Smoking, Alcohol Use, Diabetes Mellitus, and Metabolic Syndrome as Risk Factors for Community-Acquired Pneumonia

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Community-acquired pneumonia (CAP) continues to be a cause of significant morbidity and mortality worldwide. Much recent attention in this area of research has been focused on host factors associated with the infection. This article will discuss 4 diverse, yet often coexistent conditions, namely, smoking, excessive alcohol use, diabetes mellitus, and metabolic syndrome. While all these conditions can be considered to be largely associated with lifestyle factors, they represent important risk factors for CAP. All can lead to acquired host immune suppression that underlies their risk for the development of severe CAP.

Key points

- Worldwide, community-acquired pneumonia (CAP) remains a significant cause of morbidity and mortality.
- Acquired, prolonged immune suppression associated with avoidable aspects of lifestyle, as well as various comorbidities, is a key common risk factor.
- Smoking, excessive alcohol consumption, diabetes mellitus, and the metabolic syndrome are all associated with immune suppression and predisposition for development of CAP.
- Of the causative bacterial CAP pathogens, *Streptococcus pneumoniae* remains the most prominent.

Introduction

In all populations of the world, community-acquired pneumonia (CAP) is associated with significant morbidity and mortality, but especially so in individuals at specific risk for CAP; however, the exact mechanisms by which many of these host risk factors contribute to pneumonia pathogenesis and recovery are not completely elucidated, and clinical practice guidelines focus predominantly only on the management and treatment of the pneumonia.[1] Factors that need to be considered include the host risk factors that lead to the occurrence of CAP and their mechanisms, biomarkers that may reflect the host response and their utility as a means to pursue host-directed therapy, systemic effects of pneumonia on the host, and the long-term host outcomes after CAP. These gaps in knowledge were addressed in a Pneumonia Working Group of the Assembly of Pulmonary Infection and Tuberculosis of the American Thoracic Society which aimed to encourage attention and stimulate research and its funding into the host contributions to pneumonia.[1] This article reviews some of the less well-discussed host factors predisposing individuals to CAP and the current understanding of their role and consequences.

With respect to CAP, the major causative pathogens of CAP are *S . pneumoniae* (the pneumococcus) in particular, as well as influenza A virus, *Mycoplasma pneumoniae* , *Haemophilus influenzae* , and *Chlamydophila pneumoniae* , with *Staphylococcus aureus* , *Moraxella catarrhalis* , *Legionella pneumophila* , and *Mycobacterium tuberculosis* (in regions other than high-risk tuberculosis (TB) areas, such as sub-Saharan Africa) representing less frequent causative agents, together with aerobic/anaerobic bacterial pathogens such as *Pseudomonas aeruginosa* .[2,3] Notwithstanding primary and acquired stable immunodeficiency disorders, the most prominent risk factors for the development of CAP are acquired, often transient immunodeficiencies associated with very young and older age, comorbidities especially chronic obstructive lung disease (COPD), and, of course, smoking, which is the most prevalent and eminently avoidable independent risk factor.[2] Aside from CAP associated with immune dysfunction, human pathogens, including respiratory pathogens, have also been reported to be "abundant in the bacterial metagenome of cigarettes."[4]

The aim of this article is to summarize some of the host factors that are important risk factors for CAP, including some of those that are less frequently included in the studies of CAP comorbidity.

Smoking and community-acquired pneumonia

The association between smoking and susceptibility for development of often severe and protracted lower respiratory tract microbial and viral infections has been recognized for over a century. According to Chiang and colleagues, the association between smoking and tuberculosis specifically has been recognized since 1918.[5] With the passage of time, not only was this association repeatedly confirmed but also convincingly extended to other infectious respiratory pathogens.[2,3,7-10]

A multitude of studies has underscored the ominous association between smoking and risk of development of CAP, with a fairly recent systematic review and meta-analysis reported by Baskaran and colleagues in 2019 representing a microcosm of the current situation in adults aged 15 years and older.[9] These authors identified 647 studies, which covered this topic, 27 of which (encompassing 460,592 participants) were judged suitable for inclusion in the systematic review.[9] Participants were assigned to 1 of 5 categories (never, ever, ex/former, current, "not-current," and passive smokers). Of the selected studies, the clinical definition of CAP was based on radiological examination (16 studies), diagnostic coding (5 studies), and clinical criteria (5 studies), while in one, diagnostic procedures were not defined.[9]

