The Effect of Alcohol Consumption on Risk for Sepsis and ARDS

E. L. Burnham, M. Moss, and G. S. Martin

Introduction

Alcohol is the most frequently abused drug throughout the world, and alcohol-related problems are a common occurrence among patients admitted to hospitals and intensive care units (ICUs). Alcohol affects all tissues of the body. Its effects on immune function and the systemic inflammatory response syndrome (SIRS) remain topics of active investigation. In regard to immune function, alcohol consumption alters the response at several points along the inflammatory cascade. Due to these potent modulating effects on immune function, alcoholic patients have an increased incidence and severity of infection, particularly in the lung. This association between alcohol use and infection is especially evident in the post-operative setting. Among patients with sepsis, a prior history of chronic alcohol abuse confers a significant increase in the likelihood of respiratory dysfunction and development of acute respiratory distress syndrome (ARDS). Chronic alcohol abuse similarly increases the mortality from ARDS. One possible mechanism by which chronic alcohol abuse may increase susceptibility to acute lung injury (ALI) is through alterations in pulmonary glutathione homeostasis. This chapter discusses the immunomodulatory effects of alcohol and the epidemiological and experimental evidence associating chronic alcohol abuse, sepsis, and the development of ARDS.

Background

Alcohol is the most commonly abused drug in the world, with approximately half the US population consuming alcohol regularly. Fifteen to twenty million individuals meet the criteria for alcoholism [1]. The economic cost of alcohol in the USA is around $100 billion (USD), with >10% of this cost directly attributable to medical services [2]. Alcohol is a leading cause of preventable mortality, and is associated with 100 000 deaths per year.

Up to 40% of all hospitalized patients have alcohol-related disorders [3]. Alcoholism is a problem of particular concern in the ICU, where the morbidity and mortality in all alcoholic patients admitted to ICU is many-fold times higher than the rate in non-alcoholics [4]. To further illustrate this point, one study examined 435 patients admitted to the ICU of a tertiary referral center [5]. Of these admissions, 9% were alcohol-related, which generated 13% of overall costs for this ICU. Alcohol is often associated with major injuries, and nearly 50% of trauma deaths are related to alcohol ingestion [6]. The prevalence of chronic alcoholics among patients with trauma admitted to the ICU ranges from 23–68%, and these alcoholics

J.-L. Vincent (ed.), *Intensive Care Medicine*

will often have a prolonged ICU stay due to infectious complications, including sepsis [4].

Alcohol can adversely affect all tissues of the body. The liver appears to be the organ most susceptible to the effects of alcohol; early changes of fatty liver may progress to hepatitis and ultimate fibrosis with hepatic cirrhosis [1]. Alcohol can also affect other parts of the gastrointestinal system, causing acute erosive gastritis, diarrhea, and pancreatitis. Heavy alcohol consumption can lead to a myriad of cardiac abnormalities, including cardiomyopathies, arrhythmias, and possibly coronary disease. Alcohol has a potent vasopressor effect, which could explain the association between its use and hypertension [1]. In the central nervous system (CNS), protracted alcohol use has been associated with cerebellar degeneration.

The effect of chronic alcoholism in the lung is relatively unexplored. In the 1960s, a high incidence of pulmonary disorders among alcoholics was observed, believed to be attributable to these patients' coincident poor overall health [7]. Recently, the effects were described of chronic alcohol abuse on the development of ARDS, a common complication of sepsis. Given the combination of the increased incidence of sepsis [8] and the extremely high prevalence of alcohol as a drug of abuse, the effect of alcohol on sepsis bears closer examination.

Alcohol and Immune Function

Mechanisms by which infections in alcoholics can lead to sepsis include an increased risk of aspiration, malnutrition, and alterations in the gut/liver/lung/inflammatory axis [9]. More importantly, alcohol is a potent immunosuppressive drug that impairs immunity, independent of a patient's nutritional status [6].

