Multidrug Resistant Gram-Negative Bacteria in Community-Acquired Pneumonia

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36.1 Introduction: Why Is This Topic Important?

Community-acquired pneumonia (CAP) is associated with high morbidity and mortality worldwide [1]. Although several different bacteria and respiratory viruses can be responsible for CAP, *Streptococcus pneumoniae* (pneumococcus) remains the most common causative pathogen. A small proportion of CAP cases are caused by Gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Stenotrophomona maltophilia* [2, 3]. The main problem concerning the treatment of Gram-negative bacterial infections is their related antibiotic resistance, reported as multidrug resistant (MDR = resistant to at least one agent in three or more groups of antibiotics), extensively drug resistant (XDR = resistant to at least one agent in all but two or fewer groups of antibiotics) and pan-drug resistant (PDR = resistant to all groups of antibiotics) [4]. This makes the clinical management of pneumonia caused by such pathogens a challenge for physicians. Taking into account the clinical severity that may be associated with CAP caused by Gram-negative bacteria (respiratory failure, bacteremia, shock, acute respiratory distress syndrome [ARDS]) the magnitude of the global health problem is tremendous.

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We are currently living through an antibiotic resistance crisis, mainly because antibiotics tend to lose their efficacy over time due to the emergence and dissemination of resistance among bacterial pathogens, principally caused by the overuse and inappropriate use of antibiotics, as well as the extensive use of antibiotics in agriculture and the food industry. The Global Point Prevalence Survey (Global-PPS), an international network set up to measure antimicrobial prescription and resistance in the hospital setting, recently published its findings [5]. Pneumonia was the most common illness to receive antibiotic therapy worldwide, accounting for 19% of patients treated. The most frequently prescribed antibiotics for community-acquired infections were penicillins with a β-lactamase inhibitor (29%); amoxicillin with a β-lactamase inhibitor accounted for 16% and piperacillin with a β-lactamase inhibitor accounted for 8%. Third-generation cephalosporins were the second most commonly prescribed antibiotics for community-acquired infections (mainly ceftriaxone, 16%), followed by fluoroquinolones (14%).

Antibiotic resistance is a natural phenomenon in bacteria that cannot be stopped; however various measures can be taken in order to reduce the rate of its development and devise more effective strategies to control its spread [6].

Because CAP caused by MDR Gram-negative bacteria is an important clinical concern, we review the main findings concerning the epidemiology, diagnosis and clinical impact of CAP.

36.2 CAP Caused by *Pseudomonas aeruginosa*

36.2.1 The Pathogen: Why Is It Difficult to Treat?

P. aeruginosa is an opportunistic Gram-negative, non-fermentative bacterium that inhabits the soil and surfaces in aqueous environments. Its high intrinsic antibiotic resistance, broad metabolic versatility and adaptability make it especially difficult to treat. Several studies have shown that the physical characteristics (phenotype) of *P. aeruginosa* isolates vary between those derived from chronic infections, such as cystic fibrosis, and those from acute infections, such as pneumonia [7]. Common chromosomal mutations in the mucA gene can convert a non-mucous phenotype into a mucous phenotype. The adaptation of *P. aeruginosa,* which includes complex physiological changes, confers a selective advantage since it can better survive in different habitats [8].

P. aeruginosa has intrinsic, adaptive and acquired mechanisms of resistance, the main ones including the presence of β-lactamases, alterations in membrane permeability due to the presence of ejection pumps, and mutations of transmembrane porins. Furthermore, the capacity to form biofilms (intricate, highly organized bacterial communities, embedded in a matrix composed of exopolysaccharides, DNA and proteins that is attached to a surface and hinders antimicrobial action) favors the persistence of *P. aeruginosa* and makes it more difficult to treat, due to the inherent protection that biofilms provide [8] (Table 36.1).

Table 36.1 Main resistance mechanisms in Gram-negative pathogens

Microorganism	Mechanism
Pseudomonas aeruginosa	Efflux pumps
	Mutant topoisomerases
	Modifying enzymes
	AmpC/porin reduction combinations
	Metallo-b-lactamases
	Outer membrane permeability
	Extended spectrum β-lactamases
Acinetobacter baumannii	β-lactamases
	Efflux pumps
	Membrane permeability
	Aminoglycoside-modifying enzymes
	Alteration of target sites
Klebsiella pneumoniae	Modifying enzyme
	Efflux pumps
	Mutant topoisomerases
	Extended spectrum β-lactamases
	Carbapenemases
Stenotrophomonas maltophilia	β-lactamases (L1 and L2)
	Multidrug efflux pumps
	Antibiotic-modifying enzymes
	Mutations of bacterial topoisomerase and gyrase genes
	Reduction in outer membrane permeability

A large number of intrinsic *P. aeruginosa* virulence factors are required to establish infection [7]. Moreover, the differential presence or expression of some of these virulence factors may determine major inter-strain variability in virulence and thus potentially have a major impact on disease severity and mortality [8].

