Risk of Multi-Drug Resistant Pathogens in Severe Community-Acquired Pneumonia

E. Campaña-Duel[1,2], M. Camprubi-Rimblas[1,2], A. Areny-Balaguero[1,2], Sara Quero[1,2], A. Artigas[1,2], A. Ceccato[1,2,3]

1. Critical care center, Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA). Universitat Autònoma de Barcelona. Sabadell, Spain.

2. CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III, Madrid, Spain.

3. Intensive care unit, Hospital Universitari Sagrat Cor, Grupo Quironsalud, Barcelona, Spain.

Corresponding author

Adrian Ceccato

Institut d'Investigació i Innovació Parc Taulí I3PT

Plaça Torre de l'Aigua, s/n, 08208 Sabadell

aaceccato@tauli.cat

ABSTRACT

Severe community-acquired pneumonia (SCAP) is difficult to treat when caused by difficult-to-treat (DTR) pathogens because of limited treatment options and poorer clinical outcomes. Over time, several predictive scoring systems based on risk factors for infection with multi-drug resistant (MDR) pathogens have been developed. We reviewed the available tools for identifying DTR pathogens as the cause of SCAP, both predictive scoring systems and rapid diagnostic methods, to develop management strategies aimed at early identification of DTR pathogens, reducing broad-spectrum antibiotic use and improving clinical outcomes.

The scoring systems reviewed show considerable heterogeneity among them at the level of the region studied, the definition of risk factors, as well as which DTR pathogens are the target pathogens. The models described have shown limited effectiveness in reducing inappropriate antibiotic treatment or improving patient outcomes by themselves. However, predictive models could serve as a first step in identifying DTR pathogen infections as part of a larger detection algorithm.

Rapid diagnostic tools, such as multiplex polymerase chain reaction (PCR), would be useful for rapid identification of pneumonia-causing pathogens and their resistance mechanisms. In resource-limited settings, rapid tests should be limited to patients at high risk of developing SCAP due to DTR pathogens. We propose an integrative algorithm based on the different scores, taking into account local epidemiological data, where ideally each center should have an antimicrobial stewardship program.

KEYWORDS: community-acquired pneumonia; risk factors; difficult-to-treat pathogens; multidrug-resistant pathogens; antibiotic therapy; infection; pneumonia management

INTRODUCTION

Severe community-acquired pneumonia (SCAP) is a major concern worldwide as it is a leading cause of morbidity and mortality [1]. The increasing incidence of difficult-to-treat (DTR) pathogens has further complicated the management of this disease. DTR pathogens limit available treatment options and lead to poorer clinical outcomes.

The Global Burden of Disease estimated that 4.95 million deaths were associated with multi-drug resistant (MDR) pathogens in 2019, although the incidence of MDR varies according to region, the prevalence of the different pathogens in these regions, and healthcare settings [2].

The etiology of SCAP has evolved since the dawn of the antibiotic era, with viruses being one of the major causative agents [3]. *Streptococcus pneumoniae* is the most common cause of bacterial SCAP [4]. However, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Legionella pneumophila*, and enteric gram-negative bacteria may also cause SCAP in varying proportions [5].

Patients with SCAP receive empirical treatment covering the most frequent microorganisms. Guidelines suggest that patients with SCAP should receive third-generation cephalosporins, ceftaroline, or aminopenicillins plus a β-lactamase inhibitor plus a macrolide or fluoroquinolone. Over time, MDR microorganisms not covered by these antimicrobials such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, and extended-spectrum β-lactamase (ESBL)-producing or carbapenems-resistant Enterobacterales and *Acinetobacter baumannii*, have emerged as causative agents of community-acquired pneumonia (CAP). Inappropriate antimicrobial treatment has been shown to lead to poor clinical outcomes [6], and overuse of antibiotics targeting DTR pathogens promotes drug resistance and may worsen clinical outcomes, probably because of higher toxicity [7,8].

The prevalence of MDR pathogens varies worldwide. In an international transversal study analyzing the prevalence of these pathogens, MRSA prevalence was 3% [1,9], *P. aeruginosa* prevalence was 4.2% [10], and MDR *Enterobacteriaceae* 1.2% [11]. *Staphylococcus aureus* was isolated in 1.6% in the USA, MRSA only in 1% [12]. In most epidemiological studies, the prevalence of MDR pathogens is < 10% [3,5].

This review aims to revise the available tools to identify MDR pathogens as a cause of SCAP.

RISK FACTORS FOR MDR PATHOGEN INFECTION

Risk factors for infection by MDR pathogens in SCAP are those related to the healthcare setting, treatments administered to the patient, and the immunity and pathology of the host. The main risk factors for MDR pathogens are summarized in Table 1.

Prior exposure to healthcare settings, such as hospitalization or chronic hemodialysis, are risk factors that facilitate the acquisition of microorganisms [13,14]. Prior exposure time is important because gram-negative MDR bacteria persist for several months compared to MRSA.