To summarize the authors' findings, the analysis of 13 representative studies revealed that relative to never smokers, current smokers had a greater than 2-fold risk of developing CAP [pooled odds ratio (OR) 2.17, 95% confidence interval (CI) 1.70–2.76, I^2 statistic = 75%].[9] Those studies ($n = 7$) that reported hazard ratios (HRs), documented that current smokers had a 53% greater probability of developing CAP than never smokers (pooled HR 1.52, 95% CI 1.13–2.04, $I^2 = 13.3\%$, $n = 8$ studies).[9] Additional findings included the following: (i) the association of passive smoking with development of CAP in 5 studies analyzed revealed no statistically significant association with passive smoking in adult participants, but was associated with a 65% higher risk in those participants aged greater than or equal to 65 years, albeit based on the analysis of only 2 studies; and (ii) dose-response data from 5 studies revealed significant associations (2 linear and 3 nonlinear) between heavy smoking and development of CAP.[9] Based on earlier publications by other investigators, the authors mention that similar to their study, the degree of risk posed by current smoking for development of CAP

is comparable with that reported for associations of smoking with bronchial asthma, idiopathic pulmonary fibrosis, obstructive sleep apnea, stroke, and acute coronary syndrome, albeit lower than that associated with lung cancer and COPD. [11-14]

Despite the strengths of the largely confirmatory study by Baskaran and colleagues,[9] lack of data on the identities of the causative CAP pathogens, albeit a difficult undertaking due to the fastidious nature of many of these infectious agents, precluded provision of potentially interesting data with respect to pathogen prevalence and degree of risk for development of CAP, as well as possible selective associations with passive smoking.[14] Although the pneumococcus undoubtedly remains the most prominent bacterial contender, the caveat remains that the prevalence rates of other types of pathogens involved in the pathogenesis of smoking-related CAP is not entirely clear.

Smoking and the Severity of Pneumococcal Community-Acquired Pneumonia

The risk of progression to severe disease following an episode of pneumococcal CAP was convincingly highlighted in the seminal publication authored by Nuorti and colleagues in 2000, who used a population-based case-control study to investigate the relationship between cigarette smoking in particular as a risk factor for pneumococcal infection.[15] These authors enrolled immunocompetent patients (n = 228, aged 18–64 years) with microbiologically confirmed invasive pneumococcal disease (IPD) and 301 control participants selected from appropriate residential areas. Ninety-five percent of the patients were hospitalized with bacteremic pneumococcal pneumonia. Of the patients, and control participants, 58% and 24%, respectively, were current smokers, while among nonsmokers, 33% of patients and 17% of control participants were exposed to similar levels of environmental smoke.[15]

Using stringent analyses, patients were found to have an approximately 4-fold higher risk for development of IPD than control participants (OR 4.1, 95% CI 2.4–7.3), while passive smoking by patients was associated with an OR of 2.1 (95% CI 1.2–5.1). Logistic regression analyses revealed dose-response associations with daily frequency and years of duration of smoking, while the adjusted population attributable risks for development of IPD were 51%, 17%, and 14% for cigarette smoking, passive smoking, and chronic illness, respectively.[15]

The findings reported by Nuorti and colleagues[15] were confirmed in a later, albeit smaller, study, which reported that smoking was the leading risk factor for pneumococcal pneumonia, with smokers having an increased risk for progression to bacteremic forms of the disease.[16] The findings of both studies not only reinforce the risks posed by the intensity and duration of smoking for the development of both nonbacteremic and bacteremic pneumococcal CAP, but also, possibly in distinction to some other types of CAP pathogen, the risks posed by passive smoking.

In the context of pneumococcal CAP, smoking is also likely to contribute to the pathogenesis of both the acute adverse cardiac events and longer-term cardiac sequelae of pneumococcal CAP.[17] In addition, smoking has been reported to contribute to pneumococcal transmission via pro-inflammatory mechanisms, which promote pneumococcal shedding from the nasopharynx.[18-20]

Clinical Implications

Smoking is clearly a risk factor for CAP, and although there is sparse data on the association between smoking and various different causative pathogens, there is definitive evidence of an association with pneumococcal infections and tuberculosis. Regarding the former pathogen, smokers with pneumococcal infections need close monitoring as they are significantly more likely to progress to bacteremic infections, associated with more severe disease, greater risk of complications including possibly acute cardiac events and even longer-term cardiac sequelae, and higher mortality. With regard to the latter pathogen, investigation for possible infection with tuberculosis needs to be undertaken more readily in smokers, particularly in those cases not responding appropriately to initial empiric therapy.