In conclusion, the pathogenesis of *P. aeruginosa* CAP is very complex, in addition to the broad antimicrobial resistance that limits antibiotic therapy; the virulence of *P. aeruginosa* is certainly a major driver of pneumonia severity and outcome, as well as the different phenotypes described. The capacity to form biofilms provides the bacteria with a further possibility to escape the effects of antibiotics, turning it into a superbug.

36.2.2 Prevalence: What Is the Prevalence?

The reported prevalence of CAP caused by *P. aeruginosa* is controversial, largely due to data being limited to single-center studies and because of differences in the study populations [9] (Table 36.2). Recently, a multinational point-prevalence study analyzed data from 3193 CAP patients in 222 hospitals in 54 countries [10]. The study showed a low prevalence of CAP caused by *P. aeruginosa* (4.2%), which corresponded to only 11.3% of patients with culture-positive pneumonia. The prevalences of antibiotic-resistant and MDR *P. aeruginosa* were also low (2% and 1% respectively). Interestingly, the study reported the prevalence of *P. aeruginosa* in CAP in different continents: 3.8% in Europe, 4.3% in North America, 5.2% in Asia,

Table 36.2 Incidence and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia (CAP)

Study/year	Population/Country	Prevalence of *P. aeruginosa*	Risk factors for *P. aeruginosa* CAP
Aliberti et al. 2013 [2]	Prospective study of two cohorts (Barcelona and Edinburgh) n = 1591 CAP patients	Barcelona: 6.5% (32 cases) of these 12 cases (38%) were MDR *P. aeruginosa* Edinburgh: 1.6% (9 cases) of these 3 cases (30%) were MDR *P. aeruginosa*	Nursing home; hospitalization in the previous 90 days; history of chronic lung disease
Shindo et al. 2013 [51]	Prospective study of CAP and HCAP cases from Japan n = 1431	CAP 3.7% (33 cases) HCAP 8.7% (46 cases)	
Prina et al. 2015 [50]	Prospective study of CAP from Spain n = 1597	4.5% *P. aeruginosa*	Previous antibiotic use, chronic respiratory diseases, PO_2/FiO_2 ratio <200
Cillóniz et al. 2016 [11]	Prospective study of adult patients with CAP with definitive etiology n = 2023	4% *P. aeruginosa* 1.08% MDR *P. aeruginosa*	Male sex, chronic respiratory diseases, C-reactive protein <12.35 mg/dL, PSI IV to V Prior antibiotic treatment risk factor for MDR *P. aeruginosa*
Restrepo et al. 2018 [10]	Multicenter, point-prevalence study of CAP patients (22 hospitals in 54 countries) n = 3193	4.2% of all population 11.3% of cases with defined etiology 2% antibiotic-resistant *P. aeruginosa* *1%* MDR *P. aeruginosa*	Prior pseudomonas infection/colonization, prior tracheostomy, bronchiectasis, IRVS, very severe COPD

HCAP healthcare-associated pneumonia; *IRVS* intensive respiratory or vasopressor support; *PSI* pneumonia severity index; *COPD*: chronic obstructive pulmonary disease

4.9% in South America, 5.5% in Africa and 3.1% in Oceania. The prevalence of antibiotic-resistant *P. aeruginosa* in CAP was 1.6% in Europe, 2.5% in North America, 2.2% in Asia, 3.0% in South America, and 3.9% in Africa; there were no reported cases of *P. aeruginosa* antibiotic resistance in Oceania. Finally, the prevalence of MDR *P. aeruginosa* in CAP was 0.9% in Europe, 1.2% in North America, 0.5% in Asia, 2% in South America, and 2.3% in Africa; there were no cases of MDR *P. aeruginosa* in Oceania.