Pathogen colonization is mostly determined by factors such as patient immunosuppression due to treatments such as corticosteroids and previous antibiotic use [13–15], which exert selective pressure on the oropharynx and lung microbiome, favoring the persistence of MDR pathogens.

In contrast, both host immunity and pathology often play critical roles in the invasion of the lower respiratory tract. Guidelines identify that the strongest individual risk factor is previous colonization with MDR pathogens, such as MRSA or *P. aeruginosa*, especially from the respiratory tract [13,16]. The upper and lower respiratory tract or gut may be colonized by

MDR pathogens. MRSA is usually detected in nares, ESBL-producing *Enterobacteriaceae* in the gut, and *P. aeruginosa* in the lower respiratory tract or gut. If an MDR pathogen colonizes a patient, an attempt must be made to eradicate it. However, this is not always the case.

The detection of colonized patients by screening tests could be useful in identifying patients with infections caused by these pathogens. The most common method is the detection of MRSA in nares using conventional culture or polymerase chain reaction (PCR). In a meta-analysis, the detection of nasal MRSA showed a sensitivity of 85% and a specificity of 92%. This result highlights a very high negative predictive value of 98% [17]. Despite the availability of rapid PCR tests to detect MRSA, the detection of ESBL-producing *Enterobacteriaceae* and *P. aeruginosa* may be delayed, similar to that in other conventional cultures.

These risk factors must be validated at the local level and it must be verified that there are no other risk factors specific to the area. The Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) 2019 guidelines recommend covering MRSA and *P. aeruginosa* causing SCAP with empiric treatment only if the risk factors have been locally validated for these pathogens [18].

In 2005, the IDSA/ATS guidelines introduced a new concept for healthcare-associated pneumonia (HCAP)[19]. These guidelines suggested treatment with broad-spectrum antimicrobials for patients with a risk factor for MDR infection. This led to the overuse of antimicrobials and an increase in antibiotic resistance, which proved useless in terms of mortality or other clinical outcomes [20,21]. This concept has been discouraged in the latest clinical guidelines [18,22].

PREDICTIVE SCORING SYSTEMS

Various predictive scoring systems have been developed based on the risk factors mentioned above to calculate the probability of a patient being infected with an MDR pathogen (Table 2). However, different risk factors do not always have the same weight. Therefore, in some predictive systems, different scores are obtained depending on the impact of the risk factors.

Shorr et al. developed a scoring system [23] based on HCAP criteria that showed an association with resistant pathogen pneumonia through logistic regression: recent hospitalization within the last 90 days (4 points), residence in a nursing home or long-term care facility (3 points), long-term treatment with hemodialysis (2 points), or underlying immunosuppression (1 point). In a cohort of 639 patients with pneumonia, 45.2% were infected with MDR pathogens. Patients with resistant infections were more likely to meet HCAP criteria. Nevertheless, the scoring system helped to stratify the population into low-, intermediate-, and high-risk groups. Patients with MDR infection comprised less than 20% of the total number of patients with a score of 3. In contrast, 75% of the patients scored more than six points on the scoring system. This study was validated in 977 patients with pneumonia, and it was shown that there was a correlation between high scores and infection by resistant pathogens [24].

Aliberti et al. also formulated a system based on risk factors with different weights [9]: chronic renal failure (5 points), hospitalization for more than 2 days in 90 days (4 points), and residence in a nursing home (3 points). Minor risk factors (diabetes, antimicrobial therapy, home wound healing, etc.) were scored with 0.5 points. Among the 935 patients with CAP, 40% were infected by an MDR pathogen and had a score of between 3 and 12.5 provided by the scoring system. This study was compared and validated using the Shorr method in a European population [25]. These two scoring systems displayed a higher area under the ROC

curve than the HCAP classification in predicting pneumonia caused by MDR in intensive care unit patients.

Shindo et al. studied patients with pneumonia at ten institutions in Japan and developed a risk score[26]. Although MDR pathogens were detected more frequently in patients with HCAP (26.6%) than in those with CAP (8.6%), the risk factors for MDR pathogen infection were shared between HCAP and CAP. The system of Shindo et al. is an unweighted scoring system that considers risk factors such as prior hospitalization, immunosuppression, previous antibiotic treatment, gastric-acid suppression, tube feeding, and non-ambulatory status.

Self et al. performed an external validation of six different algorithms: HCAP, Summit, Brito and Niederman, Shorr, Aliberti, and Shindo [27]. Among 614 patients with CAP, all algorithms performed suboptimal classification into low- or high-risk groups for resistant bacteria compared to the HCAP criteria.