The abnormalities seen in the immune function of alcoholics are protean and include suppression of neutrophil chemotaxis, spleen cell mitogenesis, and serum immunoglobulin production [6]. The effect of alcohol on the immune system varies depending on whether the ingestion is acute or chronic (Tables 1 and 2). In acute alcohol abuse, neutrophil adhesion and chemotaxis are impaired, whereas in chronic alcohol abuse, these activities are unaffected. However, in chronic alcoholics, the marrow production of neutrophils is diminished, and these cells have reduced superoxide production [2].

Table 1. Effects of acute alcohol abuse on immune function

Immune component	Effects
Neutrophil function	Diminished adhesion and chemotaxis Normal phagocytosis Normal intracellular killing
Pulmonary clearance	Decreased ciliary activity Decreased bacterial clearance
Macrophage function	Decreased production of tumor necrosis factor Decreased production of granulocyte colony stimulating factor Decreased superoxide activity

Table 2. Effects of chronic alcohol abuse on immune function

Immune component	Effects
Neutrophil function	Decreased marrow production Decreased superoxide production Normal adherence and chemotaxis
Surfactant function	Reduced anti-pneumococcal activity
Macrophage function	Decreased superoxide production

After exposure to bacterial toxins, macrophages secrete tumor necrosis factor (TNF) and reactive oxygen intermediates. In a rat model of sepsis, lipopolysaccharide (LPS) was demonstrated to induce a dramatic release of TNF [10]. When these study animals were given alcohol shortly before an LPS infusion (to simulate acute ingestion), the release of TNF was markedly attenuated. Additionally, in another model of acute alcohol abuse [11], septic rats exhibited diminished alveolar macrophage hydrogen peroxide production. In contrast, animals chronically fed ethanol do not exhibit reductions in their TNF production [10]. However, isolated alveolar macrophages from chronic alcoholic patients release less TNF in response to stimulation than alveolar macrophages from normal individuals [12].

Alcohol has been reported to have direct suppressive effects on the bone marrow, and can inhibit neutrophilic granulopoiesis through inhibition of granulocyte colony stimulating factor (G-CSF) release from T cells [13]. Leukopenia appears to be a phenomenon of chronic alcoholics, and is not observed in acute ethanol ingestion [14].

Surfactant has a demonstrated, potent bactericidal activity against invading pulmonary pathogens, which is believed to be secondary to the detergent-like activity of surfactant long-chain free fatty acids (FFAs) [15]. Chronic alcohol abuse causes deficiencies in the amount of these FFAs produced by alveolar type II cells [16, 17], and induces the release of surfactant inhibitors, thus preventing optimal surfactant function [17]. These abnormalities lead to decreased opsonization of microorganisms and reduced bactericidal activity.

Alcohol has been reported to enhance intestinal permeability, leading to abnormalities in intestinal epithelial barrier function [18]. Increased intestinal permeability can facilitate bacterial translocation, a process by which gut flora or bacterial products traverse the abnormal intestinal barrier and ultimately reach mesenteric lymph nodes and the portal circulation. The translocation of bacteria can ultimately lead to sepsis and provoke the release of inflammatory cytokines such as TNF-α. Chronic low-grade immune system stimulation, such as this, is believed to decrease the efficacy of the defenses necessary to ward off secondary infectious challenges [9].

The Relationship between Alcohol and Infectious Diseases

The recognition of alcohol as a contributing factor for infectious diseases has been noted since the 1700s [19]. The prototypic infection of alcoholics is pneumonia and many investigations have been performed examining the association between alco-

holism and pneumonia. In 1905, Sir William Osler postulated that the single most important predisposing condition for bacterial pneumonia was alcohol abuse [20]. Typically, 25–50% of all general hospital patients admitted with pneumonia will carry a concomitant diagnosis of alcoholism. One study examined the hospital discharge data of all adults hospitalized with a principal diagnosis of pneumonia during 1992 in Massachusetts, USA [21]. Over 23 000 cases of pneumonia were identified. Although the patients who carried an alcohol-related diagnosis were younger and had fewer co-morbid illnesses (such as diabetes), hospital charges, length of stay, and ICU utilization were significantly higher for this group.

