out. However, patients who are heavy drinkers are at greater risk of infection with *Streptococcus pneumoniae*, a gram-positive organism.

In this article, we review the pathophysiologic and epidemiologic evidence regarding the organisms responsible for pneumonia in patients who drink. We also examine the impact of drinking on mortality and resource utilization.

PNEUMONIA AND ALCOHOL USE DISORDER ARE COMMON

Community-acquired pneumonia is the most common cause of death due to infectious disease.[1] Its severity is influenced by patient factors such as age, sex, immune status, smoking, and comorbidities.[2]

Alcohol use disorder (AUD) affects about 6% of the adult population in the United States.[3] It is common among patients hospitalized for pneumonia,[4] and there is a strong and consistent relationship between AUD and risk of community-acquired pneumonia.[5]

Although strictly speaking, AUD is a psychiatric diagnosis, we will use the term to describe heavy alcohol consumption in general.

ALCOHOL IMPAIRS HOST DEFENSES

Alcohol consumption contributes to development of pneumonia in a number of ways, altering the body's flora and impairing defensive mechanisms along the entire length of the respiratory tract.

Chronic alcohol intake contributes to malnutrition, which further leads to breakdown of local protective barriers in the respiratory tract.[6] It alters the oropharyngeal flora, facilitating colonization by gram-negative organisms in the oral cavity.

Alcohol blunts mental function and suppresses cough and gag reflexes, thus increasing the risk of aspiration.[7,8] It decreases mucociliary clearance,[9] impairing both innate and acquired immunity.[10] It decreases phagocytic function of the alveolar macrophages, reduces the production of chemokines, and blunts chemotaxis of neutrophils.[11] Impaired recruitment of neutrophils suppresses pulmonary clearance of bacteria.[10] Alcohol also lowers the granulocyte and lymphocyte counts.[12–14]

By impairing host defense mechanisms, alcohol increases susceptibility to a wide range of pathogens: gram-positive, gram-negative, aerobic, anaerobic, mycobacterial, fungal, and viral.[10] The combination of virulent pathogens and weakened host defenses is thought to contribute to the severity and poor outcomes of pneumonia in patients with AUD.[2,10]

Alcohol alters the body's flora and impairs defense mechanisms in the respiratory tract

SEVERE DISEASE, POOR OUTCOMES

Alcohol also adversely affects other organ systems required to support an immune response. Comorbidities associated with AUD include liver disease and cirrhosis, diabetes, hypertension, coronary artery disease, cardiomyopathy, heart failure, dementia, psychiatric disorders, kidney disorders, and cancers.[15] As a result, pneumonia in patients with AUD is characterized by worse symptoms, more complications, greater likelihood of developing resistant pathogens, and poorer outcomes.[2,10]

AUD has traditionally been associated with higher age-adjusted mortality rates[16,17] and greater resource utilization, including intensive care, mechanical ventilation, longer stay, and higher cost.[2,4,18,19] There are several potential explanations.

First, patients with AUD have a more severe presentation, often with bilateral or multilobar pneumonia[16] necessitating mechanical ventilation. Alcohol is also a major contributor to malnutrition,[6] which results in immune suppression,[6,7,10,20] with a direct toxic effect on lung health.[21,22]

Second, patients with AUD frequently have comorbid illnesses, including liver, kidney, and cardiac disorders,[15] which could complicate the pneumonia.

Lastly, abstinence can precipitate alcohol withdrawal syndrome, which may increase length of stay and risk of death.[23,24]

Epidemiologic evidence for higher mortality rates in AUD

In the early 1900s, Capps and Coleman[17] found a direct relationship between alcohol intake and higher mortality rates in patients with pneumonia. With the advent of antibiotics, however, the impact of alcohol on mortality diminished.[4] In a 1990 meta-analysis of 127 studies, Fine et al[25] found that alcohol use was not associated with mortality in patients with pneumonia, and in a prospective study, Mortensen et al[26] found no association between AUD and pneumonia-related mortality.

