

Chapter 4

The Epidemiology of Alcohol Abuse and Pneumonia

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Abstract The association between alcohol abuse and pneumonia has been recognized for more than two centuries and represents an enormous health burden worldwide. The first published notation of alcohol as a clinical risk factor for the development of pneumonia is now over 200 years old, and since then there have been over a 1,000 references in the medical literature confirming these observations. Even in this modern era of medicine pneumonia remains a common infection that afflicts over 450 million persons worldwide annually and causes 7 % of all deaths. When one considers that alcohol is the most commonly abused substance in the world, the enormous excessive burden that alcohol contributes to the morbidity and mortality of pneumonia represents a major public health consideration. In this chapter we review the foundational literature that has chronicled the evolution of our understanding of the association between pneumonia and alcohol abuse over the past century. In addition, we discuss some of the specific pathogens that are particularly associated with serious lung infections in individuals with alcohol use disorders. Finally, we consider some of the specific guidelines for the treatment and prevention of pneumonia in the setting of alcohol abuse.

Keywords Alcohol abuse • Pneumonia • Risk factor • Pneumococcus • Anaerobic pathogens • *Haemophilus influenzae* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa*

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A Historical Perspective on Alcohol Abuse and Pneumonia

Most reviews on alcohol abuse and pneumonia credit Benjamin Rush, the first Surgeon General of the USA, as one of the earliest clinicians to recognize tuberculosis and pneumonia as infectious sequelae of excessive drinking, as was elaborated in his 1785 work entitled “An Inquiry Into the Effects of Ardent Spirits Upon the Human Body and Mind” [1]. This work also laid the foundation for the description of alcoholism as a disease rather than just a behavior as was the prevailing attitude at the time. Further credence to the association of alcohol abuse and pneumonia came in 1895 when Sir William Osler, often called the “Father of Modern Medicine,” also advocated that excessive alcohol intake was a potent predisposing factor in the development of lobar pneumonia [2]. Interestingly, and quite ironically, at that time there were those who extolled the therapeutic use of alcohol as a *treatment* for pneumonia, particularly in cases with severe systemic manifestations. In his 1912 article, A.T. Jones of the London Royal College of Physicians describes his abandonment of therapeutic alcohol in cases of lobar pneumonia, after which his case mortality rate fell dramatically from 38 to 18 % after omitting alcohol as a component of his treatment regimen [3]. This experience led him to conclude that alcohol was expensive and of very little help, if any, in treating pneumonia and therefore that a patient’s money would be likely better spent on nutrients to secure their recovery. Shortly thereafter in 1923 came a somewhat more robust description of case mortality rates observed in 3,422 patients admitted to Cook County Hospital for pneumonia from 1911 to 1922. In this work, Capps and Coleman showed both a stepwise increase in the incidence of lobar pneumonia, as well as greater case mortality rates (22, 34, or 50 %) in patients who were essentially abstainers, moderate, or heavy drinkers, respectively [4]. Even when their subjects were stratified for age, substantial differences in fatality results remained with a nearly 70 % mortality rate in heavy drinkers over the age of 60. These observations were supported by subsequent studies that associated alcohol abuse with twofold to threefold increased mortality rates from pneumonia [5, 6]. These dramatic clinical observations of an association between alcohol abuse and pneumonia prompted Branch and Stillman to perform landmark experimental studies, published in a series of papers beginning in 1924, in which they demonstrated that acute alcohol administration in mice caused septicemia and death following pneumococcal aerosolization [7]. These provocative studies in the so-called “pre-antibiotic era” identified a clear and independent mechanistic association between alcohol abuse and pneumonia and laid the foundation for intensive investigations on the part of clinical and basic science researchers that continue to this day. Unfortunately, although these research efforts have elucidated the clinical features and underlying pathophysiologic mechanisms, the devastating impact of alcohol abuse and pneumonia on our society remains as problematic as when the association was first chronicled.