The type of organisms causing pneumonia in alcoholics differs from those in the general community, with a predominance of intracellular pathogens. These bacteria include *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis*. In both animal and human models, alcohol appears to increase susceptibility to these types of infections, decrease the ability of the host to clear organisms, and enhance the spread of these organisms to the bloodstream, resulting in bacteremia [22, 23]. In addition, alcoholics typically have a higher incidence of gingivodental disease and higher likelihood of aspiration, resulting in a higher frequency of anaerobic lung infections [2].

Over 15 years ago, the association of alcoholism, leukopenia, and pneumococcal sepsis was described as a distinct clinical entity [13]. This syndrome, known as ALPS, occurred mainly in younger men and carried with it an extremely high mortality. However, more recent data pertaining to mortality ascribable to pneumonia among alcoholics are conflicting, with some reports in the literature showing no effect on mortality in the post-antibiotic era [24]. A meta-analysis attempting to elucidate prognostic factors for increased mortality from community-acquired pneumonia (CAP) reviewed 120 studies of CAP, excluding those patients with nosocomial pneumonia, non-infectious pneumonia, and human immunodeficiency virus (HIV). In nine studies, alcoholism was listed as a co-morbid illness, and was found in 1414 of the 33 148 patients eligible for the study. The presence of alcohol abuse was 1.6 times more likely to be associated with a fatal case of pneumonia than with a non-fatal case [25].

Carbohydrate-deficient transferrin (CDT) has been demonstrated to be a potential biomarker of chronic alcohol abuse. Individuals who consume alcohol regularly appear to have elevated levels of this transferrin isoform. In a group of 66 male trauma patients, CDT measurements were taken on arrival to the emergency department. Patients were assigned *a priori* to either a high CDT group (> 20 U/l) or a low CDT group (< 20 U/l). The high CDT group had a significantly prolonged median ICU stay when compared with the low CDT group (13 days vs. 5 days). Morbidity was also significantly higher in the elevated CDT group, with an increase in complications, such as the alcohol withdrawal syndrome, pneumonia, and sepsis. Importantly, 32 of the 36 patients with high CDT levels were classified as alcoholics by Diagnostic and Statistical Manual (3rd ed., rev.) (DSM-III-R) criteria, compared with 9 of the 30 low CDT level patients [26].

Alcoholism in individuals undergoing an operative procedure can also have deleterious consequences. In a group of 213 patients presenting for resection of upper digestive tract tumors, 121 were diagnosed as being chronic alcoholics by DSM-III-R criteria [27]. Although the patients had no significant differences between their Acute Physiology and Chronic Health Evaluation (APACHE) III scores upon admission to the ICU, the incidence of pneumonia post-operatively was 38% in the alcoholics compared with 7% in non-alcoholics. Moreover, 13% of the alcoholics devel-

Table 3. Differences in post-operative outcomes between alcoholic and non-alcoholic patients

ICU and major intercurrent complications	Chronic alcoholics I (n=121)	Social drinkers II (n=39)	Non-alcoholics III (n=61)	p
APACHE III score on admission*	40±11	39±8	36±10	0.3742
MOF score on admission*	2.3±2.0	2.1±1.4	1.9±1.3	0.2322
Cases of mechanical ventilation on admission	118 (98%)	38 (97%)	59 (97%)	0.9880
Highest APACHE III score during stay*	56±43	39±9	40±11	0.0134 I–II, I–III
Highest MOF score during stay*	4±3	3±1	3±1	0.0000 I–II, I–III
Period of mechanical ventilation*	6±13 days	1±1 days	1±1 days	0.0010 I–II, I–III
Cases of pneumonia	46 (38%)	4 (10%)	4 (7%)	0.0000 I–II, I–III
Cases of sepsis	16 (13%)	0 (0%)	0 (0%)	0.0014 I–II, I–III
Cases of death	9 (7%)	0 (0%)	0 (0%)	0.0438 I–II, I–III