Patients with AUD also tend to be more likely to need intensive care. de Roux et al[2] and Saitz et al[4] attributed this to a direct toxic effect of alcohol, but they did not consider alcohol withdrawal syndrome. Taking this factor into account, the increase in intensive care unit transfers appears limited to patients with alcohol withdrawal syndrome, implying that there is no contribution from a direct toxic effect.[18]

Similarly, many studies have found an association between AUD and greater length of stay, leading to greater hospital cost.[2,4,16,18] Lack of social support and homelessness might contribute to a longer hospital stay. However, the increased length of stay was also limited to patients with alcohol withdrawal syndrome,[18] making it unlikely that social determinants of health contributed to the increased length of stay.

GRAM-NEGATIVE ORGANISMS: WEAK EVIDENCE FOR TREATMENT

Because the pathogen is unknown at the time of diagnosis in most patients with pneumonia, including those with AUD, treatment is

TABLE 1

Recommended treatment for pneumonia

Setting	Patients with risk factors for resistant gram-negative organisms	Patients without risk factors
Outpatient	A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin), or A beta-lactam (high-dose amoxicillin or amoxicillin-clavulanate, or ceftriaxone, cefpodoxime, cefuroxime) plus a macrolide (azithromycin, clarithromycin, or erythromycin) Doxycycline can be an alternative to a macrolide	A macrolide (azithromycin, clarithromycin, or erythromycin), or Doxycycline, or Amoxicillin
Inpatient, not in intensive care	An antipneumococcal, antipseudomonal beta-lactam (eg, piperacillin-tazobactam) plus either ciprofloxacin or levofloxacin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone For penicillin-allergic patients, substitute aztreonam for the beta-lactam	A respiratory fluoroquinolone, or A beta-lactam (cefotaxime, ceftriaxone, ampicillin, or ertapenem) plus a macrolide Doxycycline can be an alternative to macrolide A respiratory fluoroquinolone should be used for penicillin-allergic patients
Intensive care	An antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin, or An antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone For penicillin-allergic patients, substitute aztreonam for the beta-lactam	A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam

Based on information in references 1, 27, and 28.

primarily empiric. To be effective, the choice of antibiotic should be informed by an understanding of the most common microorganisms.

Guidelines for the treatment of community-acquired pneumonia from the Infectious Diseases Society of America (IDSA) recognize alcoholism as a major risk factor for infection with *P aeruginosa* and other gram-negative organisms.[1,27,28]

In inpatients, recommended empiric therapy for patients at risk of resistant infections (**Table 1**)[1,27,28] includes broad-spectrum antibiotics with activity against resistant gram-negative organisms (eg, antipneumococcal, antipseudomonal beta-lactam antibiotics, respiratory fluoroquinolones, and aminoglycosides).

However, despite long-held beliefs about the etiology of pneumonia in patients with AUD, the evidence cited in the 2007 guideline[27] in support of this recommendation is weak.

In theory, gram-negative organisms should be more common

Due to poor dental hygiene, AUD patients are more susceptible to periodontal disease and dental caries, which provide a hospitable environment for anaerobes, increasing their concentration among the oral flora.[29] Anaer-

TABLE 2

Studies finding a higher prevalence of oropharyngeal colonization with gram-negative organisms in people with alcohol use disorder