Alcohol Abuse: A Persistent Risk Factor for Pneumonia in the Age of Antibiotics

While modern medicine is characterized by several notable milestone achievements, in the context of the study of infectious diseases perhaps none is greater than the serendipitous discovery of penicillin by Alexander Fleming in 1928 [8]. Subsequent large-scale synthesis of the drug for the war effort saved the lives of many allied soldiers in World War II, and soon thereafter this wonder drug found widespread civilian application as an effective antimicrobial treatment against most pathogens causing bacterial pneumonia. As a result, pre-antibiotic pneumonia mortality rates within the US population, previously estimated at 200 deaths per 100,000, plummeted to 31 per 100,000 by 1949 [9]. In parallel, rates of serious complications such as empyema also declined precipitously [10–12]. Despite these initial and subsequent advances in antibiotic therapies, alcohol abuse as a significant risk factor for pneumonia continued. For example, in a large series of alcoholics in Canada who sought treatment for their addiction, investigators identified a threefold and sevenfold increase in pneumonia death rates in female and male drinkers, respectively, when compared to nonalcoholics with pneumonia [13]. A US study performed at that same time showed that alcoholism was an underlying condition in 35 % of hospitalized pneumonia cases [14]. Further, in a prospective series of 900 admissions to Yale’s Grace-New Haven Hospital, Nolan prospectively identified alcoholics as having three times the rate of hospitalization for pneumonia as nondrinkers, and nearly three quarters of alcoholics studied were admitted to the hospital for reasons considered directly attributable to their drinking [15]. In another well-performed study of enlisted US Navy personnel, Kolb demonstrated a doubling of the hospital admission rate for pneumonia in a cohort of 2,191 sailors who met criteria for alcohol abuse [16]. Further complicating matters, alcohol abusers are also at increased risk for developing *recurrent* pneumonia, as reflected by the observation that 40 % of patients with recurrent infection in one series had no other predisposing condition besides alcoholism [17]. Examining middle-aged adults in a case-control fashion, Fernandez-Sola found excessive alcohol intake as the only independent risk factor for community acquired pneumonia (CAP), and alcoholics had more severe symptoms, more multi-lobar involvement and parapneumonic effusions, and greater mortality than their nonalcoholic counterparts [18]. Even now as we are well into the twenty-first century, excessive alcohol consumption remains as an independent risk factor for the development of CAP and other serious lung infections [19–23], and the specific microbial pathogens that are overrepresented in these vulnerable individuals will be discussed next.

The Pneumococcus

When Osler characterized pneumonia as “the captain of the men of death”, it was undoubtedly due in large part to the intrinsic respiratory tract virulence of *Streptococcus pneumoniae* [24]. Since then, the majority of CAP series in which a specific etiologic agent could be identified have demonstrated that *S. pneumoniae* continues to be the most common pathogen, and this remains true as well in the subset of individuals with alcohol abuse [20, 22, 23, 25–31]. Even in the modern era of antibiotics and an effective vaccine, the overall case mortality rate for pneumococcal CAP in most recent series ranges from 10 to 30 % [32–36]. However, the independent effects of alcohol abuse on mortality in individuals hospitalized for pneumococcal CAP is difficult to quantify. As previously discussed, many historical studies have shown that alcohol abuse increases the risk of CAP mortality [4–6]. Consistent with this, a more recent Spanish study identified high alcohol intake as a risk factor for CAP mortality; however, pneumococcus was not a frequently isolated pathogen in that population [18]. Further, although the study of CAP in 2004 concluded that alcohol abuse was associated with increased mortality in a univariate analysis, this association was lost in the multivariate analysis [37]. Similarly, De Roux and colleagues studied a large cohort of individuals hospitalized for CAP (the majority of whom had *S. pneumoniae* infection) and found that despite a strong association between current or previous alcohol abuse and pneumococcal pneumonia, mortality in current alcoholics was not different than in nondrinkers [38]. This finding of equivalent in-hospital pneumonia mortality in alcoholics and nonalcoholics has also been reported in other recent CAP cohorts [25, 39, 40]. These apparently conflicting results on the effect of alcohol abuse on CAP mortality are at face value confounding. However, a possible explanation for these discrepancies can be found in the results of a recent study by Goss and colleagues. Specifically, they determined that in a cohort of hospitalized low-risk CAP patients who could have otherwise been treated as outpatients, 49 % of them were alcoholics, 44 % of them were homeless, and 20 % of them were acutely intoxicated on presentation [41]. Therefore, individuals with underlying active alcohol use disorders may be admitted to the hospital for treatment for reasons unrelated to the severity of their pneumonia. If so, this could decrease their overall observed hospital mortality by including many individuals with a lower pneumonia-specific severity of illness as compared to the nonalcoholic subjects in the studies.