* mean ± standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit; MOF: multiple organ failure. Adapted from [27]

oped sepsis, and 7% of this group died. No sepsis or deaths were reported in the non-alcoholic group (Table 3). In a prospective study of 106 patients with surgically documented intra-abdominal infections, the effects of several variables on the incidence of organ dysfunction and death were examined [28]. The prevalence of chronic alcoholism in this group was approximately 20%, and these alcoholic patients had a 45% mortality rate. Consistently significant risk factors of death from intra-abdominal sepsis in this study included old age, alcoholism, intestinal infarction, and malnutrition. If any of these risk factors occurred in conjunction with shock, the likelihood of a patient developing death or organ dysfunction increased substantially.

Linking Alcohol Consumption and Lung Injury

ARDS results from a diverse group of biological insults, including trauma, pancreatitis, and sepsis. Sepsis remains the most common risk factor for the development of ARDS, and is a major cause of mortality in trauma patients as well as in general medical patients. The chronic use of alcohol may enhance a patient's susceptibility to the development of sepsis, as evidenced by one study prospectively examining a cohort of 2559 patients admitted after blunt or penetrating trauma [29]. It was found that chronic, but not acute, alcohol abuse led to a two-fold higher risk for the development of pneumonia and increased risk of infection of any kind. Another study emphasizing the relationship between alcohol, sepsis, and ARDS prospec-

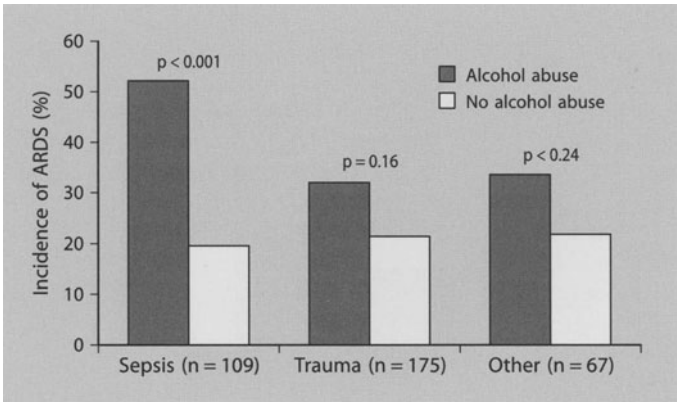

Fig. 1. The incidence of acute respiratory distress syndrome (ARDS) when stratified by the 'at risk' diagnosis and history of alcohol abuse. Adapted from [30]

tively followed a cohort of 351 critically ill individuals, all of whom had one of seven 'at risk' diagnoses for ARDS, such as sepsis, pancreatitis, or severe trauma [30]. Ultimately, patients with a prior history of chronic alcohol abuse had an increased incidence and severity of ARDS, regardless of the 'at risk' diagnosis, with a relative risk (RR) of 1.98 for the development of this disorder in alcoholic patients. Approximately 50% of the patients developing ARDS carried a prior history of alcoholism, making this a common association. In the subset of patients with sepsis, the effects of chronic alcohol abuse on the development of ARDS were even more striking, with a RR for developing ARDS of 2.59 (Fig. 1). It was also apparent from these data that alcoholic patients had a higher mortality rate from ARDS (65%) than those non-alcoholics who developed ARDS (36%). These observations distinguished chronic alcohol abuse as the first reported co-morbid variable that significantly increased a patient's risk of developing ARDS. Further, it posed questions about the pathophysiology and treatment of ARDS, and the effects of alcoholism on the lungs.

In ARDS, the type II alveolar cell, while comprising only 5–10% of the total alveolar cell surface, is critical in the regeneration of a normally functioning lung. Processes that delay alveolar repair will eventually lead to increased collagen deposition from lung fibroblasts, and thus the progression of ARDS [31]. Glutathione (GSH), a tripeptide predominantly synthesized in the liver, is involved in many important biological pathways, including:

- detoxification of reactive oxygen species (ROS)
- conjugation and excretion of toxic molecules
- control of inflammatory cytokine production.