Falcone et al. developed the ARUC score [21], which was based on PaO2/FiO2 (<300) (1.5 points), HCAP criteria (1 point), pleural effusion, and bilateral pulmonary infiltration (0.5 points). In total, 900 patients with community-onset pneumonia were included in this study. It was observed that patients showing an ARUC of ≥ 3 points comprised 41% of patients infected with MDR pathogens, while those with an ARUC of <0.5 points comprised only 3%. The ARUC score had a major negative predictive value (97%) among the Shindo (91%), Aliberti (92%), and Shorr (94%) scores. The score was validated in an external cohort in Spain that included 929 patients.

The PES score is based on the identification of *P. aeruginosa*, β-lactamase-positive Enterobacterales, and MRSA in patients with CAP [28]. The risk factors taken into account are: fever (-1 point); male sex (1 point); previous antibiotic use, chronic respiratory disorder, consciousness impairment (2 points); age (0-2 points); chronic renal disease (3 points). This

study was conducted in 1597 patients with CAP, in whom PES pathogens were identified in a small proportion of patients (6%), with high mortality. Among the patients who scored high risk for PES pathogens, 70% were infected with resistant pathogens. This score was validated in a Valencia cohort of patients with CAP and a Mataró cohort of patients with SCAP [29]. Although the PES score is accurate in detecting PES pathogens, it can lead to over- or under-treatment. Therefore, the authors propose that, owing to its high negative predictive value (96%), it could be used as the first step in a broader strategy. The PES score might be a useful algorithm for identifying patients with CAP who require different empirical antibiotic treatments. Falcone et al [30] proposed an algorithm based on PES score, epidemiological data, and clinical evaluation. This system considers the initiation of broad-spectrum antibiotic treatment in patients with a score of < 5 points, and in those with ≥ 5 points, it is advised that local epidemiology should be considered.

The DRIP score was developed in a study including 200 pneumonia patients [31]. Logistic regression was used to detect risk factors associated with pneumonia caused by MDR pathogens, and a new predictive scoring system was developed: the drug resistance in pneumonia (DRIP) score. The risk factors were classified into major risk factors scoring 2 points each (prior antibiotic use, long-term care residence, tube feeding, prior infection with MDR pathogens) and minor risk factors scoring 1 point each (prior hospitalization, chronic pulmonary disease, poor functional status, gastric acid suppression, wound care, and previous MRSA colonization). Applying the DRIP score resulted in a 46% reduction in the inappropriate prescription of broad-spectrum antibiotics compared with the use of HCAP. This algorithm was validated in an independent cohort study [31]. The electronic pneumonia clinical decision support tool (ePNa) is based on the DRIP score that guides risk stratification, diagnosis, and treatment of pneumonia. After the implementation of ePNa, the 30-day all-cause mortality showed a 38% relative reduction. Moreover, accurate antibiotic therapy was increased and

administered sooner. Nevertheless, this system could have dictated the prescription of broad-spectrum antibiotics to patients at risk of infection by resistant pathogens [32].

Despite efforts to develop a predictive model, none of the described models has demonstrated efficacy in reducing inappropriate antibiotic treatment or improving patient outcomes, outside of ePNA, which was applied only in the setting where was developed.

The various models differ from each other in terms of population, and the systems should be validated in populations distinct from those in which the model has been described. In addition, each system defines the term "MDR pathogen" differently, as well as describes risk factors. Some algorithms do not include carbapenem-resistant Enterobacterales or *A. baumannii* as they have recently emerged as pathogens causing CAP. Others, such as the PES score, narrow the spectrum of the causative pathogens. Some studies have attempted to separate MRSA [26,33], but many risk factors for MRSA infection overlap with those of other MDR pathogens [34]. Regarding the severity of pneumonia, some scores, such as DRIP or PES, do not directly consider it, while scores such as Falcone's do. However, some criteria for the Falcone system require analysis or imaging methods, which does not allow it to be a fast system. In addition, the score must be corroborated by the sample cultures, which sometimes cannot be obtained.

The IDSA/ATS guidelines recommend considering both the prevalence of different pathogens in different regions and local validation of risk factors [18]. The best scoring system should be based on risk factors specifically associated with MDR pathogens, reproducible in any region, even with different prevalence of MDR pathogens causing pneumonia, and easy to apply at the clinical level to make the selection of the initial empirical treatment effective.

One approach to integrating such systems into the clinic is the creation of automated systems based on scores integrated into electronic tools (e.g. ePNa) or artificial intelligence that incorporates predictive systems that support clinical decision-making; however, it should be combined with clinical judgment.

RAPID DIAGNOSTIC TOOLS

Conventional cultures do not always identify the causative organisms, and standard methods achieve a maximum of 50% etiological diagnoses [35]. These methods are based on Gram staining and sample culture followed by Maldi-TOF (Matrix-Assisted Laser Desorption/Ionization – Time-Of-Flight) mass spectrometry, which usually takes 24-48 hours and has low sensitivity, particularly when performed after antibiotic treatment. Difficulties in obtaining high-quality specimens and in the use of prior antibiotics are common in patients with pneumonia. The presence of non-cultivable pathogens, the need for special media, and obtaining results two or three days after starting antibiotics have led to the need for rapid diagnostic tools that are different from traditional culture methods.