Similarly, a Spanish study of clinical outcomes and risk factors for CAP caused by MDR and non-MDR *P. aeruginosa* reported a prevalence of MDR *P. aeruginosa*

of 1.1% in a prospective cohort study of 2023 culture-positive CAP patients [11]. The authors also reported that *P. aeruginosa* was an individual risk factor associated with mortality in the study population.

A study by Ferrer et al. [12] of 664 severe CAP cases requiring mechanical ventilation showed that 336 patients had a final microbiological diagnosis; *P. aeruginosa* was reported in 7% (n = 25) of cases (4% in the non-invasive mechanical ventilation group and 5% in the invasive mechanical ventilation group).

36.2.3 *P. aeruginosa* Risk Factors

Antibiotic therapy for *P. aeruginosa* is totally different from the standard antimicrobial therapy used to treat common CAP pathogens. Current recommendations provided by international guidelines stratify therapy on the basis of *Pseudomonas* risk factors [1, 13].

Risk factors for *P. aeruginosa* include structural lung disease (bronchiectasis, chronic obstructive pulmonary disease [COPD]), nursing home residence, C-reactive protein (CRP) <12.35 mg/dL, prior use of oral steroids, antibiotic therapy within the previous 90 days, and malnutrition [1, 11]. Chronic *P. aeruginosa* colonization in patients with bronchiectasis and COPD can be an important preliminary step to pneumonia. Non-cystic fibrosis bronchiectasis and COPD account for 2–55% and for 20–46% of CAP cases, respectively. These two structural lung conditions facilitate chronic colonization by *P. aeruginosa*, mainly due to failure to eradicate the bacterium during acute infections. As mentioned earlier, *P. aeruginosa* can transform from a non-mucous phenotype to a mucous phenotype which can then adapt to the lung environment and grow as a biofilm.

Interestingly, a recent case-control study [14] identified risk factors for pneumonia due to *P. aeruginosa* susceptible to all routinely tested antipseudomonal β-lactams (APBL-S) and resistant to at least one antipseudomonal β-lactam (APBL-R). The authors identified bronchiectasis, interstitial lung disease, prior airway colonization with *P. aeruginosa* and recent exposure to an antipseudomonal β-lactam as risk factors for APBL-S P. *aeruginosa* in adults with acute bacterial pneumonia.

In the last few years, cases of *P. aeruginosa* infection in previously healthy individuals have been reported; in the majority, heavy exposure to aerosols of contaminated water has been identified [15].

P. aeruginosa can establish polymicrobial interactions, mainly with *Staphylococcus aureus* and *Candida albicans* that may affect disease management. The relationship between *S. aureus* and *P. aeruginosa* is competitive in nature. The association of *C. albicans* with *P. aeruginosa* or *S. aureus* enhances disease severity in several ways. *In vivo* studies in rats have shown that pre-colonization of lung tissue by *C. albicans* increases the rate of pneumonia caused by *P. aeruginosa.* This microbial interaction should be taken into account in patients with COPD or non-cystic fibrosis bronchiectasis who are frequently colonized with *P. aeruginosa* and *S. aureus* [16].

According to a recent study, prior antibiotic treatment is a risk factor for *P. aeruginosa*, especially for MDR *P. aeruginosa* [11]. It has been demonstrated that low levels of antibiotics contribute to strain diversification in *P. aeruginosa*; sub-inhibitory and sub-therapeutic antibiotic concentrations induce alterations that effect changes in gene expression, horizontal gene transfer and mutagenesis, which can promote and spread antibiotic resistance.

Given that *P. aeruginosa* CAP has been related to poor clinical outcomes, largely because of inappropriate empiric antibiotic treatment, it is recommended to use empiric anti-pseudomonal cover in all cases of highly suspected MDR *P. aeruginosa* CAP. Risk stratification should take into account the local ecology (prevalence of the pathogen in a specific area) and the patient's risk factors, especially in cases of severe CAP that are associated with higher mortality rates (20–50%) [1].

36.3 CAP Caused by *Acinetobacter baumanii*

36.3.1 The Pathogen: How Important Is *A. baumanii* In CAP?

A. baumannii is an aerobic Gram-negative coccobacillus. In 2017, the World Health Organization (WHO) included it in the list of "Priority Pathogens", a group of bacteria that poses the greatest threat to human health and for which new antibiotics are urgently needed [17].

In recent years, isolates of *A. baumannii* have been recovered from multiple extra-hospital sources, such as vegetables, water treatment plants, fish and shrimp farms, apart from its known natural habitat (soil and humid environments). This broad source of the bacteria may explain the occurrence of community-acquired infections [18].