What appears less controversial is the increased risk for developing invasive (i.e., bacteremic) pneumococcal pneumonia in alcoholics. Using 1999 and 2000 data, the Centers for Disease Control (CDC) estimated that pneumococcal bacteremia occurs ten times more often in alcoholics compared to otherwise healthy adults [42]. Approximately 20–25 % of pneumococcal pneumonia cases are associated with bacteremia [21, 43], and mortality rates for bacteremic pneumonia are generally somewhat higher than in non-bacteremic disease [44, 45]. In a prospective series of 100

cases of proven pneumococcal pneumonia, alcohol abuse was the only demographic risk factor predictive of bacteremia [33]. Indeed, results from multiple studies in separate cohorts have consistently demonstrated clear and convincing evidence of a heightened risk for invasive pneumococcal disease, including bacteremic pneumococcal pneumonia, in alcohol abusers [25, 46–52], and alcoholics are four times more likely to die from bacteremic pneumococcal pneumonia than nonalcoholics [53]. A particularly poor outcome is seen in alcoholics with bacteremic pneumococcal pneumonia, sepsis, and leukopenia in whom mortality exceeded 80 % [54]. This series led to the coining of the term “Alcoholic Leukopenic Pneumococcal Sepsis Syndrome” or ALPS Syndrome. Many of these patients developed a severe form of lung injury known as the acute respiratory distress syndrome (ARDS), and a subsequent chapter in this book discusses in detail the more recently identified association between alcohol abuse and ARDS in critically ill individuals [55].

An unavoidable consequence of the widespread use of antibiotics is the eventual selection of resistant pathogens, and drug-resistant *S. pneumoniae* (DRSP) is now prevalent in several countries [56]. In the joint American Thoracic Society and Infectious Diseases Society of America CAP guidelines published in 2007, alcoholism is cited as a risk factor for infection with *S. pneumoniae* resistant to beta-lactam antibiotics [22]. A study published subsequent to these guidelines found a fivefold increased risk for DRSP infection in alcohol abusers [57], although other studies have not found such a significant association [38, 58].

Anaerobic Pathogens

Commensal anaerobes make up the dominant microbial population of the oropharynx [59] and although not particularly virulent, these pathogens are quite capable of causing pneumonia if they are aspirated into the lower airways. As a direct result of impaired consciousness and depressed cough reflex, alcohol intoxication facilitates the aspiration of substantial amounts of oropharyngeal secretions in which colonizing bacteria (commensal or otherwise) gain access to the usually sterile lower airways where they can cause pneumonia [60, 61]. Dominant pathogens in anaerobic pneumonia include *Peptostreptococcus*, *Bacteroides*, *Prevotella*, and *Fusobacterium* species, although mixed flora, including gram negative rods, are increasingly recognized participants [62–64]. Due to significant exotoxin production by anaerobic bacteria, many cases evolve into a necrotizing pneumonia or lung abscess, with or without frank empyema formation [29]. Case series of anaerobic pleuropulmonary disease have suggested that up to 70 % of cases are associated with alcohol abuse [65–70]. Fortunately, the mortality rates from these infections have dropped considerably (from 34 to 5 %) since the introduction of antibiotics, and, equally fortunately, at least to date the pathogens causing anaerobic pleuropulmonary disease generally remain antibiotic-susceptible [71].