Based on extensive evidence implicating the depletion of GSH in the pathogenesis of alcohol-mediated liver disease [32], abnormal GSH homeostasis within the lungs of chronic alcoholics may represent one mechanism contributing to these individuals' susceptibility for ALI. The lung is unable to synthesize its own supply of GSH and is dependent upon its importation from the liver. Alveolar type II cells normally maintain a concentration in the epithelial lining fluid > 80 times that found in the plasma.

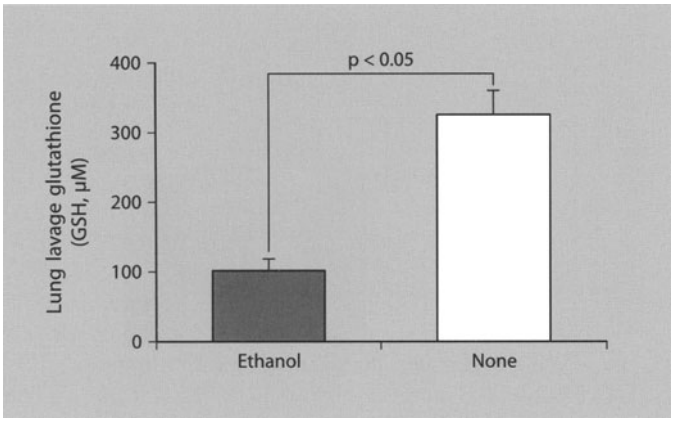

Fig. 2. Levels of glutathione (GSH) in the lung lavage fluid of rats fed on a standard control diet with or without ethanol (20% v/v in water). Adapted from [33]

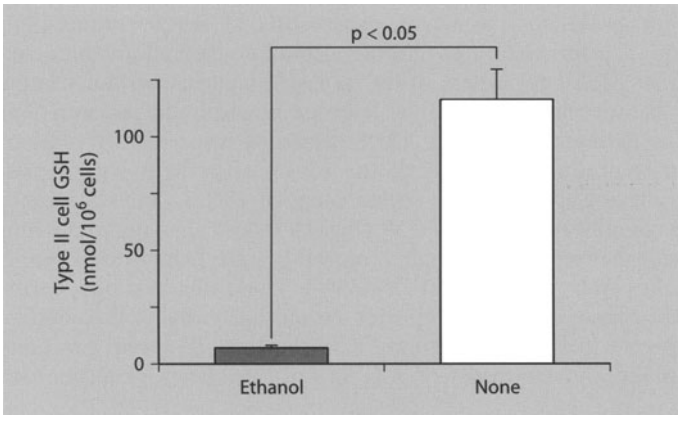

Fig. 3. Levels of glutathione (GSH) in alveolar type II cells isolated from rats fed on a standard control diet with or without ethanol (20% v/v in water). Adapted from [33]

ARDS is characterized by oxidant stress to the lung, and GSH represents an important anti-oxidant in the human body. It follows that an inadequate supply of GSH to the lung may render these patients more likely to develop ALI.

To support this hypothesis, we examined the effects of chronic alcohol consumption on an *in vivo* rat model. When rats were fed a diet containing 20% v/v ethanol, GSH levels in the plasma, lung tissue, and lung lavage fluid were significantly decreased, with a large percentage of the remaining GSH present in its oxidized form (Fig. 2). Additionally, the chronic alcohol diet appeared to deplete alveolar type II cell GSH concentration (Fig. 3), and decrease the synthesis and secretion of surfactant by these cells. Furthermore, the viability of alveolar type II cells was reduced [33].

A central feature of alcohol-induced liver disease is the inhibition of GSH transport from the cytosol to the mitochondria within hepatocytes. GSH transport may similarly be impaired in alveolar type II cells, as demonstrated in a study examining rats chronically fed alcohol. These animals exhibited depletion of their mitochondrial GSH within alveolar type II cells. Additionally, TNF-α induced generation of mitochondrial ROS and apoptosis were enhanced. These activities could be normalized by the addition of GSH replacement therapy when this was added to the rats' diet [31].