A. baumannii has a natural resistance to desiccation due to morphological changes that justify its viability for months. Infections caused by *A. baumannii* may be very difficult to treat due to the ability of the bacterium to evade the host immunity and to form biofilm. Furthermore, *A. baumannii* has several resistance mechanisms, including β-lactamases, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects and modifications of target sites [19] (Table 36.1).

The majority of *A. baumannii* isolates from CAP have a lower antibiotic resistance than isolates from nosocomial infections. Despite this lower rate of antibiotic resistance, severe CAP is the most frequent clinical presentation of *A. baumannii* pneumonia. Caution should be taken when choosing the empirical antibiotic therapy. Although use of a ß-lactam plus a macrolide or a fluoroquinolone is the current international guideline recommendation for severe CAP [1], these drug combinations do not completely cover *A. baumannii*, mostly because of its frequent resistance to ceftriaxone [20].

Several studies have reported isolates of MDR *A. baumannii* in community-dwelling patients and in nursing-home patients. Recently, a prospective cohort study of 651 newly admitted patients in six nursing facilities in the USA reported that 95% of patients were admitted for post-acute care; 57% of patients were

colonized with MDR pathogens at enrollment. Prolonged hospitalization (>14 days), functional disability, antibiotic use, or device use were the main risk factors for colonization at enrollment. The rate per 1000 patient-days of acquiring a new resistant Gram-negative bacillus was 13.6%. MDR colonization at discharge for resistant Gram-negative bacilli was 34% [21].

In a study from west China [22], investigating the antimicrobial susceptibility of 32 isolates of *A. baumannii* causing CAP, the authors reported that 30% of the isolates were resistant to the majority of the antibiotics; the resistant rates to imipenem and meropenem were 19% and 9%, respectively. An important finding of this study is that approximately 80% of the patients had had a previous hospital admission.

An MDR *A. baumannii* was recently isolated in a previously healthy patient with CAP from Hong Kong. The patient was treated with intravenous colistin and oral monocycline and recovered fully [23]. This case is not isolated and more and more reports of cases of CAP caused by MDR *A. baumannii* are being published.

In conclusion, although *A. baumannii* is not a frequent cause of CAP, the capacity to rapidly develop resistance mechanisms to antibiotics and the fulminant clinical presentation (with a mortality rate around 50%) make this pathogen an important health problem, especially in tropical and subtropical areas.

36.3.2 Prevalence: What Is the Prevalence?

During the last 10 years, *A. baumannii* has been described as a rare cause of CAP but with clinical relevance. The great majority of CAP cases caused by *A. baumannii* occurs in countries with tropical or sub-tropical climates. *A. baumannii* is an emerging pathogen in the regions of Asia-Pacific, with a higher prevalence in Hong Kong, Singapore, Taiwan, South Korea and Australia [24, 25].

CAP cases caused by *A. baumannii* are very rare in Europe and USA. A recent USA case report of severe CAP and review of the literature found that 19 cases of CAP caused by *A. baumannii* have been reported in the USA to date [26].

Unlike nosocomial pneumonia caused by *A. baumannii,* CAP cases caused by *A. baumannii* have a seasonal presentation, with the highest prevalence during the warm and humid months of the year [25].

36.3.3 *A. baumannii* Risk Factors

The clinical presentation of *A. baumannii* CAP is fulminant with acute onset of fever, dyspnea and rapid progression to respiratory failure and shock. *A. baumannii* CAP is associated with a mortality rate ranging from 40% to 60% especially in cases presenting with bacteremia and shock. The main risk factors related to this infection are alcoholism, diabetes mellitus and chronic lung disease [24].

It is known that alcohol abuse impacts on the innate and adaptive immune response. A study published in 2013 described the impact of alcohol on macrophage-like cell

antimicrobial functions in *A. baumannii* infections [27]. The authors demonstrated that alcohol plays an important role in inhibiting nitric oxide (NO) production which is essential to eradicate bacteria exposed to macrophages after phagocytosis. Alteration of intra- and extra-cellular NO production promotes microbial survival, facilitating intracellular replication. Furthermore, macrophages exposed to alcohol have lower production of pro-inflammatory tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-12 and increased levels of IL-6. This imbalance in the production of cytokines affects the differentiation of naïve T cells into Th1 cells because of low IL-12 production, and the production of interferon (IFN)-γ from T and natural killer (NK) cells. Moreover, it is known that low levels of TNF-α and IL-1β are associated with septic shock and the risk of bacterial infections [27].