Study	Population	Findings
Dao et al,[32] 2014	613 men, rural Vietnam	*Klebsiella pneumoniae* was the most common gram-negative organism, isolated in the nasopharynx in 28% *K pneumoniae* was found in 23% of light drinkers, 30% of moderate drinkers, and 34% of heavy drinkers Weekly alcohol consumption was associated with *K pneumoniae* oropharyngeal carriage (OR 1.7; 95% CI 1.04–2.8)
Mackowiak et al,[31] 1978	124 people with AUD and 84 controls, Dallas, TX	Colonization with gram-negative bacilli in 35% of those with AUD vs 18% of controls Of those with AUD who had gram-negative colonization, 33% had *Enterobacter* species and 23% had *Escherichia coli*
Fuxench-Lopez et al,[33] 1978	34 with AUD and 28 controls, Puerto Rico	Gram-negative colonization in 59% of those with AUD and 14% of controls Among AUD samples, *K pneumoniae* accounted for 40% of the pharyngeal secretions and 76% of the isolates were in the *Klebsiella-Enterobacter* group of organisms
Golin et al,[34] 1998	58 with AUD and 59 controls, Brazil	Gram-negative organisms in 49% of those with AUD and 40% of controls Anaerobic microbes were present in 85% of those with AUD vs 31% of controls

AUD = alcohol use disorder

obes are important pathogens in aspiration pneumonia in patients with AUD.[30]

Alcohol also induces changes in the defense mechanisms of the upper respiratory tract. Inability of the host to block the attachment of the microorganisms by coating them with specific immunoglobulin A or nonspecific glycoproteins[31] allows gram-negative organisms to adhere to the mucosal surface more easily, while impairment of leukocyte function also favors gram-negative colonization.

As a result, the pharynx of patients with AUD may be colonized with gram-negative organisms, which might predispose to gram-negative pnemonia.[31–33] Indeed, studies in which swabs of the oropharynx of patients with AUD were compared with those of controls without AUD found higher prevalences of gram-negative organisms, in particular *K pneumoniae* (**Table 2**).[31–34]

Aspiration of commensal oropharyngeal bacteria

Alcohol is a potent inhibitor of the central nervous system and depresses the cough reflex.[10] In addition, loss of consciousness and vomiting due to alcohol intoxication is one of the most common reasons for aspiration.[35] Aspiration of oropharyngeal bacteria including anaerobic ones such as *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, and *Bacteroides fragilis* could result in a wide variety of lung infections ranging from simple pneumonitis to necrotizing pneumonia, lung abscesses, and empyema.[36]

CLINICAL STUDIES OF ALCOHOL AND ORGANISMS

Because pneumonia remains a clinical diagnosis and the causative organism is not known in most patients, there is always some uncertain-

TABLE 3

Prevalence of gram-negative organisms in pneumonia patients with or without alcohol use disorder

Study	No. of patients, location	Gram-negative organisms	With AUD	Without AUD	Gram-positive organisms	With AUD	Without AUD
Fernández-Solá et al,[16] 1995	50, Barcelona	Gram-negative bacilli	19%	0[a]	*Streptococcus pneumoniae*	6%	6%
Marik,[39] 2000	148, United States and Canada	*Pseudomonas aeruginosa* and *Acinetobacter* species	22%	5%[a]			
Arancibia et al,[38] 2002	559, Barcelona	Gram-negative bacilli	11%	11%			
Paganin et al,[37] 2004	112, Réunion Island	*Klebsiella pneumoniae*	30%	10%[a]			
Saitz et al,[4] 1997	23,198, Massachusetts	*Haemophilus influenzae* Gram-negative bacilli	5% 2.5%	3.5%[a] 4%	*S pneumoniae* *Staphylococcus sp.*	15% 3%	6%[a] 2%
de Roux et al,[2] 2006	1,347, Europe	Gram-negative bacilli *Pseudomonas aeruginosa* *H influenzae*	9% 5% 2%	11% 3% 4%	*S pneumoniae*	27%	16%[a]
Gupta et al,[18] 2019	137,496, United States	*Escherichia coli* *K pneumoniae* *P aeruginosa*	7% 6% 1%	10%[a] 7%[a] 1%	*S pneumoniae* *Staphylococcus aureus*	6% 4%	2%[a] 3%

[a]Statistically significant ($P < .05$).
AUD = alcohol use disorder

ty in treating it. The cause might be a virus or it could be a bacteria that can't be cultured. When an organism is present it is most often *Staphylococcus* or *Streptococcus* spp.