Haemophilus influenzae

A moderate amount of evidence supports the conclusion that alcohol abuse also increases the risk of pneumonia caused by *H. influenzae*. Several studies in the mid- to late twentieth century described a high prevalence (up to 50 %) of alcohol abuse in cases of *H. influenzae* pneumonia [72–75], although there is some suggestion that alcoholic liver disease must also be present for there to be a significantly increased susceptibility to this pathogen [76]. It is not clear which capsular subtypes and/or untypeable strains are responsible for these pneumonias in alcohol abusers, and therefore at least at this time the current CDC recommendations do not include alcoholism per se as an indication for routine *H. influenzae* B vaccination in adults [77].

Klebsiella pneumoniae

Initially described in the nineteenth century as by Friedlander and therefore known as “Friedlander’s bacillus”, this highly virulent gram negative rod is often found in the pharyngeal flora of alcoholics [78] and is a deadly respiratory pathogen that is often identified as the etiology of pneumonia in these susceptible individuals [14, 79–83]. Early studies noted the majority of patients with *Klebsiella* infection were alcoholic, many of whom produced a characteristically thick and bloody sputum that was often referred to as “currant jelly sputum” that was believed to consist of necrotic lung, hemorrhage, and the bacteria’s mucoid capsule. Highlighting the prognostic value of the blood leukocyte count in such cases, in 1956 Limson described a series of 22 individuals with *K. pneumoniae* lung infection in whom all of those who were alcoholic and had a low or even normal circulating leukocyte count succumbed to their acute disease [84]. More recent studies continue to show an association between *Klebsiella* pneumonia and alcohol abuse including excessive rates of bacteremia and death despite aggressive antibiotic therapy and supportive management in the intensive care unit [18, 85–89]. Many of these recent (and some older) studies attest to the antibiotic resistance of this pathogen, and this challenge of antibiotic resistance has worsened in recent years [90]. Some experts now consider *K. pneumoniae* as the prototypical organisms to express extended spectrum beta lactamase (ESBL) activity [91], and more recently some *K. pneumoniae* isolates from several countries have even been found to express carbapenemase, thereby rendering them resistant to one of the most effective gram-negative antibiotic classes [92]. Therefore, clinicians caring for individuals with underlying alcohol use disorders presenting with pneumonia, particularly those who are severely ill, need to consider these factors carefully in selecting appropriate therapy.

Pseudomonas aeruginosa and Acinetobacter Species

Although not commonly considered community-acquired lung infections, pneumonias caused by virulent gram negative pathogens such as *P. aeruginosa* and *Acinetobacter* species nevertheless do occur and carry excess morbidity and mortality [22]. In a study of individuals with severe CAP, Marik found that infection with these pathogens imposed a very high mortality (82 %), and the only clinical factor that appeared to increase the risk of infection with these microbes was a history of alcohol abuse [93]. Subsequent work in Taiwan found that alcoholism frequently accompanied severe CAP caused by *Acinetobacter baumannii* [94], and it is concerning that this association was seen in relatively younger individuals. A recent and comprehensive summary of community-acquired *Acinetobacter* infections consistently identified alcohol abuse as a risk factor in the majority of case series [95]. In developed countries, pneumonia caused by these pathogens is more commonly associated with a nosocomial infection (i.e., acquired in the hospital) and usually in the context of a critically ill individual receiving mechanical ventilation. In this setting, individuals with underlying alcohol abuse experience increased rates of pneumonia with these and other drug-resistant pathogens, and they are more likely to succumb to infection than are their nonalcoholic counterparts [96–101]. As those who abuse alcohol are ostensibly forced to suspend their drinking while they are hospitalized, many develop an acute alcohol withdrawal syndrome. To complicate matters further, the occurrence of this acute withdrawal syndrome increases the risk of nosocomial pneumonia [97, 100], and the development of pneumonia in this setting is a strong predictor of increased hospital mortality [101]. Additional discussion of the care for hospitalized alcoholics can be found in a subsequent chapter (Chap. 14).