Multiplex PCR platforms can also identify multiple pathogens, including viruses, bacteria, and fungi in respiratory and blood samples. The advantages of these methods are that they can detect genetic material in low proportions and can be used in patients receiving antimicrobial treatment. Most importantly, they were able to identify the presence of genes for different resistance mechanisms. Some PCR panels, such as the Unyvero or the Species-Specific Bacterial Detector (SSBD), have been reported to take 4-5h to obtain results [36]. These advantages allowed us to escalate or de-escalate antimicrobial treatment within hours of sample collection.

In a clinical trial, 208 patients were randomized to a strategy based on multiplex PCR or conventional culture results. Patients enrolled in the PCR group had a significantly shorter duration of inappropriate antimicrobial treatment and a higher rate of prompt antibiotic change[37].

In a retrospective study, Monard et al, found that in 83% of the samples, the multiplex PCR gives an etiologic result and allows its modification in 77% of the cases[38]. Some studies,

such as that of Buchan [39], determined that PCR panels, such as the FilmArray Pneumonia panel (BioFire Diagnostics, United States), are not a replacement for conventional methods and that they have to be combined with other supports and interpreted with proper judgment. The MULTI-CAP trial (NCT03452826) aimed to combine a multiplex PCR panel with procalcitonin analysis to reduce exposure to inadequate treatment in SCAP [40].

The European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Latin American Thoracic Association (ALAT) in their last guideline about severe CAP recommend the use of multiplex PCR for etiological diagnosis of CAP [41].

Next-generation sequencing of metagenomes enables the broad identification of pathogens; however, the utility of this approach is still unknown. The possibility of contamination and the inability to differentiate colonization from infection limits its clinical applicability [42].

CLINICAL MANAGEMENT

Nonetheless, the predictive models described could serve as a first step in discarding MDR pathogen infections as part of a major algorithm to detect which resistant pathogens cause pneumonia.

We proposed an integrative algorithm (Figure 1) in which each center has local epidemiological data and knows the best score to identify patients at risk of developing infections by MDR pathogens. We propose that each center should have an antimicrobial stewardship program. If a patient does not have a risk factor for MDR pathogens, they should be treated according to the latest guidelines [18,41], with a β-lactam plus macrolide or fluoroquinolone. Adherence to guideline recommendations improves the short- and long-term outcomes [43]. If one or more risk factors are present, we suggest calculating a score (the best for each local epidemiology); if the

result is low risk, we suggest against adding broad-spectrum antimicrobials given the high negative predictive value of the scores. If a moderate or high risk is the result of the calculated score, we suggest administering the first dose of broad-spectrum antimicrobials, using a rapid diagnostic test (if available), and adjusting treatment based on the results. If rapid diagnostic tests are not available, broad-spectrum antimicrobials should be administered and reassessed based on the results of conventional culture.

In recent years, several antibiotics have been introduced for the treatment of SCAP [44]. Some of them could be used to treat DTR pathogens such as MRSA, P aeruginosa or β-lactamase positive enterobacteria (including carbapenemase). Among these new antibiotics tested in pneumonia, ceftaroline, a cephalosporin with activity against MRSA, S pneumoniae and similar activity as 3º generation cephalosporin against gram-negative bacilli, has been tested in several clinical trials[45–47] and was recommended as an alternative to treat SCAP in the latest ATS/IDSA guidelines[48]. It is worth noting that ceftaroline showed superiority compared to ceftriaxone to treat CAP, but this study did not include patients with severe disease[45]. Ceftobiprole another cephalosporin that covers MRSA showed non-inferiority compared to ceftriaxone with or without linezolid in patients with CAP[49]. Delafloxacin a novel fluoroquinolone has proven efficacy in patients with CAP compared with moxifloxacin[50]. Delafloxacin covered MRSA and some gram-negative DTR bacilli[51]

Other new antibiotics include β-lactam plus new β-lactamase inhibitors or new β-lactam with coverage of ESBL-producing gram-negative bacilli, *P. aeruginosa* or non-fermenting gram-negative bacilli are available, however, it is less likely that broad-spectrum antibiotics can be used as empirical treatments and should be reserved for those patients at risk of DTR as we suggested above. According to the prevalence of DTR, each hospital should decide on its

empirical treatment, covering the most common pathogens and according to the efficacy/effectiveness and safety profile of the available antibiotics.

CONCLUSIONS

The increasing prevalence of MDR pathogens causing pneumonia is a global concern. Although these rates are not high enough to change empirical treatments, epidemiologic surveillance is needed to implement changes. Identification of risk factors for having an MDR pathogen could help to change antimicrobial treatments in these high-risk patients or implement algorithms for rapid diagnostic tests. Inappropriate antimicrobial treatment and/or overuse of broad-spectrum antibiotics may affect outcomes; therefore, the correct identification of at-risk patients is mandatory. A multistep integrated algorithm appears to be the best approach because the use of risk factors or scores is not sufficiently accurate.

