Review Article

Community-acquired pneumonia due to gram-negative bacteria

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ABSTRACT

Community-acquired pneumonia (CAP) is a frequent infectious disease that can be usually treated in an ambulatory setting. A small percentage of these cases require hospitalization and yet it is the leading infectious cause of hospitalization and death in some countries. A number of these infections is caused by gram-negative bacteria (GNB), which have repeatedly been found to bear an adverse prognostic potential. Its incidence is variable (0-9%) and some species carry a special pathogenicity. Enterobacteriaceae in these studies were more commonly isolated than *P. aeruginosa* while *Acinetobacter* spp. and *B. cepacia* were only occasionally described. The present review has the aim to update the current knowledge about the etiology, classification, antimicrobial resistance, diagnosis, and therapy in CAP due to GNB.

Key words: Community-acquired pneumonia (CAP), gram-negative bacteria (GNB), pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) is a frequent infectious disease, ranking as the fifth leading cause of death globally.[1] Key early decisions in CAP management are based on severity scores and presumed pathogens guided according to the clinical presentation, age, presence of comorbidities, and other significant antecedents and site of care.[2]

The vast majority of the patients with CAP are treated in an ambulatory setting[3] while a small percentage requires hospitalization; however, CAP is the leading infectious cause of hospitalization and death among US adults.[4,5] The 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines listed gram-negative bacteria (GNB) among the most common etiologies of CAP in those patients who need to be admitted in the intensive care unit (ICU) for pneumonia but it warns that it that the presence of risk factors for certain specific etiologies must also be taken into account including alcoholism and aspiration for aerobic gram-negative bacilli (AGNB), and chronic obstructive pulmonary disease (COPD), late human immunodeficiency virus (HIV) infection, and lung structural disease (i.e., bronchiectasis) for *P. aeruginosa*.[6,7]

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GNB have repeatedly been found to bear an adverse prognostic potential. On the other hand, the reported incidences of GNB CAP in the general population have been quite variable, ranging 0% to 9% for aerobic GNB overall and from 0% to 3% for *P. aeruginosa*.[8]

The present review has the aim to update the current knowledge about the etiology, classification, antimicrobial resistance, diagnosis, and therapy in CAP due to GNB.

ROLE OF GRAM NEGATIVES IN THE ETIOLOGY

The recognition of the role of GNBs in the etiology of CAP has become more frequent during the last decades due to several reasons including a more efficient microbiological research, a trend to a worsening of the severity of illness of the patients admitted in the ICU and the increase of the life expectancy of the population as old patients have CAP more frequently and they are more usually colonized by GNB.[9,10] Most of the studies that performed a carefully systematic and comprehensive evaluation of the etiology of CAP found a frequency of these microorganisms in percentages that varied, considering 10 studies performed during the last 15 years, from 0% to 6.7% of cases (mean 2.3%) and 0% to 16% considering those with etiology defined (mean 4.5%) [Table 1].[11-20] Members of the family Enterobacteriaceae were more commonly isolated in these studies than *P. aeruginosa*, while *Acinetobacter* spp. and *B. cepacia* were only occasionally described. Most of the reports of CAP due to *Acinetobacter* species were described in specific areas in patients with underlying conditions, leading to an increased risk for the acquisition of CAP due to this bacterium. Cystic fibrosis (CF) patients and those with chronic granulomatous disease are predisposed to *B. cepacia* pneumonia.

THE PATHOGENS

There are a number of GNB that could be the potential causative organism of CAP; this review will be focused on a number of these bacteria including some from the family Enterobacteriaceae, *P. aeruginosa*, *B. cepacia*, and *Acinetobacter* spp.[21]

Members of the family Enterobacteriaceae are referred to as "enterics" because the principal habitat of many (but not of all) of these organisms is the lower gastrointestinal tract of several animal species.[22] However, these terms are not synonymous because several species do not typically inhabit the human gastrointestinal tract, and other intestinal pathogens that do not fall within the family are also recognized as enteric bacteria. Alcoholism and diabetes mellitus predispose highly to oropharyngeal colonization with members of this family.[23] *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter cloacae*, *Proteus mirabilis*, and *Serratia marcescens* are among the commonest representatives of this family that were occasionally found to be the pathogenic organisms in CAP.