A number of retrospective and prospective studies have examined the association between AUD and types of organisms (**Table 3**).[2,4,16,18,37–39] In total, nearly 6,000 patients with AUD were compared with nearly 160,000 patients without AUD. However, we could find no studies of the impact of AUD on the ability to isolate specific pathogens.

Gram-negative organisms

In support of the association between AUD and gram-negative infections, the IDSA guideline cites 2 studies, one by Paganin et al[37] and the other by Arancibia et al.[38]

Paganin et al[37] performed a prospective study at a tertiary hospital on Réunion Island in the Indian Ocean in the 1990s. Among 112 patients with community-acquired pneumonia admitted to the intensive care unit, those with *K pneumoniae* were more likely than those with pneumonia due to other pathogens to abuse alcohol (84% vs 56%, $P < .001$).

Arancibia et al[38] prospectively studied 559 patients hospitalized in Barcelona, Spain. Interestingly, their findings do not support the assertion in the guideline—the prevalence of gram-negative bacteria was the same (13%) in patients with or without AUD.

Fernández-Solá et al,[16] in a retrospective study of patients with community-acquired pneumonia in an emergency department also in Barcelona, found that gram-negative bacilli were present in 3 of 16 patients with AUD and 0 of 34 patients without AUD.

Another retrospective study,[39] in 148 patients with septic shock, 23 of whom had

AUD, found that *Pseudomonas* and *Acinetobacter* were more common in patients with AUD than in those without AUD (22% vs 5%, $P = .01$).

In contrast, 2 prospective[2,38] and 2 retrospective[4,18] studies, including nearly 6,000 patients with AUD and more than 150,000 without AUD, found no association between AUD and gram-negative infections.[18] In fact, the largest study found that gram-negative infections were *less* common in patients with AUD.[18]

The reason for these discrepancies is unclear. It may be related to differing populations, due either to region—it has been suggested that *Klebsiella* is associated with AUD around the Indian Ocean in particular—or patient factors that have evolved over time.[40] Patients with pneumonia are generally sicker now than they were 30 years ago, with more comorbidities that may predispose them to gram-negative infections.

Streptococcus pneumoniae is more common in AUD

By impairing host defenses, alcohol increases susceptibility to a wide range of pathogens

S pneumoniae has long been known as a common cause of community-acquired pneumonia.[27] Several studies (**Table 3**)[2,4,16,18] have confirmed that it is more common among patients with AUD than those without AUD.

In a large retrospective study conducted almost 25 years ago, Saitz et al[4] found that of 23,198 patients who were admitted to hospitals in Massachusetts with a principal diagnosis of pneumonia, 824 (4%) had AUD. *S pneumoniae* was present in 15% of patients with AUD compared with 6% in those without AUD ($P < .0001$).

In a prospective study conducted in Europe, de Roux et al[2] also found that *S pneumoniae* was significantly associated with pneumonia in patients with AUD (27% vs 16%, $P = .005$).

In the largest and most recent study, Gupta et al[18] found that *S pneumoniae* was present in 6% of pneumonia patients with AUD compared with 2% of patients without AUD ($P < .0001$).

With the advent of pneumococcal vaccine 2 decades ago and the recommendation for vaccination in high-risk AUD patients, the incidence of *S pneumoniae* pneumonia was expected to drop. Instead, the percent of pneumonia cases that were due to *S pneumoniae* pneumonia in the most recent study was higher than in studies conducted more than 20 years ago.[2,4,18] This was particularly true for patients with AUD, which suggests failure to follow vaccination guidelines in this population.