REFERENCES

1. Aliberti S, Dela Cruz CS, Amati F, Sotgiu G, Restrepo MI. Community-acquired pneumonia. *Lancet*. 2021;398(10303):906-919. doi:10.1016/S0140-6736(21)00630-9

2. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0

3. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med*. 2015;372(9):835-845. doi:10.1056/NEJMOA1405870

4. Ferrer M, Travierso C, Cilloniz C, et al. Severe community-acquired pneumonia: Characteristics and prognostic factors in ventilated and non-ventilated patients. *PLoS One*. 2018;13(1):e0191721. doi:10.1371/JOURNAL.PONE.0191721

5. Cillóniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. *Thorax*. 2011;66(4):340-346. doi:10.1136/THX.2010.143982

6. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med*. 2009;169(16):1525-1531. doi:10.1001/ARCHINTERNMED.2009.259

7. Webb BJ, Sorensen J, Jephson A, Mecham I, Dean NC. Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia: a cohort study. *Eur Respir J*. 2019;54(1). doi:10.1183/13993003.00057-2019

8. Jones BE, Ying J, Stevens V, et al. Empirical Anti-MRSA vs Standard Antibiotic Therapy and Risk of 30-Day Mortality in Patients Hospitalized for Pneumonia. *JAMA Intern Med*. 2020;180(4):552-560. doi:10.1001/JAMAINTERNMED.2019.7495

9. Aliberti S, Pasquale M Di, Zanaboni AM, et al. Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia. Clin Infect Dis. 2012;54(4):470-478. doi:10.1093/cid/cir840

10. Restrepo MI, Babu BL, Reyes LF, et al. Burden and risk factors for Pseudomonas aeruginosa community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur Respir J*. 2018;52(2). doi:10.1183/13993003.01190-2017

11. Villafuerte D, Aliberti S, Soni NJ, et al. Prevalence and risk factors for Enterobacteriaceae in patients hospitalized with community-acquired pneumonia. *Respirology*. 2020;25(5):543-551. doi:10.1111/RESP.13663

12. Self WH, Wunderink RG, Williams DJ, et al. Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. *Clin Infect Dis*. 2016;63(3):300-309. doi:10.1093/CID/CIW300

13. Gross AE, Van Schooneveld TC, Olsen KM, et al. Epidemiology and Predictors of Multidrug-Resistant Community-Acquired and Health Care-Associated Pneumonia. *Antimicrob Agents Chemother*. 2014;58(9):5262-5268. doi:10.1128/AAC.02582-14

14. Ma HM, Ip M, Woo J, et al. Risk factors for drug-resistant bacterial pneumonia in older patients hospitalized with pneumonia in a Chinese population. QJM, 2013;106(9):823-829. doi:10.1093/qjmed/hct152

15. Metersky ML, Frei CR, Mortensen EM. Predictors of Pseudomonas and methicillin-resistant Staphylococcus aureus in hospitalized patients with healthcare-associated

pneumonia. *Respirology*. 2016;21(1):157-163. doi:10.1111/RESP.12651

16. Shorr AF, Myers DE, Huang DB, Nathanson BH, Emons MF, Kollef MH. A risk score for identifying methicillin-resistant Staphylococcus aureus in patients presenting to the hospital with pneumonia. *BMC Infect Dis*. 2013;13(1):1-7. doi:10.1186/1471-2334-13-268

17. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The Clinical Utility of Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications. *Clin Infect Dis MRSA Nasal Screen Meta-analysis • CID*. 2018(1):67. doi:10.1093/cid/ciy024

18. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):E45-E67. doi:10.1164/RCCM.201908-1581ST

19. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416. doi:10.1164/RCCM.200405-644ST

20. Ewig S, Welte T, Torres A. Is healthcare-associated pneumonia a distinct entity needing specific therapy? *Curr Opin Infect Dis*. 2012;25(2):166-175. doi:10.1097/QCO.0B013E32835023FB

21. Falcone M, Russo A, Giannella M, et al. Individualizing Risk of Multidrug-Resistant Pathogens in Community-Onset Pneumonia. PLoS One. 2015;10(4):e0119528. Published 2015 Apr 10. doi:10.1371/journal.pone.0119528

22. Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63(5):e61-e111. doi:10.1093/cid/ciw353

23. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of Infection Due to Antibiotic-Resistant Bacteria by Select Risk Factors for Health Care–Associated Pneumonia. *Arch Intern Med*. 2008;168(20):2205-2210. doi:10.1001/ARCHINTE.168.20.2205

24. Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a Clinical Score for Assessing the Risk of Resistant Pathogens in Patients With Pneumonia Presenting to the Emergency Department. Clin Infect Dis. 2012;54(2):193-198. doi:10.1093/cid/cir813