Alcohol use and community-acquired pneumonia

It has been suggested for well over a century that alcohol abuse is a significant risk factor for serious pulmonary infections,[21.22,] including infections with common pathogens such as *S . pneumoniae* (which may be associated more commonly in this situation, with the presence of bacteremia and septic shock), infections with "tissue damaging" gram-negative pathogens, especially *Klebsiella pneumoniae* , as well as infections with *M. tuberculosis* . What is less well recognized, however, is that alcohol abuse increases the risk of acute lung injury, including acute respiratory distress syndrome (ARDS), after major trauma or other severe acute illnesses, including infections.[22] Therefore, while pneumonia occurring in otherwise healthy young patients may be relatively mild, requiring only oral antibiotics that can be administered as an out-patient, in patients requiring hospitalization, the mortality increases significantly, and in those admitted to intensive care unit (ICU), with respiratory failure, the mortality may exceed 50%.[22]

In the first instance, it is important to note that alcohol use remains an important public health issue, and that the spectrum of alcohol use disorder (AUD) is wide ranging, from, as an example, acute intoxication in a young, otherwise health college student, to the older person with manifestations of long-term alcohol use, which may include withdrawal and cirrhosis.[23] AUD is defined by 11 criteria related to inability to stop or control alcohol use in the past year despite significant social, occupational, and health consequences, and the severity ranges from mild to severe, and then there are also the consequences of binge drinking. Regardless of the differences in the patterns of alcohol use, pneumonia and poor outcomes have been well described in individuals with AUD in the literature.[23]

Several earlier studies indicated that alcohol abuse was associated with worse morbidity and mortality in patients with pneumonia.[21,22] In people living with HIV, alcohol (and/or crack/cocaine) use was associated with an increased pneumonia severity.[24] A very recent large retrospective cohort study of substance misuse, including that of alcohol, and the outcome of critically ill patients with pneumonia, noted that alcohol misuse was present in 5%.[25] In unadjusted analysis, alcohol misuse was associated with an increased hospital mortality (OR 1.12; 95% CI 1.06–1.19), which persisted in adjusted analyses. In a retrospective cohort study conducted in 137,496 adults admitted to 177 ICUs in the United States with pneumonia, when adjusted for demographic characteristics and insurance, AUD was associated with higher mortality (OR 1.40; 95% CI 1.25–1.56), as well as longer length of hospital stay, and costs.[26] However, after additional adjustments for comorbidities and risk factors for resistant organisms, AUD was no longer associated with higher mortality, but remained associated with late mechanical ventilation, length of stay, and costs. Thus, it appears that the high age-adjusted

risk of death in patients with AUD appears largely attributable to differences in comorbidities, whereas greater use of health care resources appears to be attributable to alcohol withdrawal.

A relatively recent systematic review and meta-analysis of alcohol use and the risk for pneumonia found 17 papers eligible for inclusion, of which 14 reported results that could be pooled.[27] Meta-analysis of the latter publications identified an 83% increased risk of CAP in patients who consumed alcohol in general or consumed alcohol in higher amounts, versus those who did not consume alcohol, or consumed alcohol in lower amounts [relative risk (RR) 1.83; 95% CI 1.30–2.57]. There was significant between-study heterogeneity, attributable in part to differences between different study continents, adjustment for confounders, and pneumonia diagnosis (clinical vs death). However, dose-response analysis found that for every 10 to 20 g higher alcohol intake per day, there was an 8% increase in the risk of CAP.

Case studies have highlighted the occurrence of less common infections in patients misusing alcohol, such as fulminant community-acquired *Acinetobacter* pneumonia (in patients regularly consuming home-brewed alcohol)[28] and *Mycobacterium abscessus* pneumonia (in severe alcoholism).[29] Furthermore, studies of the effects of alcohol intake/misuse in patients with infections, including COVID-19, have yielded differing results. For example, one study documented no deleterious association between alcohol consumption and risk of infectious diseases, including pneumonia and COVID-19,[30] while another indicated that in patients hospitalized with COVID-19, alcohol misuse was associated with an increased use of critical care resources including ICU admission and mechanical ventilation.[31] In that study, delirium was an important modifiable risk factor, which was associated with worse outcome (including increased odds of death) in hospitalized patients with alcohol misuse. A relatively recent review, which indicated the likelihood that alcohol lung represented an important comorbidity for the negative consequences of COVID-19 susceptibility and outcome, presented very succinctly the known ramifications of alcohol use on the lung in the context of the current coronavirus pandemic, and the manifestations of AUD on lung diseases.[32]