Additional investigation using an *in vivo* rat model of chronic alcohol abuse examined rats fed a liquid diet containing 36% of caloric intake from ethanol for 6 weeks. Net vectorial fluid transport across the alveolar epithelium decreased, while bidirectional protein permeability increased in the alcoholic animals compared with controls. These findings are indicative of impaired alveolar liquid clearance and increased alveolar epithelial permeability to protein. Treatment of these alcoholic animals with the GSH precursor, L-2-oxothiaxolidine-4-carboxylate, normalized GSH levels in alveolar epithelial cells and epithelial lining fluid, and appeared to help maintain alveolar epithelial barrier function [34].

Examining the effects of chronic alcohol on sepsis in animal models has been revealing. In the lungs of rats fed a diet of ethanol (20% in water for >3 weeks) then given endotoxin (2 mg/kg peritoneally), a significantly greater hydrostatic weight gain was observed when compared to controls, indicating pulmonary edema formation. When the septic, alcohol-fed rats were treated with the GSH precursors *S*-adenosyl-L-methionine and *N*-acetylcysteine (GSH precursors) in the final week of their ethanol ingestion, the development of lung edema was ameliorated [33].

Matrix metalloproteinases (MMPs) are enzymes that contribute to the development of ALI through degradation of the extracellular matrix. The activity of MMPs is influenced by GSH homeostasis. We hypothesized that the abnormal GSH homeostasis seen in chronic alcoholics may increase MMP activity within the alveolar epithelial space [35], leading to damage of the extracellular matrix during sepsis. In a septic rat model of chronic alcohol consumption [35], MMP-9 and MMP-2 activity within the lungs was increased. Elevated levels of the 7S fragment of type IV collagen were also present in the lung lavage fluid of the ethanol-fed rats, suggesting increased degradation of the alveolar epithelium. The administration of a GSH supplement significantly increased lung GSH levels, blocked MMP-9 and MMP-2 activation, and decreased levels of the 7S fragment of type IV collagen in these ethanol-fed septic animals. These findings in septic animal models suggest that GSH may have a vital role in protecting the lung from the oxidative damage associated with sepsis, and also allude to possible treatment modalities for ALI and ARDS.

Mechanisms of Disease Related to Alcoholism

The effects of chronic alcohol abuse on pulmonary GSH homeostasis and alveolar permeability have also been examined in humans. A recent study examined plasma and bronchoalveolar lavage (BAL) fluid from otherwise healthy alcoholics (normal liver function tests, spirometry, and chest radiographs). GSH in both its reduced and oxidized (GSSG) forms were measured in blood and epithelial lining fluid (determined from the BAL fluid). Although GSH levels were decreased only slightly in plasma, the concentration of reduced GSH in epithelial lining fluid was dramati-

cally decreased in alcoholic patients compared with controls. In contrast to this, the percentage of GSH present as GSSG was elevated, indicating increased utilization of an already diminished store of GSH [36]. Recent data show that the decrease in GSH appears to persist in the alcoholic patients despite a week of abstinence from alcohol [37]. Additionally, increased levels of total protein present in the epithelial lining fluid of the alcoholic patients are increased when compared with controls. These findings may indicate a relationship between the abnormality in GSH homeostasis and alveolar epithelial permeability in humans, and are consistent with the observation that alcoholic ARDS patients have significantly greater extravascular lung water than non-alcoholic ARDS patients [38].

ALI is characterized by neutrophil activation with the release of oxygen-free radicals. The production of these compounds may play a role in the pathophysiology of this disorder. As mentioned previously, the concentration of oxidized glutathione is significantly elevated in individuals who abuse alcohol chronically, despite a period of abstinence, perhaps signifying on-going oxidative stress. We recently measured hydrogen peroxide levels from the lavage fluid of chronic alcoholic patients and found the level of this oxygen-free radical to be significantly higher when compared to the level measured in control patients, indicating the occurrence of oxidative stress without overt disease (Burnham et al., unpublished data).