P. aeruginosa is the major pathogenic species in the family Pseudomonadaceae and is readily identified as a gram-negative straight or slightly curved rod with a length of range 1-3 μm and a width of 0.5-1.0 μm [Figure 1]. This bacterium emerged as a major human pathogen in the 1960s because of its ability to cause infections in immunocompromised and burned hosts as well as CF patients. The establishment of *P. aeruginosa* infection in the lung can have serious consequences, particularly for patients with underlying comorbidities or a genetic predisposition such as in CF. Older reports

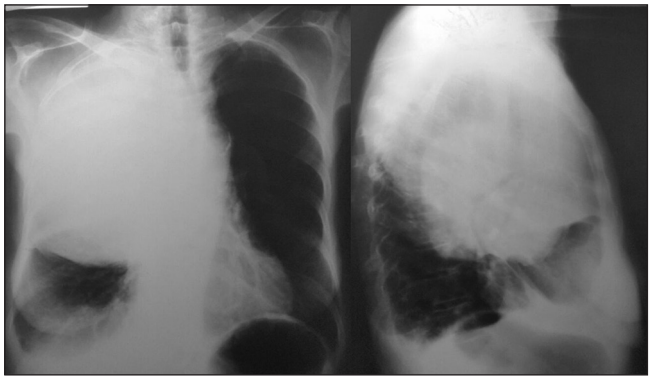

Figure 1: Chest x-ray showing homogeneous parenchymal consolidation due to the presence of a voluminous inflammatory exudate that produces the bulging of an interlobar fissure. This radiographic presentation was considered to be typical of *Klebsiella* infection

Table 1: Number and percentage of gram-negative bacteria (GNB), aerobic gram-negative bacilli and *P. aeruginosa* in the etiology of CAP

	N	*N* with etiology	% with etiology	% due to GNB	% of AGNB	% of *P. aeruginosa*
Luna CM, *et al*.[11]	343	144	42,0%	23 (6.7%)	15 (4.4%)	8 (2.3%)
Almirall J, *et al*.[12]	241	107	44,5%	1 (0.4%)	0 (0%)	1 (0.4%)
Laing R, *et al*.[13]	474	199	42,0%	3 (0.6%)	0 (0%)	3 (0.6%)
Jokinen C, *et al*.[14]	183	83	45,6%	0 (0%)	0 (0%)	0 (0%)
Garbino J, *et al*.[15]	380	190	50,0%	2 (0.6%)	2 (0.6%)	0 (0%)
Diaz A, *et al*. Chest.[16]	176	99	56,0%	4 (2.3%)	4 (2.3%)	0 (0%)
Charles PG, *et al*.[17]	885	404	45,6%	27 (3.1%)	14 (1.6%)	13 (1.5%)
Mermond S, *et al*.[18]	137	51	37,3%	5 (3.6%)	4 (2.9%)	1 (0.7%)
Capelastegui A, *et al*.[19]	700	390	55,7%	7 (1.0%)	6 (0.9%)	1 (0.1%)
Tao LL, *et al*.[20]	593	436	73,5%	22 (3.7%)	13 (2.2%)*	9 (1.5%)

of *P. aeruginosa* pneumonia describe patients with an acute clinical syndrome and a necrotizing pneumonia.[24] The pathogenesis of this disease is believed to be a direct inoculation of large numbers of the organism into the lungs by aspiration or inhalation.

B. cepacia is usually resistant to almost all the available antimicrobials. Uncommonly it causes CAP in previously normal patients. CF patients are particularly prone to acquire pneumonia due to this microorganism.

The genus *Acinetobacter* has a complex taxonomic history and is a common pathogen of hospital-acquired pneumonia. This pathogen occasionally produces CAP.[25,26] Risk factors associated with community-acquired *Acinetobacter* infection include alcoholism, cigarette smoking, chronic lung disease, diabetes mellitus, and residence in a tropical developing community.[23] Acinetobacter Gram-stained sputum examination could be misinterpreted to be other gram-negative or even gram-positive organisms [Figure 2].