The putative mechanisms by which alcohol use may increase the risk for CAP are diffuse and likely multifactorial and are shown in Box 1 . During the past decade, researchers have attempted to understand these mechanisms in more detail. Stanford and colleagues, who had previously shown in vitro that alcohol decreased ion transport via the cystic fibrosis transmembrane (CFTR) channels, undertook an in vivo experimental study to validate these findings further.[33] In a rat model, alcohol-induced defects in CFTR ion transport that reduced airway surface hydration and delayed mucus clearance, which was associated with diminished ability to clear bacterial pathogens. Since CFTR dysfunction correlates with reduced protein kinase A-dependent CFTR phosphorylation and channel gating due to increased cyclic adenosine monophosphate (AMP) degradation by phosphodiesterase-4 (PDE-4) enzymes, the authors studied, and documented, that roflumilast, a PDE-4 inhibitor, significantly increased CFTR activity in both control and alcohol-fed rats.

Box 1. Putative mechanisms by which alcohol use/abuse may be related to an increased risk of community-acquired pneumonia.

Mechanisms by which alcohol abuse may increase the risk of pneumonia

- Alterations in oropharyngeal flora (increase colonization by gram-negative pathogens)
- Blunted cough and gag reflexes (increased risk of aspiration)
- Impaired mucociliary function
- Impaired innate and/or adaptive immune function
  - Impaired alveolar macrophage function
  - Decreased cytokine/chemokine production
  - Abnormal neutrophil function
- Other (malnutrition, aspiration, poor oral hygiene)

Most of the earlier studies of alcohol and pneumonia in animal models used high concentrations of ethanol or chronic exposure and had conflicting results about how ethanol altered immunity to pathogens.[34] In addition, some used very high bacterial inoculates, which overwhelmed the immune system and produced obscure results often not applicable to human infections.34 In a mouse model, Martins and colleagues documented that chronic ethanol exposure altered the inflammatory response during *S . pneumoniae* lung infection, with a reduction of the inflammatory infiltrate despite the presence of increased levels of CXCL1 and nitric oxide levels. [35] Hulsebus and colleagues, using a short and more moderate ethanol exposure regimen in mice, noted that respiratory dysfunction and impaired pneumococcal clearance occurred in ethanol-exposed mice, associated with increased gene expression of the chemokines, CXCL1 and CXCL2, in whole lung homogenates, elevated concentrations of granulocyte-colony stimulating factor and higher neutrophil numbers in the lung, 24 hours after infection.[34] Furthermore, Malacco and colleagues documented in a mouse model that ethanol affected activation, recruitment, phagocytosis, and killing functions of neutrophils causing an increased susceptibility to pulmonary *Aspergillus fumigatus* infection.[36] Downregulated neutrophil function and increased levels of serum CXCL1 in ethanol-fed mice induced the internalization of CXCR2 chemokine receptor in circulating neutrophils. Tsuchimoto and colleagues noted in a mouse model that most monocytes polarized to an M2b-type phenotype in association with alcohol abuse, and that this appears to contribute to the increased susceptibility of alcoholics to gut and lung infections.[37] Others have shown that alcohol-induced intestinal dysbiosis mediates increased susceptibility to pneumococcal pneumonia and impaired pulmonary host defences against *K . pneumoniae.*[38,39] Furthermore, other workers have shown that while AUD increases the risk of respiratory infections, extracellular matrix component, HA, is increased in chronic respiratory diseases and HA signaling through hyaladherins are affected by alcohol use.[40] This could modify inflammation and immune cell activity during bacterial pneumonia; however, the role of hyaladherins in alcohol-induced immune dysfunction is largely unknown, and further studies are needed to understand the role of HA and its binding partners in host immune defense following excessive alcohol use.[40]

Clinical Implications

Alcohol use has been recognized for a considerable period of time not only to be a significant risk factor for CAP but also to be associated with a much broader spectrum of likely pathogens that may need extensive investigation, as well as a higher morbidity and mortality. Such patients need to be closely monitored because of a greater risk of acute lung injury leading to need for ICU admission, as well as mechanical ventilation, associated with the highest

mortality for patients with CAP. Such cases also need to be followed for alcohol withdrawal symptoms that need specialized management.