Mycobacterium tuberculosis

Just as long-recognized as the association between alcohol abuse and bacterial pneumonia is the increased incidence of pulmonary tuberculosis in the alcoholic patient [1]. Although also a bacterial pathogen, the acquisition of pulmonary tuberculosis is quite different than that of other “typical” bacterial pneumonias. While most cases of bacterial pneumonia are caused by the pulmonary aspiration of pathogen-colonized oropharyngeal secretions, *M. tuberculosis* inoculates the lung by direct inhalation of aerosolized organisms (as is true of *Legionella*, influenza, and other respiratory viruses) [102]. As a result, person-to-person spread is a major feature of tuberculosis not seen in most bacterial pneumonias, making it a major public health scourge over many centuries in which epidemics rise and fall over many decades within a discrete population. In this regard, an individual’s environment and community strongly influence the chance of being exposed to and contracting tuberculosis. Unfortunately, individuals with chronic alcohol use disorders are more likely to be homeless and to subsequently reside in dense cohorts (e.g., shelters,

group homes, jails, and prisons), environments that are conducive to effective tuberculosis transmission [103–105]. This confounding effect has led some investigators to caution against a definitive conclusion regarding a causative effect of excessive alcohol intake on tuberculosis incidence [106–108], while others conclude that alcohol abuse does indeed confer increased susceptibility to this pathogen [109–111]. In support of a causal effect of alcohol abuse on pulmonary tuberculosis is a collective body of experimental evidence from animal studies showing that a multitude of pulmonary host defenses mechanisms against tuberculosis are adversely impacted by alcohol [112–115]. For example, live infection with tuberculosis in a mouse model has shown that chronic alcohol feeding is associated with impaired pulmonary clearance of pathogen, a defect likely caused by reduced T cell responses and granuloma formation in the lung [115]. More recently, statistically robust international analyses of the association between alcohol use and tuberculosis conclude that alcohol abuse confers a nearly threefold increase in the relative risk for active tuberculosis infection [116, 117]. Equally concerning from a clinical perspective are the findings that active alcohol users exhibit altered pharmacokinetics of anti-tuberculous medicines, and, not surprisingly, are less compliant with their treatment regimen [108, 118]. The latter facet is likely a key determinant in the alarming findings that alcoholics are more likely to become reinfected with tuberculosis and are more likely to harbor a drug-resistant tuberculosis strain [119–121]. While the emergence of infection with the human immunodeficiency virus (HIV) is the overwhelming factor underlying the global resurgence of tuberculosis rates, it is nevertheless still currently estimated that 10 % of tuberculosis cases worldwide can be attributed to alcohol abuse [117]. A thorough discussion of the pulmonary sequelae of alcohol abuse and HIV infection is provided in a subsequent chapter (Chap. 15).

Alcohol and Pneumonia: The Current Socioeconomic Burden

According to the 2010 National Survey on Drug Use and Health, 16.9 million Americans reported heavy alcohol use, representing 6.7 % of the US population over the age of 12 [122]. Globally, the World Health Organization estimates that 2.5 million persons die each year as a result of alcohol use [123], which represents 4 % of global deaths and reflects a greater impact than the number of deaths caused by HIV, violence, or tuberculosis. In fact, worldwide alcohol abuse is the third greatest risk factor for the development of disease and disability, and in upper middle income countries it is now the greatest risk factor, with Russia and the former Soviet Union countries exhibiting some of the highest alcohol-attributable death rates. Although the exact contribution of alcohol to current pneumonia incidence and death is difficult to determine, a recent and large meta-analysis by Samokhvalov demonstrated a dose–response curve to drinking and CAP incidence, with individuals clinically classified as having an alcohol use disorder exhibiting eight times the risk for CAP [124]. Given these findings and recent data indicating that pneumonia and influenza were the 8th leading cause of death in America in 2011 [125], it is

clear that alcohol abuse remains a pertinent, pervasive, and potentially modifiable adverse health factor from a public health policy perspective.