The presence of gram-negatives as a pathogen of CAP has been found to a factor associated with higher risk of failure among those patients hospitalized because of the presence of CAP.[24]

Community-acquired *Acinetobacter* has been reported to be the causative microorganism of community-acquired bronchiolitis and tracheobronchitis in healthy children[27] and can also occur in immunocompromised adults. Adult community-acquired *Acinetobacter* pneumonia generally occurs in patients with diminished host defenses (e.g., alcoholism, tobacco use, diabetes mellitus, renal failure, underlying pulmonary disease).[27-29] Reports from developing tropical regions document a higher local prevalence of community-acquired *Acinetobacter* pneumonia compared with temperate climates.[28,30] One series from tropical northern Australia found community-acquired *Acinetobacter* pneumonia to account for 10% of all community-acquired bacteremic pneumonias and 21% of gram-negative pneumonias.[28] Mortality in various published series has been 40-64%. The prevalence of community-acquired *Acinetobacter* pneumonia was speculated to be a consequence of the generally poor health of persons in the communities under study, frequent use of penicillins, and/or genetic predisposition.

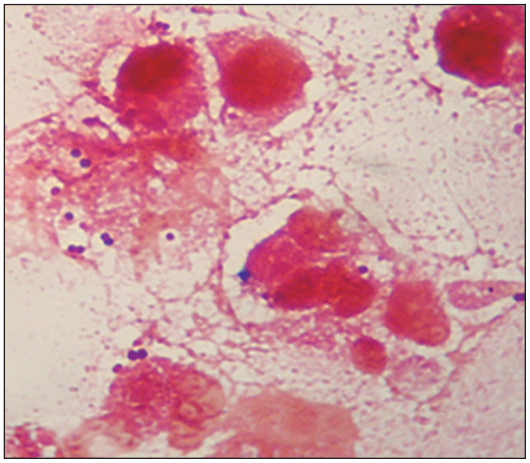

Figure 2: Microphotograph from a Gram-stained smear obtained from a bronchoalveolar lavage showing intracellular gram-positive diplococci. Culture from the bronchoalveolar fluid yielded *Acinetobacter* spp. at concentration >104 colony-forming units per mL. *Acinetobacter*-like Moraxella can be pleomorphic, and sometimes appear as gram-positive cocci. These organisms tend to retain the crystal violet stain and appear to be gram-positive

Acinetobacter spp. (*A. baumannii* is the prevalent genomic species but others may cause infection) became an increasingly important cause of nosocomial pneumonia, particularly in ventilator-associated pneumonia (VAP). This organism has intrinsic resistance to some antimicrobials but acquires easily resistance to many others, and survives for a long time in the environment. *Acinetobacter* is a short, plump, gram-negative (but sometimes difficult to destain) rod, typically 1.0-1.5 mm by 1.5-2.5 mm in the logarithmic phase of growth but often becoming more coccoid in the stationary phase. Pairing or clustering of cells often occurs. Gram stain variability as well as variations in cell size and arrangement can often be observed within a single pure culture.[31] Some rare cases of CAP caused by *Acinetobacter* spp. happen.

DIAGNOSIS

Apart from the severity of illness and a more frequent association with older age, there are few data that could help to anticipate the possible role of GNBs in the etiology of CAP in any patient. From the radiologic standpoint, it is worth mentioning that the bulging fissure sign that has been described is characteristic of *K. pneumoniae* pneumonia [Figure 1] although it could be present in pneumonia due to *S. pneumoniae*, *P. aeruginosa*, and *S. aureus*. Bulging fissures, sharp margins of the advancing border of the pneumonic infiltrate, and early abscess formation are radiologic signs said to be distinctive for *Klebsiella* pneumonia but are only occasionally observed today.

The most frequent methods for discovering the microbial agent of gram-negative CAP are blood and sputum cultures.[32] In patients with severe pneumonia invasively mechanically ventilated, it is easy to obtain lower respiratory tract secretions either by tracheal aspiration or by more representative specimens present in a significant concentration obtained by invasive or noninvasive bronchoalveolar lavage ($\geq 10^4$ colony forming units per mL) or protected specimen brush ($\geq 10^3$ colony forming units per mL). Multiplex real-time polymerase chain reaction (PCR) methods could be useful for the rapid and simultaneous detection of some gram-negative pathogens and the presence of specific

mechanisms of resistance in a clinical specimen. By multiplex real-time PCR assay, it is possible to simultaneously detect and differentiate numerous causative agents of CAP rapidly with high sensitivity and specificity and without being affected by antecedent antibiotics administration. A set of real-time PCR for the detection of eight bacterial species from positive blood culture bottles including *E. coli*, *P. aeruginosa*, A. *baumannii*, *E. faecalis*, and *E. faecium* among the GNBs was described.[33,34]