Type 2 diabetes mellitus and community-acquired pneumonia

In their recent review, Berbudi and colleagues highlighted the broad spectrum of acquired immune deficiencies, encompassing both the innate and adaptive immune systems, in type 2 diabetes mellitus (T2DM) persons with hyperglycemia.[41] The abnormalities of immune function included defects of cytokine production and neutrophil function, including pathogen recognition, phagocytosis, and elimination by these cells.[41] These mechanisms are likely to underpin the well-recognized vulnerability of hyperglycemic diabetics for development of CAP and other types of bacterial infection.[42]

In an earlier population-based cohort study, Jackson and colleagues investigated risk factors for the development of CAP in elderly persons ($n = 79{,}237$ age ≥ 65 years, study period 1998–2001).[43] The study population comprised persons hospitalized with severe CAP, as well as those whose disease was treated on an outpatient basis. Among others, the authors identified DM as a risk factor associated with severe disease, specifically an increased risk for a first-time hospitalization for CAP (HR 1.52, 95% CI 1.29–1.78). This was not the case for outpatient treatment for CAP (HR 0.90, 95% CI 0.77–1.06), while a small increase was noted in the case of all-cause CAP (HR 1.13, 95% CI 1.01–1.27).[43]

In a more recent study, Brunetti and colleagues undertook a systematic review and meta-analysis of observational studies to probe the association between TD2 and development of CAP.[44] The systematic review comprised 13 cohort studies and 4 case-control studies, encompassing a total of 14,538,966 patients age ≥ 18 years. The pooled RRs for the development of CAP across all studies and for the cohort studies were 1.64 (95% CI 1.55–1.73, T^2 0.0001) and 1.70 (95% CI 1.63–1.77, T^2 0.002), respectively, while the OR for the case-control studies was 1.54 (95% CI 1.14–2.09, T^2 0.07).[44] Although the authors interpreted their data as being consistent with an association between T2DM and risk for development of CAP, they cautioned against the complicating potential of bias in a number of the studies selected for analysis, emphasizing the requirement for future studies of higher quality to confirm their findings.[44]

With respect to associations of DM and hyperglycemia with severity of CAP, Kornum and colleagues undertook a population-based, case-control study to identify the risk of hospitalization with pneumonia associated with diabetes and hyperglycemia, the latter measured according to the levels of glycated hemoglobin (HbA1c).[45] Diabetic persons with types 1 and 2 DM ($n = 34{,}239$, age range 15 to ≥80 years) were recruited to the study, which covered the period 1997 to 2005. Each patient was matched for age and sex with 10 population control subjects.

In comparison with nondiabetic controls, the adjusted overall RR for diabetics hospitalized with pneumonia was 1.26 (95% CI 1.21–1.31).[45] The adjusted RRs for those participants with types 1 and 2 DM were 4.43 (95% CI 3.40–5.77) and 1.23 (95% CI 1.19–1.28), respectively, which increased with disease duration of greater than or equal to 10 years. With respect to associations with HbA1c levels, the respective RRs for hospitalization with pneumonia for those patients with levels of less than 7% and greater than or equal to 9% were 1.22 (95% CI 1.14–1.30) and 1.60 (95% CI 1.44–1.76). The authors concluded that both types 1 and 2 DM,

particularly the former, are risk factors for a pneumonia-related hospitalization, which increases with duration and severity of disease.[45]

In a more recent retrospective, observational study, Huang and colleagues investigated the risk of mortality of persons with T2DM hospitalized with severe CAP.[46] The study included 1262 T2DM hospitalized patients with severe CAP and 2524 matched control patients identified by propensity score matching. Analysis of data revealed that patients with T2DM had significantly increased duration of ICU stay and 14-day, 30-day, ICU, and hospital mortality rates (P <.001 to P = .046), as well as clinical and laboratory indices of disease activity. These findings demonstrate that persons with T2DM who develop CAP have a significantly increased probability of a longer hospital stay, ICU admission, and risk of death.[46]

The aforementioned studies focused on the association of DM with susceptibility for the development and severity of CAP are summarized in Table 1 .