Conclusion

Alcohol is a common drug of abuse that can adversely alter the immune system through a variety of mechanisms, causing an increased risk of infection among individuals who abuse this substance. Its use has been implicated in injuries such as trauma and burns, where it may exacerbate already abnormal immune functioning elicited by these injuries. Alcoholism is a contributing factor causally in sepsis, and also leads to more adverse outcomes from sepsis. A variety of organs are affected by this drug, including ones not usually thought of as being prone to alcohol's deleterious effects, such as the lung. Alcoholics are believed to be susceptible to the development of ARDS secondary to their decreased levels of pulmonary GSH. GSH replacement has been used therapeutically in ARDS patients with encouraging results. The role of GSH replacement in the treatment of alcohol-related ARDS is presently not known. The mechanisms behind these abnormalities are myriad, and have only recently begun to be elucidated, mostly in animal models. Outcomes of sepsis in alcoholic patients remain poor; however, with new approaches to treating what are perhaps fundamental abnormalities on the cellular level in these patients, there is hope for better therapy in the future.

References

1. Lieber CS (1995) Medical disorders of alcoholism. N Engl J Med 333:1058–1065
2. Moss M (2001) The role of alcohol in severe pneumonia and acute lung injury. In: Rello J, Leeper KV (eds) Severe Community Acquired Pneumonia. Kluwer Publishers, Boston, pp 119–138
3. Adams WL, Yuan Z, Barboriak JJ, et al (1993) Alcohol-related hospitalizations of elderly people. Prevalence and geographic variation in the United States. JAMA 270:1222–1225
4. Spies C, Neuner B, Neumann T, et al (1996) Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. Intensive Care Med 22:286–293