Less-common organisms

***Mycobacterium tuberculosis*.** A meta-analysis by Lönnroth et al[41] found that compared with the general population, the risk of pulmonary tuberculosis is substantially higher in people with AUD (pooled effect size 2.94, 95% CI 1.89–4.59). In patients with tuberculosis, excessive alcohol consumption is also a risk factor for more extensive disease, hospitalization, and death.[10] Also, patients with tuberculosis who have AUD tend to have recurrent hospitalizations and thus greater resource utilization.[42]

However, baseline rates of tuberculosis in the United States are low, and patients with AUD should not be immediately suspected of having it unless they have other risk factors such as immunocompromised status, close contact with patients with tuberculosis, or occupational risk.[43]

Pneumocystis jirovecii (formerly called *P carinii*) is a common cause of pneumonia in immunocompromised patients. Because patients with AUD have depressed cell-mediated immunity, they are in theory susceptible to it,[13] but we found only 1 case report of *P jirovecii* pneumonia in a human immunodeficiency virus-negative patient with AUD.[44]

IMPLICATIONS FOR TREATMENT

When they come to the hospital with pneumonia, patients with AUD are often empirically treated with broad-spectrum antimicrobials of different classes to cover resistant gram-negative and gram-positive organisms.[2,16,18,26,45] The IDSA guidelines support this approach. In addition, the more severe presentation of pneumonia in this population may influence physicians to choose broader coverage.

However, despite sound theoretical reasons that patients with AUD should be at risk for gram-negative infections, the epidemiologic data do not support this association. If anything, patients with AUD are at lower risk of gram-negative infections. This is important

because broader-spectrum antibiotics may put patients at higher risk of acute kidney injury, *Clostridioides difficile* infection, and future antimicrobial resistance. Quinolones in particular have been the subject of recent concern regarding hypoglycemia and cognitive disturbances, including delirium.

AUD is a risk factor for *S pneumoniae* and perhaps invasive infections. All recommended regimens for community-acquired pneumonia provide adequate coverage for *S pneumoniae*, and should have fewer side effects than broader-spectrum agents. Patients with AUD should therefore receive the same empirical therapy as other patients with community-acquired pneumonia unless they also have other risk factors for resistant infections such as hospitalization in the past 90 days or previous infection with a resistant gram-negative organism.

If a patient with AUD does not respond to initial treatment, clinicians should consider less-common causes of pneumonia, including resistant gram-negative organisms, anaerobes, *M tuberculosis*, and *P jirovecii*.

Abstinence from alcohol during hospitalization can lead to alcohol withdrawal syndrome, especially when a patient's alcohol use is not known to the treating physician. Delirium tremens, seizures, and hallucinations increase the risk of adverse outcomes in alcohol withdrawal syndrome.[23,24] Prompt recognition and management of alcohol withdrawal syndrome can improve outcomes and may help reduce resource utilization.

Pneumococcal vaccination is recommended for all patients with AUD. For those between the ages of 19 and 65 years, only the 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended. Because widespread use of the 13-valent pneumococcal conjugate vaccine (PCV13) in children has markedly reduced the prevalence of those strains included in the vaccine, sequential use of PCV13 plus PPSV23 is reserved for patients at very high risk, including those with chronic kidney disease or immunocompromised status, and is now optional for patients older than 65 years.[46] Shared decision-making is recommended in this age group, and alcohol use may be considered a risk factor. Although there is little harm in receiving PCV13, it is costly and offers limited benefit. Because patients with AUD may neglect self-care and lack a primary care provider, vaccination prior to discharge is a reasonable strategy to prevent future pneumonias.

SUMMARY

Despite pathophysiologic theories for why patients with AUD should be at increased risk for resistant gram-negative infections, a number of prospective and retrospective studies demonstrate that they are at increased risk for *S pneumoniae* but not resistant gram-negative infections. Patients with AUD also tend to use more medical resources, primarily because of alcohol-related comorbidities and alcohol withdrawal syndrome. Unless other risk factors for drug-resistant organisms are present, patients with AUD should receive guideline-recommended empirical therapy for community-acquired pneumonia, with attention to early signs of alcohol withdrawal syndrome.

Abstinence from alcohol during hospitalization can lead to alcohol withdrawal syndrome

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