Table 1. Studies describing associations of diabetes mellitus with susceptibility for development of community-acquired pneumonia

Type of Study	Primary Endpoint(s)	Risk	Reference
Population-based cohort study	Identify risk factors for CAP in elderly persons hospitalized or treated on an outpatient for their infection	DM identified a significant risk in the hospitalized group (HR = 1.52), but not those treated on an outpatient basis (HR = 0.90)	Jackson et al, [43] 2004
Systematic review of observational studies (13 cohorts and 4 case-controls)	Identify risk for development of CAP in patients with T2DM aged ≥ 18 y	Pooled RR values across all studies and for cohort studies = 1.64 and 1.70, respectively, OR of 1.54 for case-control studies	Brunetti et al, [44] 2021
Population-based case-control study	Identify risk of hospitalization for severe pneumonia associated with types 1 and 2 DM and hyperglycemia	Adjusted overall RR for diabetics hospitalized with pneumonia = 1.26, with corresponding RRs of 4.43 and 1.23 for those with T1DM and T2DM, respectively. With respect to hyperglycemia, the RR values of those with Hb1Ac levels of <7% and ≥9% were 1.22 and 1.60, respectively	Kornum et al,[45] 2008
Retrospective observational study	Identify the risk of mortality rate of persons with T2DM hospitalized with severe CAP	Persons with T2DM who develop CAP have a significantly increased probability of a longer hospital stay, ICU admission, and risk of death.	Huang et al,[46] 2021

Abbreviations : CAP, community-acquired pneumonia; DM, diabetes mellitus; Hb1Ac, glycated hemoglobin; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; RR, relative risk/ratio; T1, type 1; T2, type 2.

Clinical Implications

The importance of diabetes mellitus is that these patients are at greater risk of CAP, and when they acquire this infection, they need close monitoring as they are more likely to develop severe disease.

Pneumonia in people with the manifestations of metabolic syndrome

A cluster of risk factors for cardiovascular disease and T2DM, which occur together more frequently than by chance alone, has become known as the metabolic syndrome, with these risk factors including raised blood pressure, dyslipidemia (raised triglyceride and lowered levels of high-density lipoprotein cholesterol), raised fasting glucose, and central obesity.[47] However, various diagnostic criteria have been proposed by different organizations. The main difference concerns the measure for central obesity, with this being an obligatory component in some definitions, lower in other criteria of metabolic syndrome, and ethnic specific. This earlier publication under discussion represents the outcome of a meeting between several organizations attempting to unify the criteria, where it was agreed that there should not be any obligatory component, but that waist measurement would be a useful preliminary screening tool. The presence of 3 out of the 5 abnormal findings mentioned earlier would qualify a person for the metabolic syndrome, and a single set of cut-off points would be used for all components except for waist circumference for which additional work was required; but in the interim national or regional cut-off points for waist circumference could be used. [47]

Although obesity and the associated metabolic syndrome have been found to impact negatively on health outcomes, a paradoxic relationship between obesity and mortality has been reported for specific patient populations, such as patients with CAP, but including patients with several other medical conditions, and in the elderly, a phenomenon that has been termed the "obesity paradox."[23] While the exact mechanisms of this paradox, if it exists, remain unclear, several possible mechanisms have been suggested. A true protective effect could be possible through differences in the immune and inflammatory response and in the presence of more metabolic reserves in obese patients. With regard to the former possible mechanism, obesity is known to be associated with a state of chronic inflammation, and a heightened and more pronounced inflammatory response, as evidenced by factors such as a higher body temperature and higher increases in C-reactive protein (CRP) levels, which have been associated with a more favorable outcomes in patients with CAP. However, there is no evidence of a different immune response in obese patients.

The other side of the argument is that this may all be about bias.[48] Most of the epidemiologic studies suggesting the occurrence of obesity paradox have been observational so they do not prove causality and are prone to significant confounding, which has been thoroughly discussed elsewhere.[48] Among the various biases are "confounding bias" related to factors such as smoking and potential cancer, "collider stratification bias," which occurs when several medical conditions which interact with each other, are risk factors for the disease under consideration, "assessment bias" which occurs in studies in which body mass index (BMI) data were not assessed, "performance bias" where, for example, obese patients are given "better treatment," such as statins, which may modify the disease process, "measurement bias" concerning whether the measurement of BMI is the best assessment of body composition. Therefore, other authors indicate that in their opinion, "obesity paradox" is misleading, is not a scientific term, but is just a figure of speech, which has no specific definition, and its use should be abandoned.[49]