A related study recently published by Kamoshida et al. [28] described for the first time the ability of *A. baumannii* to inhibit the formation of neutrophil extracellular traps (NETs), thus suppressing neutrophil adhesion. It is well known that the main role of NETs is to prevent microbial dissemination and to eradicate pathogens. The ability of *A. baumannii* to escape the immune response may explain the fulminant clinical presentation of CAP caused by this pathogen.

An Australian study suggested that microaspiration of pharyngeal *A. baumannii* may be responsible for CAP in alcoholic patients [29]. In this study, 10% of community residents attending the Emergency Department in the wet-season (March–April) with non-respiratory diseases, no episode of previous hospitalization and a history of alcohol abuse (alcohol intake >6 standard drinks/day) had *A. baumannii* in their throat [29].

The susceptibility to pneumonia in patients with diabetes can be ascribed to several factors. Patients with diabetes have an increased risk of hyperglycemia (which reduces the mobilization of polymorphonuclear leukocytes, chemotaxis and phagocytic activity), increased risk of aspiration, impaired immunological defenses, and deterioration in lung function and chronic complications, such as neuropathy [30].

Patients with underlying chronic lung disease, such as COPD or bronchiectasis, also show reduced innate defense mechanisms. Generally, these patients are smokers, passive smokers or ex-smokers and the frequent use of inhaled corticosteroids make them more vulnerable to infections such as pneumonia [10, 11, 27].

In conclusion, because of its possible fulminating course, CAP caused by *A. baumannii* should be suspected in patients with specific risk factors and a severe presentation of pneumonia. Early recognition and prompt initiation of broad empirical antibiotic coverage are mandatory to limit the high mortality related to this infection.

36.4 CAP Caused by *Klebsiella pneumoniae*

36.4.1 The Pathogen: What Is So Special About *K. pneumoniae* in CAP?

K. pneumoniae is a Gram-negative capsulate bacterium responsible for severe pneumonia especially in immunocompromised patients. In the last two decades, there

has been an increase in antibiotic resistance in *K. pneumoniae* isolates globally. The emergency of MDR and hypervirulent *K. pneumoniae* strains has been reported in immunocompromised patients and in healthy persons [31].

The main mechanisms of antibiotic resistance in *K. pneumoniae* are the expression of extended spectrum β-lactamases (ESBLs), which confers resistance against penicillins, cephalosprins and monobactams, and the expression of carbapenemases, which confers resistance against all β-lactams including carbapenems (Table 36.1).

Interestingly, hypervirulent *K. pneumoniae* strains produce a hypercapsule, also known as being hypermucoviscous. The capsule, a polysaccharide matrix that coats the cell, is necessary for *K. pneumoniae* virulence and is arguably the most thoroughly studied virulence factor of *K. pneumoniae* [31]. Although antimicrobial resistance in hypervirulent *K. pneumoniae* is generally lower than in non-hypervirulent *K. pneumoniae* strains, cases with more resistant strains of hypervirulent *K. pneumoniae* have recently been reported [32].

K. pneumoniae has the ability to avoid phagocytosis. A recent experimental study found that the capsule is dispensable for intracellular *Klebsiella* survival if bacteria are not opsonized. *K. pneumoniae* survives the killing by macrophages by manipulating phagosome maturation, which may contribute to *Klebsiella* pathogenesis [33].

In conclusion, CAP caused by MDR and hypervirulent *K. pneumoniae* represents a great challenge in terms of treatment and management, especially in Asian countries, where the majority of cases are reported.

36.4.2 Prevalence: What Is the Prevalence?

A recent 5-year study in a French ICU [34] described 59 infections caused by *K. pneumoniae*; 26 (44%) of them were community-onset infections. Interestingly, the authors reported 12 hypervirulent *K. pneumoniae* strains in the group of community-onset infections, 6 (50%) of which were isolated from patients with CAP. The authors observed that hypervirulent *K. pneumoniae* cases had higher rates of organ failure compared with non-hypervirulent cases. However, mortality rates were similar in the two groups.

In a study performed in Cambodia [35], 2315 patients with acute lower respiratory infections were enrolled, including 587 (25%) whose bacterial etiology could be assigned. *K. pneumoniae* was identified in 8% (n = 47) of the microbiologically-confirmed cases. ESBL-producing strains were found in 8 (17%) patients. The main risk factors related to *K. pneumoniae* infection were female sex and diabetes mellitus. The overall mortality rate due to *K. pneumoniae* infection was 38%.