25. Aliberti S, Cilloniz C, Chalmers JD, et al. Multidrug-resistant pathogens in hospitalised patients coming from the community with pneumonia: a European perspective. *Thorax*. 2013;68(11):997-999. doi:10.1136/THORAXJNL-2013-203384

26. Shindo Y, Ito R, Kobayashi D, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2013;188(8):985-995. doi:10.1164/RCCM.201301-0079OC

27. Self WH, Wunderink RG, Williams DJ, Barrett TW, Baughman AH, Grijalva CG. Comparison of clinical prediction models for resistant bacteria in community-onset pneumonia. *Acad Emerg Med*. 2015;22(6):730-740. doi:10.1111/ACEM.12672

28. Prina E, Ranzani OT, Polverino E, et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc*. 2015;12(2):153-160. doi:10.1513/ANNALSATS.201407-305OC/

29. Ceccato A, Mendez R, Ewig S, et al. Validation of a Prediction Score for Drug-Resistant Microorganisms in Community-acquired Pneumonia. *Ann Am Thorac Soc*. 2021;18(2):257-265. doi:10.1513/ANNALSATS.202005-558OC

30. Falcone M, Tiseo G, Menichetti F. Community-acquired pneumonia owing to multidrug-resistant pathogens: A step toward an early identification. *Ann Am Thorac Soc*. 2021;18(2):211-213. doi:10.1513/ANNALSATS.202009-1207ED

31. Webb BJ, Dascomb K, Stenehjem E, et al. Derivation and multicenter validation of the drug resistance in pneumonia clinical prediction score. *Antimicrob Agents Chemother*. 2016;60(5):2652-2663. doi:10.1128/AAC.03071-15

32. Dean NC, Vines CG, Carr JR, et al. A Pragmatic, Stepped-Wedge, Cluster-controlled Clinical Trial of Real-Time Pneumonia Clinical Decision Support. *Am J Respir Crit Care Med*. 2022;205(11):1330-1336. doi:10.1164/RCCM.202109-2092OC

33. Madaras-Kelly KJ, Remington RE, Fan VS, Sloan KL. Predicting antibiotic resistance to community-acquired pneumonia antibiotics in culture-positive patients with healthcare-associated pneumonia. *J Hosp Med*. 2012;7(3):195-202. doi:10.1002/JHM.942

34. Zielonka M, Amati F, Bindo F, et al. Identify Drug-Resistant Pathogens in Patients with Community-Acquired Pneumonia. Adv Respir Med. 2023;91(3):224-238. doi:10.3390/ARM91030018

35. Ferrer M, Travierso C, Cilloniz C, et al. Severe community-acquired pneumonia: Characteristics and prognostic factors in ventilated and non-ventilated patients. *PLoS One*. 2018;13(1):e0191721. doi:10.1371/JOURNAL.PONE.0191721

36. Wang Y, Liang X, Jiang Y, et al. Novel fast pathogen diagnosis method for severe

pneumonia patients in the intensive care unit: randomized clinical trial. *Elife*. 2022;11. doi:10.7554/ELIFE.79014

37. Darie AM, Khanna N, Jahn K, et al. Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial. *Lancet Respir Med*. 2022;10(9):877-887. doi:10.1016/S2213-2600(22)00086-8

38. Monard C, Pehlivan J, Auger G, et al. Multicenter evaluation of a syndromic rapid multiplex PCR test for early adaptation of antimicrobial therapy in adult patients with pneumonia. *Crit Care*. 2020;24(1):1-11. doi:10.1186/S13054-020-03114-Y

39. Buchan BW, Windham S, Balada-Llasat JM, et al. Practical Comparison of the BioFire FilmArray Pneumonia Panel to Routine Diagnostic Methods and Potential Impact on Antimicrobial Stewardship in Adult Hospitalized Patients with Lower Respiratory Tract Infections. *J Clin Microbiol*. 2020;58(7). doi:10.1128/JCM.00135-20

40. Voiriot G, Fartoukh M, Durand-Zaleski I, et al. Combined use of a broad-panel respiratory multiplex PCR and procalcitonin to reduce duration of antibiotics exposure in patients with severe community-acquired pneumonia (MULTI-CAP): a multicentre, parallel-group, open-label, individual randomised trial conducted in French intensive care units. *BMJ Open*. 2021;11(8). doi:10.1136/BMJOPEN-2020-048187

41. Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Intensive Care Med 2023 496*. 2023;49(6):615-632. doi:10.1007/S00134-023-07033-8

42. Lin T, Tu X, Zhao J, et al. Microbiological diagnostic performance of metagenomic next-generation sequencing compared with conventional culture for patients with community-acquired pneumonia. *Front Cell Infect Microbiol*. 2023;13.