Nevertheless, based on various clinical studies, it is not entirely clear whether there is an impact of obesity on outcome of patients with pneumonia.[50-54] In one retrospective study of hospitalized patients with pneumococcal or *Haemophilus* CAP, patients were classified, based on BMI, as underweight (BMI < 18.5), normal weight (BMI 18.5 to <25), overweight (BMI 25 to <30), or obese (BMI ≥ 30). The authors investigated the association between absolute BMI values and BMI categories and mortality at 30 days after admission for CAP. Increasing BMI values were associated with reduced 30-day mortality even after adjustment for significant covariates (OR 0.88; 95% CI 0.81–0.96; *P* <.01) with a significant trend toward lower mortality in the overweight and obese patients.[50] Nie and colleagues conducted a meta-analysis of cohort studies identified from PubMed and Embase and included 13 cohort studies on risk of pneumonia and 10 cohort studies on mortality.[51] Overweight and obese individuals had an increased risk of pneumonia (RR 1.33; 95% CI 1.04–1.71; *P* = .02). In the dose response analysis, RR of pneumonia per 5 kg/m ^{2} increase in BMI was 1.04; 95% CI: 1.01–1.07; *P* = .01. In contrast, overweight and obese patients had a reduced risk of pneumonia mortality (RR 0.83; 95% CI 0.77–0.91; *P* <.01) with an estimated summary RR of mortality per 5 kg/m ^{2} increase in BMI being 0.95; 95% CI: 0.93–0.98; *P* <.01. However, the authors concluded that because the meta-analysis was based on observational studies, more studies were needed to confirm the results. A secondary data analysis of the University of Louisville Pneumonia Study database found a protective benefit of obesity on mortality in CAP patients; however, the association between BMI and mortality was not linear, and no incremental benefit of increasing BMI levels was found in those with obesity classes II and III.[52] A study from Denmark of patients hospitalized with various non-COVID-19 acute infections, including CAP, found that higher BMI (overweight, obese) was associated with improved survival, whereas underweight increased the risk for death.[53] Mortality reductions were consistent for all infection types and remained robust, irrespective of recent weight changes, smoking status, or comorbid conditions. However, a recent secondary analysis of a randomized controlled trial showed neither a beneficial nor an adverse outcome in patients with obesity, hospitalized with CAP.[54]

Very interestingly, the "obesity paradox" does not ever appear to have been described in relationship to COVID-19 infection, but the majority of data from several reports of thousands of patients indicate, in fact, just the opposite; namely that in patients with COVID-19 infection those with obesity and/or components of the metabolic syndrome, have more severe disease, and worse prognosis.[55,56] In fact, some authors have suggested there is an obesity "anti-paradox" in COVID-19. Such cases are admitted to the ICU more frequently, with an increased need for intubation and mechanical ventilation, and they have a higher mortality.[55] Early publication during COVID-19 suggested that the reasons for the increased risk in obesity, was, among other reasons, because of multiple associated comorbidities, especially a higher presence of cardiovascular disease and also that adipocytes in obese individuals express angiotensin-converting enzyme 2 receptors, which may be in a greater amount than in lung tissue, and therefore, fat may be a potential reservoir for the SARS-CoV-2 virus.[55] Thus, cases with the metabolic syndrome, as well as those with individual components of the metabolic disorders such as obesity, diabetes, CVD, and liver disease face a higher risk of COVID-19 infection, which greatly affects the development and prognosis of the disease. Several reviews have described in more detail the spectrum of clinical features, the likely pathophysiologic mechanisms and the potential implications for the management of the metabolic syndrome in COVID-19 patients.[56, 58-61]

A multicenter cohort study was undertaken using data from the Society of Critical Care Medicine Discovery Viral Respiratory Illness Universal Study, which collected data from 181 hospitals across 26 countries from February 15, 2020 to February 18, 2021.[62] Outcomes were

compared between patients with metabolic syndrome (≥3 of the following criteria—obesity, prediabetes or diabetes, hypertension, and dyslipidemia) and a control population without metabolic syndrome in patients hospitalized for COVID-19 during the time-period, and who had completed discharge status. While the primary outcome was in-hospital mortality, secondary outcomes included ARDS, ICU admission, need for invasive mechanical ventilation and length of stay. The main findings were that metabolic syndrome was associated with increased risk of ICU admission, invasive ventilation, ARDS, and mortality and both prolonged hospital and ICU length of stay. Each metabolic syndrome criterion was associated with increased risk of ARDS in an additive fashion.