TREATMENT

According with the recommendations of the 2007 IDSA/ATS guidelines, patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48-72 h, and should have ≤1 CAP-associated sign of clinical instability (temperature <37.8, heart rate <100 beats/min, respiratory rate <24 breaths/min, systolic blood pressure >90 mmHg, arterial oxygen saturation >90% or PaO2 >60 mmHg on room air, ability to maintain oral intake, and normal mental status) before discontinuation of therapy. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection such as meningitis or endocarditis.[2] According with such guidelines when *P. aeruginosa* infection is a concern, an antipneumococcal, antipseudomonal β-lactam antimicrobial (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose) or the above β-lactam plus an aminoglycoside and azithromycin or the above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone should be used [Table 2]. For penicillin-allergic patients, the indication is to substitute aztreonam for the above β-lactam. Pseudomonal CAP requires combination treatment to prevent inappropriate initial therapy, just as *Pseudomonas* nosocomial pneumonia does. For Enterobacteriaceae, third-generation cephalosporins provide enough coverage; however, a carbapenem should be the drug of choice if an extended-spectrum β-lactamase producer enteric bacteria is to be covered[2,35] [Table 2]. Alternatives for such pathogens could be β-lactam/β-lactamase inhibitor (piperacillin-tazobactam for gram-negative bacilli, ticarcillin-clavulanate, ampicillin-sulbactam, or amoxicillin-clavulanate), or a fluoroquinolone. For *Acinetobacter* spp., third-generation cephalosporin + aminoglycoside or ampicillin-sulbactam were recommended;[35] however, *Acinetobacter* spp. could be multidrug resistant and could need to adapt the regime. Considering the known susceptibility of such an agent, occasionally intravenous and/or inhaled colistin could be considered as an option[2,35] [Table 2]. *B. cepacia* is a concern limited to CF or chronic granulomatosis disease patients with pneumonia; the isolation of *B. cepacia* antimicrobial-resistant variants has been found to be associated with CF patients with chronic lung infection exhibiting a severely compromised lung function, subjected to aggressive and longstanding antibiotic therapy. During periods of pulmonary exacerbation the use of combinations, rotating strategies, high doses, and inhaled antimicrobials are used.[36] The role of inhaled antimicrobials for GNB pneumonia is under clinical research, particularly for VAP. Ceftazidime, the more extensively used β-lactam for the prevention and treatment of VAP, had improved clinical outcomes in chronic *P. aeruginosa* lower respiratory tract infections in patients with CF or bronchiectasis. Inhaled fluoroquinolones (levofloxacin and ciprofloxacin) and a combination of fosfomycin and tobramycin was associated with improved microbiological or clinical outcomes in chronic lower respiratory tract infection (LRTI) in patients with CF or bronchiectasis. For multiple drug-resistant GNBs, it could be possible that inhaled antimicrobials could have some role in the therapy of selected cases of GNB CAP.[37]

Newer antibiotics: Ceftaroline, an advanced-generation, parenteral cephalosporin has been described as a "fifth generation" cephalosporin in the literature.[38] GNB spectrum activity includes non- Extended-spectrum β-lactamase (ESBL)-producing strains of *E. coli* and *K. pneumoniae* but not *P. aeruginosa*. The *in vitro* activity of ceftaroline against Enterobacteriaceae is similar to that of other expanded spectrum cephalosporins, including ceftriaxone and another third generation agent, as ceftazidime. Ceftaroline fosamil demonstrated noninferiority to intravenous ceftriaxone in patients hospitalized with CAP [Pneumonia Outcomes Research Team (PORT) risk class III or IV]; patients with CAP admitted to the ICU were not evaluated. Diarrhea was a common reported adverse event but the risk of *Clostridium*

Table 2: Recommended antimicrobial therapy for specific pathogens, from ATS and ERS guidelines[2,33], modified

Organisms	Preferred antimicrobial (s)	Alternative antimicrobial (s)
Enterobacteriaceae	Third-generation cephalosporin, carbapenem[a] [drug of choice if extended-spectrum β-lactamase (ESBL) producer] Third-generation cephalosporin, carbapenemc (drug of choice if ESBL producer)	β-Lactam/β-lactamase inhibitor[b], fluoroquinolone
Pseudomonas aeruginosa	Antipseudomonal β-lactame[c] plus (ciprofloxacin or levofloxacin[d] or aminoglycoside)	Aminoglycoside plus (ciprofloxacin or levofloxacin[d])
Acinetobacter species	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
Burkholderia cepacia		