doi:10.3389/FCIMB.2023.1136588

43. Corrales-Medina VF, van Walraven C. Guideline-Concordant Antibiotic Therapy for the Hospital Treatment of Community-Acquired Pneumonia and 1-Year All-Cause and Cardiovascular Mortality in Older Adult Patients Surviving to Discharge. *Chest*. 2023;163(6). doi:10.1016/J.CHEST.2022.12.035

44. Kollef MH, Betthauser KD. New antibiotics for community-acquired pneumonia. *Curr Opin Infect Dis*. 2019;32(2):169-175. doi:10.1097/QCO.0000000000000526

45. Zhong NS, Sun T, Zhuo C, et al. Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: A randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. *Lancet Infect Dis*. 2015;15(2):161-171. doi:10.1016/S1473-3099(14)71018-7

46. File TM, Low DE, Eckburg PB, et al. FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J. Antimicrob. Chemother.* 2011. 66 Suppl 3, iii19–iii32. https://doi.org/10.1093/jac/dkr096.

47. Low DE, File TM, Eckburg PB, et al. FOCUS 2: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J. Antimicrob. Chemother.* 2011. 66 Suppl 3, iii33–iii44. https://doi.org/10.1093/jac/dkr097

48. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):E45-E67. doi:10.1164/RCCM.201908-1581ST

49. Nicholson SC, Welte T, File TM, et al. A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. *Int J Antimicrob Agents*. 2012;39(3):240-246. doi:10.1016/J.IJANTIMICAG.2011.11.005

50. McCurdy S, Keedy K, Lawrence L, et al. Efficacy of delafloxacin versus moxifloxacin against bacterial respiratory pathogens in adults with Community-Acquired Bacterial Pneumonia (CABP): Microbiology results from the delafloxacin phase 3 CABP trial. *Antimicrob Agents Chemother*. 2020;64(3). doi:10.1128/AAC.01949-19/

51. Gómez-Zorrilla S, Sendra E, Horcajada JP. A profile of delafloxacin in the treatment of adults with community-acquired bacterial pneumonia. *Expert Rev Clin Pharmacol*. 2022. 15:6, 671-688. doi:10.1080/17512433.2022.2100346

52. Park SC, Kim EY, Kang YA, et al. Validation of a scoring tool to predict drug-resistant pathogens in hospitalised pneumonia patients. *Int J Tuberc Lung Dis*. 2013;17(5):704-709. doi:10.5588/IJTLD.12.0723

53. Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia?. Chest. 2010;137(6):1283-1288. doi:10.1378/chest.09-2434

54. Park SC, Kang YA, Park BH, et al. Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia. Respir Med. 2012;106(9):1311-1319. doi:10.1016/j.rmed.2012.04.003

55. Ma HM, Ip M, Woo J, Hui DS. Development and validation of a clinical risk score for predicting drug-resistant bacterial pneumonia in older Chinese patients. Respirology. 2014;19(4):549-555. doi:10.1111/resp.12267

56. Wang PH, Wang HC, Cheng SL, Chang HT, Laio CH. Selection of empirical antibiotics for health care-associated pneumonia via integration of pneumonia severity index and risk factors of drug-resistant pathogens. J Formos Med Assoc. 2016;115(5):356-363. doi:10.1016/j.jfma.2015.03.009

57. Rothberg MB, Haessler S, Deshpande A, et al. Derivation and validation of a risk assessment model for drug-resistant pathogens in hospitalized patients with community-acquired pneumonia [published online ahead of print, 2022 Sep 29]. Infect Control Hosp Epidemiol. 2022;1-8. doi:10.1017/ice.2022.229

Figure 1. Proposed integrative algorithm for therapeutic decision of severe community-acquired pneumonia patients. MDR: multidrug-resistant.

Table 1. Risk factors for multidrug-resistant (MDR) pathogen infection producing severe community acquired pneumonia (SCAP). MRSA: Methicillin-resistant *Staphylococcus aureus.*

Healthcare exposure
• Prior hospitalization • Recent intensive care unit stay • Long-term care residence • Haemodialysis • Nursing home residence • Wound care • Tube feeding • Indwelling catheter
Host immunity and disease
• Age • Tobacco smoker • Prior colonization by *P. aeruginosa* or MRSA • Immunosupression • Bronchiectasis • Aspiration risk • Gastric acid supression

- Diabetes mellitus
- Cerebrovascular disease
- Chronic lung disease
- Chronic kidney disease
- Cognitive impairment
- Overall poor functional status

Therapies selective pressure

- Corticosteroids and immunosupresive therapies
- Prior Broad-spectrum antibiotics
- Gastric acid supression

Table 2. Predictive scoring systems for MDR pathogen infection. MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum β-lactamases; HCAP: healthcare-associated pneumonia; ICU: intensive care unit.