A retrospective cohort study conducted in Turkey comparing hospitalized COVID-19 pneumonia patients with and without metabolic syndrome noted that the former patients had lower oxygen saturations at hospital admission, higher neutrophil counts and CRP levels, more extensive radiological involvement in the lung on tomography, longer of length of hospital stay and need for ICU care, as well as higher mortality rates than in the latter patients.[63] An additional small retrospective study from China, noted that in patients with COVID-19 infection, those with metabolic syndrome, were more likely to develop severe complications and have a worse prognosis than those without metabolic syndrome.[64] In the former group of patients, concurrent metabolic syndrome and lymphopenia were independent risk factors for severe COVID-19 illness.

Lastly, a prospective cohort study of 303 patients hospitalized for COVID-19 was first characterized for the presence of obesity and then according to whether they had metabolic syndrome or not.[65] Patients with obesity were found to present with moderate COVID-19 symptoms and pneumonia, bilateral pulmonary infiltrates and need for tocilizumab therapy more frequently. Patients with overt metabolic syndrome presented more frequently with severe pneumonia and respiratory failure; they had a higher mortality and showed higher levels of creatinine and troponin. The authors' conclusions were that IL-6 was a predictive biomarker of COVID-19 severity in patients with obesity, while troponin and LDH could be used as potential predictors of COVID-19 severity in patients with metabolic syndrome. The major conclusions from all these metabolic studies in COVID-19 are that the treatment for those patients with COVID-19 infection and associated obesity or metabolic syndrome needs to be intensified and personalized.

Clinical Implications

With regard to metabolic syndrome, it is important to recognize that while earlier studies suggested that there was an "obesity paradox," and that overweight and obese patients with pneumonia had a better outcome, other authors have suggested that this finding may simply be due to bias, and that being overweight or obese itself was not "protective" in any way. Importantly, such as possible beneficial effect of being overweight or obese has not been confirmed in COVID-19 pneumonia, in fact the opposite has been found, which some have referred to as the "anti-paradox."

Multimorbidity in patients with community-acquired pneumonia

Multimorbidity is defined as 2 or more chronic health conditions occurring in one individual and has been noted to be very common.[66] However, many studies of individuals hospitalized for various medical conditions, such as heart failure, chronic respiratory conditions, DM, and even pneumonia, have tended to focus on the study and management of the individual disease,

rather than address all the associated conditions.[66] This is particularly so in the case of CAP. Even the current authors have largely thus far, concentrated descriptions on specific disease entities and/or conditions in the discussion of risk factors for CAP.

Importantly, studies have suggested that multimorbidity was present in a third of patients with CAP[66] and is independently associated with death, hospitalization, or return to the emergency department, within 90 days of discharge. For example, one study indicated that DM was present in 10.2% of patients with CAP (number = 5565) yet was associated with multimorbidity in 35.5% (number = 1602).[66] In fact, not only the specific comorbidities but also the number of combined comorbidities, and the combination of at-risk and high-risk conditions, appear to impact the outcome of hospitalized CAP, including specifically, pneumococcal CAP.[67] In fact, one critical review of the evidence indicated that the ORs for the occurrence of pneumococcal CAP, and IPD in cases with multiple comorbidity was similar to that in patients currently defined as high-risk cases and was previously underestimated.[68]

Summary

Compelling evidence has identified smoking and excessive alcohol consumption as eminently avoidable risks for both development and severity of CAP, while various comorbid disorders, including diabetes mellitus and the metabolic syndrome, also represent known risk factors, albeit of a more intransigent nature. Acquired immune suppression is the common thread underpinning these diverse, often co-existent, risk factors for development of severe CAP even in the face of seemingly appropriate antimicrobial chemotherapy. Importantly, in addition to a keen awareness of these risks on the part of infectious disease clinicians, the acquisition of innovative host-targeted immunotherapies represents a promising adjunctive approach to improving the outcome of persons at high-risk for development of severe CAP.

Clinics care points

- Community-acquired pneumonia (CAP) remains a significant public health concern worldwide.
- Those with prevalent chronic comorbidities and/or unhealthy lifestyles linked to acquired immune dysfunction are at high risk for development of, and hospitalization from, severe CAP.
- Promoting awareness of the pro-infectious risks of smoking, possibly vaping and excessive alcohol consumption, especially when exacerbated by co-existent comorbidities such as diabetes mellitus and the metabolic syndrome is a public health priority.
- Although *Streptococcus pneumoniae* is the most prominent bacterial cause of CAP, greater insight into the prevalence of CAP caused by other types of bacterial respiratory pathogens may enable the acquisition of innovative, adjunctive pathogen-targeted immunotherapies.

Disclosure

The authors have nothing to disclose.

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