Note: Choices should be modified on the basis of susceptibility test results and advice from local specialists. Refer to local references for appropriate doses; ATS: American Thoracic Society; CDC: Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; TMP-SMX: trimethoprim-sulfamethoxazole; [a]Imipenem-cilastatin; meropenem; ertapenem; [b]Piperacillin-tazobactam for gram-negative bacilli; ticarcillin-clavulanate; ampicillin-sulbactam or amoxicillin-clavulanate; [c]Ticarcillin; piperacillin; ceftazidime; cefepime; aztreonam; imipenem; meropenem; [d]750 mg daily

difficile-associated diarrhea with ceftaroline fosamil was low. One limitation of the drug is the lack of an oral formulation and the requirement for twice daily administration.[38]

OUTCOME

Luna *et al*. looking at the risk factors for mortality in a study looking at the etiology, epidemiology, and outcome in the general population with CAP observed that aerobic GNB as the pathogen of CAP was one of the prognostic factors associated with mortality in multivariate analysis.[10]

Similarly, Arancibia *et al*. found that the mortality of patients with GNB pneumonia in their cohort was 32% (19/60), significantly higher than the mortality observed in those in the non-GNB group, which was 9%, (44/499).[7] They found that in the multivariate analysis in their cohort, GNB pneumonia was one of the few conditions that were independently predictors of death.[7]

RISK FACTORS

Arancibia *et al*. reported their experience in a cohort of 559 patients admitted with CAP. They found that the incidence of GNB CAP (including *P. aeruginosa*) was 11% (60/559).[7] Although the age tended to be higher in those patients with CAP due to GNBs (69/72-year-old), this difference was not significant. These authors defined the following risk factors as independent predictors of GNB pneumonia: Probable aspiration, odds ratio (OR), 2.3; 95% confidence interval (CI): 1.02-5,2; $P = 0.04$; previous hospital admission, OR, 3.5; 95% CI, 1.7-7.1; $P < 0.001$; previous antimicrobial treatment, OR, 1.9; 95% CI, 1.01-3.7; 9 = 0.049 and the presence of pulmonary comorbidity, OR, 2.8; 95% CI, 1.5-5.5; $P = 0.02$.[7] In a subgroup analysis of *P. aeruginosa* pneumonia, pulmonary comorbidity OR 5.8, 95% CI, 2.2-15.3, $P < 0.001$ and previous hospital admission OR 3.4, 95% CI, 1.6-7.4, $P = 0.002$ were predictive.[7] A number of these cases of GNB CAP are related to the presence of an underlying risk of aspiration.

Aspiration pneumonia, in most of the cases, is due to microorganisms that colonize the oropharynx, an essential step in its pathogenesis. The elderly have increased oropharyngeal colonization and aerobic GNB as *K. pneumoniae* and *E. coli* are among those colonizers.[39-41] Although this increased colonization may be transient, it underlies the increased risk in the elderly of pneumonia due to these pathogens.

PREVENTION

There are no specific prevention measures for GNB CAP, as in most of the cases of GNB CAP, airway colonization apparently appears to precede the development of pneumonia; rational use of antimicrobials to avoid the colonization due to the unnecessary administration of antibiotics, prevention of aspiration and general measures of treatment for chronic respiratory conditions in COPD, bronchiectasis, and CF patients, and the control of other underlying conditions (smoking, diabetes mellitus, congestive cardiac failure, etc.) should be among the preventive measures. Vaccination for influenza and *S. pneumoniae* should be offered to all the patients by the time of discharge or during outpatient treatment.[2] Smoking cessation should be attempted while smokers are hospitalized; this is something particularly important in those patients who are admitted for pneumonia.[2]

CONCLUSION

GNB is the etiological agent of CAP in a relatively low number pneumonia of patients. These pathogens produce lung infection, especially in older patients harboring chronic respiratory diseases. The commonest agents producing GNB CAP are Enterobacteriaceae and *P. aeruginosa* although *Burkholderia cepacia* and *Acinetobacter* spp. could be present under some epidemiological and personal conditions.

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Conflicts of interest
There are no conflicts of interest.

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