Approximately 1–7% of cases of CAP are caused by *K. pneumoniae*, with 5–36% of these being MDR strains [2, 36]. Interestingly, in Asian countries (Taiwan, Cambodia, Shanghai) *K. pneumoniae* is described as a frequent pathogen causing bacteremia [37, 38]. Although reports of cases from Europe and USA are generally rare, an increasing incidence from these regions has been registered in recent years [34, 39].

36.4.3 *K. pneumoniae* Risk Factors

The recognized risk factors for K. pneumoniae CAP are female sex, diabetes mellitus and alcoholism. MDR *K. pneumoniae* can be recognized as a virulent pathogen causing severe CAP, frequently associated with septic shock, respiratory failure and bacteremia. Morbidity and mortality rates are high especially in Asian countries were the pathogen is reported in younger patients with no chronic conditions. This pattern may be explained by the virulence of the strains (especially hypervirulent *K. pneumoniae*) and the high rate of antibiotic consumption in these regions [35, 40].

36.5 CAP Caused by *Stenotrophomonas maltophilia*

36.5.1 The Pathogen: What Is So Special About *S. maltophilia* in CAP?

S. maltophilia is a motile, aerobic, non-fermentative Gram-negative bacillus with the ability to survive on any humid surface, form biofilm and colonize humid surfaces. It is an emerging opportunistic pathogen with multidrug resistance, which particularly affects immunocompromised patients (i.e., with malignances, post-organ transplantation) worldwide [41, 42].

S. maltophilia is intrinsically resistant to carbapenems and frequently carries genetic elements that provide resistance to other β-lactams, fluoroquinolones, aminoglycosides and tetracyclines. *S. maltophilia* has the ability to acquire genes involved in antibiotic resistance from other bacterial species. The most relevant mechanisms of antibiotic resistance include β-lactamase (L1 and L2) production, multidrug efflux pumps (which confer resistance to macrolides, quinolones, aminoglucosydes, polymyxins), antibiotic-modifying enzymes, mutations of bacterial topoisomerase and gyrase genes and reduction in outer membrane permeability [42] (Table 36.1).

Although *S. maltophilia* has been reported in patients with cystic fibrosis, it can affect healthy individuals through contaminated wounds or infected catheters [43, 44]. Transmission of *S. maltophilia* may occur through direct contact with contaminated source such as contaminated water or medical devices [42].

In conclusion, CAP caused by *S. maltophilia* is associated with high mortality rates. Hemorrhagic pneumonia is one of the most severe forms of *S. maltophilia* infection [45]. It is associated with poor outcome despite appropriate antibiotic therapy.

36.5.2 Prevalence: What Is the Prevalence?

There is limited information on the worldwide prevalence of community-acquired *S. maltophilia* pneumonia. The majority of data comes from case reports [46]. *S. maltophilia* has been reported as an important cause of CAP in patients with hematologic diseases, with a prevalence of bacteremia ranging between 2% and 7%. The mortality rate is approximately 35% (ranging between 30% and 40%) in this special population.

36.5.3 *S. maltophilia* Risk Factors

The majority of patients affected by this pathogen have previous chronic comorbidities, such as COPD, cystic fibrosis, malignancy (especially hematologic diseases), human immunodeficiency virus (HIV)-infection (acquired immunodeficiency syndrome [AIDS]) or other immunodeficiencies. Patients with prior antimicrobial therapy, prolonged hospitalization, indwelling catheters, mechanically ventilated and receiving corticosteroids have an increased risk of *S. maltophilia* CAP [42, 46].

36.6 Diagnosis: Is It Possible to Predict Gram-Negative MDR Pathogens in CAP?

The reference microbiological diagnostic tools for bacteria causing respiratory tract infections remain the Gram stain and semi-quantitative conventional cultures from direct respiratory samples. Bacterial identification is currently based on matrix-assisted latex laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and susceptibility testing. As a consequence of the time needed for microbiological diagnosis, many patients initially receive inappropriate antibiotic treatment, which may increase morbidity and mortality.