The estimated total cost of excessive alcohol consumption in the USA alone in 2006 was over 200 billion dollars [126]. While only a part of this cost is direct health-care utilization, this figure nevertheless reflects the considerable economic burden of alcohol abuse to our society. A study of pneumonia hospitalizations in Massachusetts found that cases associated with alcohol-related diagnoses had a longer length of stay, a 50 % greater intensive care unit utilization, and a significant increase in hospital charges—although mortality rates were similar (10 %) [127]. A more recent large cross-sectional study of Danish persons aged 50–64 revealed a nearly doubling of risk for pneumonia hospitalization in heavy drinkers, as defined by greater than 50 drinks per week [128]. Similar studies from European nations have also demonstrated a greater length of stay, increased ICU use, and increased need for mechanical ventilation in alcohol abusers with CAP [38, 39, 129–131]. A further contributor to the economic burden of pneumonia in alcoholics is the previously discussed need to hospitalize a greater proportion of these patients than would otherwise be warranted on the basis of their infection severity [41]. A similar picture has emerged in the context of hospital-acquired pneumonia; specifically, alcoholics are more likely to develop nosocomial pneumonia despite a lower overall illness acuity, and the cost to care for such events is substantial [98, 132]. Even after discharge from the hospital following a pneumonia admission, alcohol abusers are more likely to return to a primary care center or emergency department within 30 days of discharge [133].

Preventative measures against bacterial pneumonia in the individuals suffering from alcohol use disorders at present are essentially limited to addressing the alcohol consumption behavior itself and vaccination against infection, and more data are needed to assess the cost effectiveness of these expenditures in preventing pneumonia. Currently, the CDC Advisory Committee on Immunization Practices recommends pneumococcal and yearly influenza vaccination for all alcohol abusing persons [134, 135]. Unfortunately, in practice there appears to be less frequent vaccination against these pathogens in alcohol abusers, even in those with additional risk factors for pneumonia such as COPD or advanced age [136–139]. This finding is quite disappointing, particularly as the available clinical data support the efficacy of the 23-valent polysaccharide pneumococcal vaccine in heavy drinkers, including those who are elderly [140, 141]. Whether the newer peptide-conjugate pneumococcal vaccine is of lesser, equal, or greater benefit in heavy alcohol users is yet to be determined, and therefore at the time this chapter was prepared its administration to this population is not currently recommended.

Summary

Alcohol abuse remains common throughout the world, and the medical literature is incontrovertible in its depiction of alcohol abuse as a risk factor for both an increased incidence and severity of bacterial pneumonia, whether acquired in the community

or the hospital setting. The spectrum of pathogens causing pneumonia in the alcohol abuser is somewhat wider and more virulent than in non-abusers, such that the clinical history of alcohol abuse has a direct impact on the clinical care and outcome of such patients. In an era of spiraling global health care costs and regionally scarce health care resources, it would seem prudent to continue or even expand efforts to determine optimal prevention and treatment strategies for bacterial pneumonia and other sequelae of alcohol abuse in these persons. Such measures could have a significant effect not only on the outcome of disease for an individual, but also on the incidence of disease and alcohol's overall economic burden to society. Although not discussed in this chapter, the association between alcohol and other health concerns such as HIV infection, tobacco use, and illicit substance use further supports comprehensive and robust research programs to identify and intervene in those alcohol abusing populations most amenable to response.

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