Predictive system	**Patient cohort**	**MDR Definition**	**Percentage of MDR pathogens**	**Risk factors (points)**	**Risk for MDR pathogen**	**External validation**
Shorr et al (2008) [23]	639 USA	MRSA, *P. aeruginosa,* extended-spectrum β-lactamase-producing *Klebsiella* species, nonfermenting gram-negative rods.	45.2%	Recent hospitalization (4) Residence in long-term care facility (3) Hemodyalisis (2) Immunosuppression (1)	≥1	[21,24–27]
Schreiber et al (2010) [53]	190 USA	MRSA, *P. aeruginosa,* ESBL-producing *Enterobactericeae*.	33%	Immunosupression (3) Admission from long-term care (2) Prior antibiotics (1)	≥2	No

Aliberti et al (2012) [9]	935 Italy	MRSA; *P. aeruginosa* resistant to antipseudomonal penicillins, cephalosporins, carbapenems, and quinolones; *Stenotrophomonas maltophilia;* vancomycin-resistant *Enterococcus*; *A. baumannii;* ESBL-producing *Enterobacteriaceae*; nonfermenting gram-negative bacilli.	18.8%	Chronic renal failure (5) Recent hospitalization (4) Nursing home residence (3) Diabetes, antimicrobial therapy, home wound healing (0.5)	≥3	[25–27]
Madaras-kelly et al (2012) [33]	375 USA	Any organism nonsusceptible to non-pseudomonal third generation cephalosporins or non-pseudomonal 8-methoxy	31.46%	Prior MRSA colonization or infection (45-100) Nursing home (45)	NA	No

		fluoroquinolones, MRSA, *P. aeruginosa.*		Infusion therapy (35) Cephalosporin antibiotics, diabetes (30) ICU admission (25)		
Park et al (2013) [54]	339 South Korea	MRSA, *P. aeruginosa, A. baumannii, S. maltophilia,* and ESBL-producing *Enterobacteriaceae.*	36%	Tube feeding (5) Recent hospitalization (3) Recent intravenous antibiotics (2) Recent chemotherapy, wound care, chronic dialysis (1)	≥3	[52]
Shindo et al (2013) [26]	1413 Japan	MRSA, *P. aeruginosa,* ESBL-producing *Enterobacteriaceae*.	15,3%	Unweighted. Prior hospitalization, immunosuppression, previous antibiotic treatment, gastric-acid suppression, tube feeding, non-ambulatory status.	≥3	[27]

Ma et al (2014) [55]	354 China	MRSA, *P. aeruginosa,* ESBL-producing *Enterobacteriaceae, A. baumannii*	13,55%	Bronchiectasis (14) Recent hospitalization (5) Severe pneumonia (2) Nursing home residence, home infusion therapy, chronic wound care, chronic dialysis, or immunosuppression (0.5)	≥2.5	[14]
Falcone et al (AUROC score) (2015) [21]	900 Italy	MRSA, *S. maltophilia,* ESBL-producing or carbapenem-resistant *Enterobacteriaceae,* any bacterial strain non-susceptible to at least one agent in three or more antimicrobial categories.	33% of isolations (n=300)	PaO2/FiO2 (<300) (1.5) HCAP criteria (1) Pleural effusion, and bilateral pulmonary infiltration (0.5).	≥3	[21]

Wang et al (2015) [56]	530 Taiwan	MRSA, *K. pneumoniae, Escherichia coli, Proteus mirabilis, P. aeruginosa, A. baumannii, S. maltophilia, Cheryseobacterium.*	38.9%	PSI score plus risk factors Wound care (PSI V) Nasogastric tube feeding and bronchiectasis (PSI III and IV)	PSI III and IV and risk factor ≥1	No
Prina et al (PES score) (2015) [28]	1597 Spain	*P. aeruginosa,* ESBL-producing *Enterobacteriaceae*, and MRSA.	6%	Fever (-1) Male sex (1) Previous antibiotic use, chronic respiratory disorder, consciousness impairment (2) Age (0-2) Chronic renal disease (3)	≥5	[29]
Webb et al (DRIP score) (2016) [31]	200 USA	Organisms resistant to drug regimens recommended for the treatment of CAP (ceftriaxone	25%	Major risk factors (2): prior antibiotic use, long-term care residence, tube feeding, prior infection with MDR pathogen)	≥4	[31]

		plus azithromycin or levofloxacin)		Minor risk factors (1): prior hospitalization, chronic pulmonary disease, poor functional status, gastric acid suppression, wound care, and previous MRSA colonization)		
Rothberg (CARM score) (2022) [57]	138762 USA	Any organism resistant to either a quinolone or the combination of a third-generation cephalosporin and a macrolide.	8.8%	Unweighted. Prior resistant organism, invasive mechanical ventilation, pressure ulcer, vasopressor administration, paralysis, admission to ICU, poor functional status, prior hospital admission, nursing care facility, chronic pulmonary disease, male sex, current tobacco smoker.	>4	No

Figure 1. Clinical management for patients with pneumonia.