5. Baldwin WA, Rosenfeld BA, Breslow MJ, Buchman TG, Deutschman CS, Moore RD (1993) Substance abuse-related admissions to adult intensive care. Chest 103:21–25
6. Napolitano LM, Koruda MJ, Zimmerman K, McKowan K, Chang J, Meyer AA (1995) Chronic ethanol intake and burn injury: Evidence for synergistic alteration in gut and immune integrity. J Trauma 38:198–207
7. Burch GE, DePasquale (1967) Alcoholic lung disease – an hypothesis. Am Heart J 73:147–148
8. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1989) Sepsis syndrome: A valid clinical entity. Methylprednisolone Severe Sepsis Study Group. Crit Care Med 17:389–393
9. Mason CM, Dobard E, Kolls J, Nelson S (1998) Effect of alcohol on bacterial translocation in rats. Alcohol Clin Exp Res 22:1640–1645
10. Nelson S, Bagby G, Summer WR (1989) Alcohol suppresses lipopolysaccharide-induced tumor necrosis factor activity in serum and lung. Life Sci 44:673–676
11. Nelson S, Bagby G, Andreson J, Nakamura C, Shellito J, Summer W (1991) The effects of ethanol, tumor necrosis factor, and granulocyte-colony stimulating factor on lung antimicrobial defenses. Adv Exp Med Biol 288:245–253
12. Omidvari K, Casey R, Nelson S, Olariu R, Shellito JE (1998) Alveolar macrophage release of tumor necrosis factor alpha in chronic alcoholics without liver disease. Alcohol Clin Exp Res 22:567–572
13. Perlino CA, Rimland D (1985) Alcoholism, leukopenia, and pneumococcal sepsis. Am Rev Respir Dis 132:757–760
14. Spagnuolo PJ, MacGregor RR (1975) Acute ethanol effect on chemotaxis and other components of host defense. J Lab Clin Med 86:24–31
15. Coonrod JD, Lester RL, Hsu LC (1984) Characterization of the extracellular bactericidal factors of rat alveolar lining material. J Clin Invest 74:1269–1279
16. Baughman RP, Roselle GA (1987) Surfactant deficiency with decreased opsonic activity in a guinea pig model of alcoholism. Alcohol Clin Exp Res 11:261–264
17. Rubins JB, Charboneau D, Prigge W, Mellencamp MA (1996) Ethanol ingestion reduced anti-pneumococcal activity of rat pulmonary surfactant. J Infect Dis 174:507–512
18. Keshavarzian A, Fields J, Vaeth J, Holmes EW (1994) The differing effects of acute and chronic alcohol on gastric and intestinal permeability. Am J Gastroenterol 89:2205–2211
19. Rush B (1943) An inquiry into the effects of ardent spirits upon the human body and mind. Q J Stud Alcohol 4:321–341
20. Osler W (1905) The Principles and Practices of Medicine. Appleton, New York
21. Saitz R, Ghali W, Moskowitz M (1997) The impact of alcohol-related diagnoses on pneumonia outcomes. Arch Intern Med 157:1446–1452
22. Carpenter JL, Huang DY (1991) Community-acquired pulmonary infections in a public municipal hospital in the 1980s. South Med J 84:299–306
23. Szabo G (1999) Consequences of alcohol consumption on host defense. Alcohol Alcohol 34:830–841
24. Mufson MA, Kruss DM, Wasil RE, Metzger WI (1974) Capsular types and outcome of bacteremic pneumococcal disease in the antibiotic era. Arch Intern Med 134:505–510
25. Fine MJ, Smith MA, Carson CA, et al (1996) Prognosis and outcomes of patients with community-acquired pneumonia: A meta-analysis. JAMA 275:134–141
26. Spies CD, Kissner M, Neumann T, et al (1998) Elevated carbohydrate-deficient transferrin predicts prolonged intensive care unit stay in traumatized men. Alcohol Alcohol 33:661–669
27. Spies CD, Nordmann A, Brummer G, et al (1996) Intensive care unit stay is prolonged in chronic alcoholic men following resection of the upper digestive tract. Acta Anaesthesiol Scand 40:649–656
28. Pine RW, Wertz MJ, Lennard ES, Dellinger EP, Carrico CJ, Minshew BH (1983) Determinants of organ malfunction or death in patients with intra-abdominal sepsis. A discriminant analysis. Arch Surg 118:242–249
29. Jurkovich GJ, Rivara FP, Gurney JG, et al (1993) The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. JAMA 270:51–56
30. Moss M, Bucher B, Moore F, Moore EE, Parsons PE (1996) The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50–54

31. Brown LA, Harris FL, Guidot DM (2001) Chronic ethanol ingestion potentiates TNF-alpha-mediated oxidative stress and apoptosis in rat type II cells. Am J Physiol 281:L377–386
32. Lieber CS (1993) Biochemical factors in alcoholic liver disease. Semin Liver Dis 13:136–153
33. Holguin F, Moss I, Brown LA, Guidot GM (1998) Chronic ethanol ingestion impairs alveolar type II cell glutathione homeostasis and function and predisposes to endotoxin-mediated acute edematous lung injury in rats. J Clin Invest 101:761–768
34. Guidot DM, Modelska K, Lois M, et al (2000) Ethanol ingestion via glutathione depletion impairs alveolar epithelial barrier function in rats. Am J Physiol 279:L127–135
35. Lois M, Brown LA, Moss IM, Roman J, Guidot DM (1999) Ethanol ingestion increases activation of matrix metalloproteinases in rat lungs during acute endotoxemia. Am J Respir Crit Care Med 160:1354–1360
36. Moss M, Guidot DM, Wong-Lambertina M, Ten Hoor T, Perez RL, Brown LA (2000) The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. Am J Respir Crit Care Med 161:414–419
37. Burnham EL, Brown LAS, Eaton S, et al (2001) Prolonged glutathione deficiency and increased total protein concentrations in epithelial lining fluid of chronic alcoholics. Am J Respir Crit Care Med 163:A816 (abst)
38. Eaton S, Moss IM, Martin GS (2002) Extravascular lung water correlates with oxygenation and lung injury in patients with severe sepsis. Am J Respir Crit Care Med 165:A712 (abst)