Molecular techniques based on multiplex PCR have also been developed in recent years in order to simultaneously identify and quantify multiple respiratory pathogens from different types of samples in a single procedure [47]. However, the main challenge for the rapid diagnosis of respiratory infections is the early detection of the antibiotic resistance profile of the various bacteria. The biggest obstacle in the use of molecular techniques for detecting resistance is the discrepancy between genotype and phenotype, the continuous discovery of new resistance mechanisms and, as a result, the potential presence of unknown mechanisms, which may lead to false negative results using molecular techniques [47].

Recognizing patients at risk of colonization with MDR Gram-negative bacteria, such as patients with bronchiectasis or COPD (frequently colonized by *P. aeruginosa*), is essential, since several studies have reported the association between previous colonization and risk of pneumonia [48, 49].

Currently, there is no specific score to predict MDR Gram-negative pathogens in CAP. However, several scoring systems have been proposed to identify patients with risk factors for developing CAP caused by MDR pathogens. The Aliberti score [2] takes into account different variables and gives a specific score to each of them: chronic renal failure (5 points), prior hospitalization (4 points), nursing home residence (3 points) and other variables (0.5 points each). CAP patients with an Aliberti score ≥3 points have a reported prevalence of MDR of 38%, whereas CAP patients with an Aliberti score of ≤0.5 have a reported prevalence of MDR of 8%. The PES (*P. aeruginosa*, Enterobacteriaceae ESBL-positive, methicillin-resistant *S. aureus* [MRSA]) score includes 1 point each for age 40–65 years and male sex; 2 points each for age >65 years, previous antibiotic use, chronic respiratory disorder, and impaired consciousness; 3 points for

chronic renal failure; and minus 1 point if fever is present initially. The risk of MDR pathogens is higher with 5 points or more [50]. Unfortunately, studies validating the Aliberti and PES score do not include immunocompromised patients. The ability of these scores to identify risk factors for CAP by MDR pathogens in this population is still unclear.

An important study by Shindo et al. [51] investigated the main risk factors for MDR pathogens in 1413 patients with CAP. Six risk factors were identified: prior hospitalization, immunosuppression, previous antibiotic use, use of gastric acid-suppressive agents, tube feeding and non-ambulatory status. Unlike the Aliberti and PES studies, Shindo's study included immunocompromised patients. Interestingly, the authors analyzed risk factors for Gram-positive (MRSA) and Gram-negative pathogens separately. The authors observed that the risk of MDR Gram-negative pathogens did not increase in the presence of ≥3 risk factors; conversely, for Gram-positive (MRSA) pathogens, the risk increased in the presence of ≥2 risk factors, especially if one of the risk factors was specific for MRSA, such as previous colonization or previous hospitalization.

36.7 Therapy: How is it Possible to Treat These Pathogens?

Since antibiotic treatment for *P. aeruginosa* is completely different from standard therapy to cover the most common pathogens in CAP, current international guidelines for severe CAP stratify therapy recommendations on the basis of *P. aeruginosa* risk factors [1]. MDR *P. aeruginosa* should be covered only in cases that are strongly suspected because of concurrent risk factors. It is important to underline that prior antibiotic therapy has been reported as the only risk factor for MDR *P. aeruginosa* in CAP patients [11].

Empirical antibiotic treatment based on the evaluation of the patient's risk factors is also of pivotal importance in the management of *A. baumannii* CAP.

Because CAP caused by *A. baumannii* has a fulminant clinical presentation with a high mortality rate (approximately 50%), greater attention should be paid in elderly patients with multi-comorbidities, and patients with alcohol abuse, chronic lung disease and prior antibiotic therapy, especially in Asian countries where this pathogen is frequently reported. Early appropriate antimicrobial therapy is critical. Recommended empirical antibiotic therapy for *A. baumannii* CAP includes anti-pseudomonal penicillins, aminoglycoside, ciprofloxacin, and imipenem. Tigecycline, colistin, ceftazidime, doxycycline, minocycline, piperacillin/tazobactam, tobramycin, rifampin, fosfomycin and levofloxacin are active against variable percentages of strains. The treatment should include an association of two or more of these antibiotics according to the antibiogram of the isolated pathogen. Moreover some countries, notably Asia [52] and Australia [53], have implemented specific antibiotic recommendations in cases of severe CAP in order to cover pathogens such as *A. baumannii*.

In CAP caused by *K. pneumoniae*, depending on the clinical severity and the risk of infection by a strain with resistance mechanisms (production of ESBLs,

cefaminases or carbapenemases), a 3rd generation cephalosporin (cefotaxime or ceftriaxone) or a fluoroquinolone (ciprofloxacin or levofloxacin) should be used. Another possibility, in case of infection by carbapenemase-producing or carbapenem-resistant strains (due to loss of porin and hyperproduction of Amp-C), is the use of associations of two or three of the following antibiotics: colistin, tigecycline, fosfomycin (if the strain is sensitive), an aminoglycoside (amikacin or gentamicin) and meropenem (if the minimum inhibitory concentration [MIC] = 16 mg/L), administered in high doses and by continuous perfusion. Hypervirulent strains (serotypes K1 and K2) are usually more sensitive to antibiotics, but production of *K. pneumoniae*-type carbapenemase has also been observed.

For the antibiotic treatment of *S. maltophilia* pneumonia, trimethoprim-sulfamethoxazole (TMP-SMX) is still considered the drug of choice despite increasing resistance. It is preferably used in association with another antibiotic depending on the severity of the pneumonia and the sensitivity of the pathogen. Other alternative antibiotics include β-lactams (i.e., ceftazidime), fluoroquinolones (i.e., levofloxacin, moxifloxacin), minocycline or tigecycline. *In vitro*, the following associations are often synergistic: cotrimoxazole with colistin, tigecycline, ceftazidime and rifampicin; colistin with tigecycline, ceftazidime and rifampin; ceftazidime with levofloxacin, moxifloxacin and aztreonam.

Figure 36.1 proposes an algorithm for the empiric antibiotic therapy of CAP in patients with risks factors for MDR pathogens.

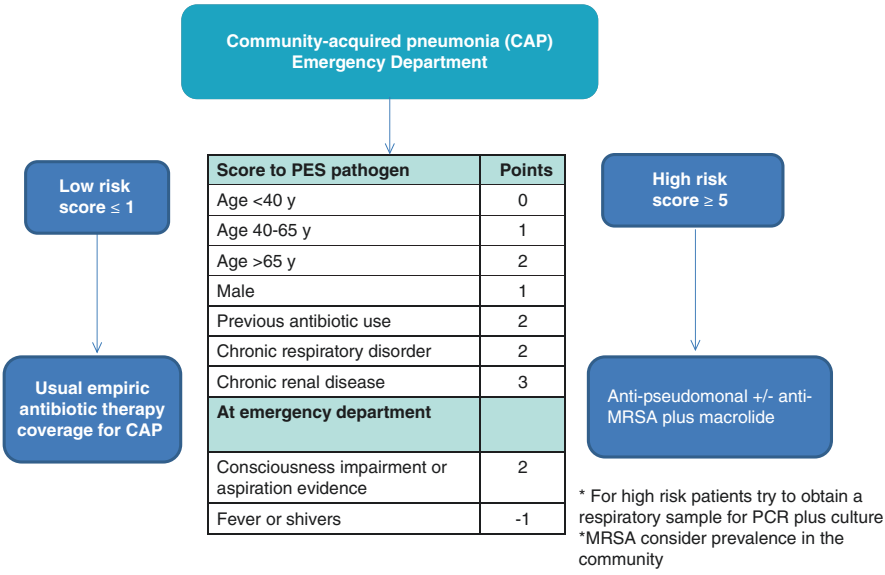

Fig. 36.1 Proposed algorithm for empiric antibiotic therapy in community-acquired pneumonia for patients with risk of multidrug resistant (MDR) pathogens using the PES (*Pseudomonas aeruginosa*, Enterobacteriaceae extended-spectrum β-lactamase-positive, methicillin-resistant *Staphylococcus aureus* [MRSA]) score from [50]. *PCR* polymerase chain reaction

36.8 Conclusion

Correct identification of CAP patients suspected of being infected with MDR Gram-negative pathogens is crucial. Specific risk factors, local ecology and resistance patterns should always be considered in order to determine the adequate empirical antibiotic therapy. Early hemodynamic and respiratory support is critical in these patients since the majority of cases of pneumonia may become fulminant systemic disease with both respiratory failure and multiple organ dysfunction.

The collaboration of a multidisciplinary team (critical care specialists, pneumologist, infectious disease specialists, microbiologists) improves management of the most severe cases. The role of the microbiology laboratory, in particular, is of pivotal importance to determine the antimicrobial susceptibility pattern of the pathogen causing CAP, so that appropriate antibiotic therapy can be initiated as soon as possible, avoiding excessive use of broad spectrum antimicrobials, which increase the selection of resistant pathogens.

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