Pneumonia Update for Emergency Clinicians

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Abstract
Purpose of Review Many new concepts in diagnosis, management, and risk stratification of patients with pneumonia have been described recently. The COVID pandemic made importance of viruses as dangerous pathogens of pneumonia quite clear while several non-invasive measures for patients with respiratory failure gained a more widespread usage.
Recent Findings Studies continue to examine feasibility of bedside ultrasound as a tool in accurate diagnosis of pneumonia in the emergency department, and several new antibiotics have been approved for treatment while others are in late-stage clinical trials. Additionally, the Infectious Diseases Society, American Thoracic Society, and their European counterparts published updated guidelines in recent years. For differences important to emergency medicine clinicians and new emphasis as compared to the prior guidelines, please see Table 1. Several new antibiotics have been approved recently but remain relatively unknown to emergency clinicians as their use is frequently restricted to infectious disease specialists.
Summary As the emergency physicians gain new tools to rapidly diagnose, treat, and appropriately disposition pneumonia cases that appear to become more complex as people unfortunately accumulate more comorbidities, we hope to offer better care and improve outcomes for our patients while allowing staff to enjoy coming to work.

Keywords Pneumonia · Guidelines · Emergency

Introduction and Causes

Pneumonia, whether community-acquired or healthcare-associated, remains an important emergency condition with high morbidity and mortality [1, 34]. Known since ancient times, its grave prognosis was known to Hippocrates, while Osler described it as “the captain of the men of death” in pre-antibiotic era [27] and it is still the number one cause of death from infectious disease [3]. It accounted for approximately one million hospitalizations annually in the USA before the current COVID pandemic [3] and its incidence continues to rise [1]. Whether protean or sudden in onset, pneumonia is one of the leading causes of emergency department visits and hospital admissions [9, 18]. While commonly thought of as an acute, short-term disease, recent studies suggest significant increase in mortality over the following 5 years as compared to controls even in patients without comorbidities [17]. Cardiovascular complications, such as acute coronary syndrome, congestive heart failure, and arrhythmias, both during the acute phase and for weeks and months afterwards are common with bacterial and viral pneumonia varieties alike [31••] and COVID-19 also carries well-described risks of thromboembolism, acute cerebrovascular disease, and cardiomyopathy. The precise mechanism of these complicating cardiovascular events is unclear. Alveoli were long thought to be a sterile place until the discovery of normal lung microbiome that can contain Streptococcus pneumoniae and Mycoplasma spp [18]. One hypothesis is that an antecedent viral infection causes a dysbiosis allowing the bacterial flora previously harmless to cause an invasive disease [18]. Pneumonia can be classified as community-acquired (non-hospitalized, non-nursing home patient, without history of > 2 days hospitalization in the prior 3 months, kidney replacement therapy, chemotherapy, or presence of a large open wound) [13] although new guidelines deemphasize this classification as a base for continuing broad-spectrum antibacterial coverage. Hospital-acquired, and especially ventilator-associated pneumonia, and healthcare-associated pneumonia, as well as pneumonia developing after foreign travel to regions with unique endemic pathogens, in habitual intravenous drug users, or in patients with severe immunodeficiency may require a different diagnostic approach and initial antibiotic choice.
Table 1  Differences important to emergency medicine clinicians and new emphasis [8, 16, 18, 19••, 30, 34]

| New recommendations                                                                 | Difference with prior guidelines if any | Comment                                                                                                                                 |
|------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Blood and sputum cultures recommended in severe disease and in inpatients treated   | Similar from the ED perspective        | Clinical gestalt performs as well as various decision instruments in deciding who needs blood cultures [13]                           |
| for MRSA or *P. aeruginosa*                                                        |                                        |                                                                                                                                       |
| Obtaining procalcitonin level not recommended to guide antibacterial therapy        | Was not covered in prior guidelines    |                                                                                                                                       |
| Recommend using validated risk factors to determine the need for *P. aeruginosa* or | Emphasized healthcare-associated pneumonia category | MDRO prevalence varies widely between communities challenging study interpretation [8]                                                |
| MRSA coverage instead of using hospital-acquired and ventilator-associated guidelines|                                        |                                                                                                                                       |
| Macrolide monotherapy conditional for outpatients based on local resistance patterns| Was strongly recommended              | *S. pneumonia* is increasingly resistant to macrolides                                                                                |
| Amoxicillin or doxycycline monotherapy for outpatients with no comorbidities or     | Amoxicillin, amoxicillin/clavulanate,  | The recommendation for including doxycycline in the treatment protocols is conditional and is based on weak evidence and is only... |
| risk factors for MDRO. Amoxicillin/clavulanate or cephalosporin (cefuroxime or      | and doxycycline were not considered    |                                                                                                                                         |
| cepodoxime) combined with a macrolide or doxycycline monotherapy with a respiratory | prominently in treatment regimens      |                                                                                                                                         |
| fluoroquinolone such as moxifloxacin for patients with comorbidities                |                                        |                                                                                                                                         |
| Do not give corticosteroids to pneumonia patients except in possibly decompensated | Was not considered                     | Note that in certain special forms of pneumonia (not considered CAP), such as *Pneumocystis jirovecii* pneumonia, corticosteroid... |
| refractory septic shock or known adrenal insufficiency                             |                                        | therapy may still be necessary. Corticosteroids increase mortality in patients with influenza infection who develop pneumonia   |
| When treating a patient with severe CAP b-lactam/macrolide combination preferred   | B-lactam/macrolide combination OR     | Influenza therapy in hospitalized patients has not been validated in a randomized controlled trial                                    |
| over b-lactam/fluoroquinolone combination, the use of anti-influenza therapy is     | b-lactam/fluoroquinolone combination; |                                                                                                                                         |
| recommended if influenza viral test is positive (expert recommendation)            | use of anti-influenza therapy was      |                                                                                                                                         |
| Limiting the length of antibiotic therapy to 7–10 days including in                | Recommended 14–21 days of therapy      |                                                                                                                                         |
| ventilator-associated pneumonia                                                    |                                        |                                                                                                                                         |
| Follow-up chest imaging after symptoms of pneumonia improve recommended only as     | Follow-up chest imaging was not       | In one study, CAP patients who received a single dose of intravenous ceftriaxone did just as well as patients who got it daily for... |
| necessary for lung cancer screening                                                | addressed                               |                                                                                                                                         |
with more broad-spectrum coverage [19••, 28, 34]. While Streptococcus pneumonia along with the atypical quartet (Mycoplasma pneumoniae, Legionella spp., Chlamydia, and Moraxella catarrhalis) remain the most common bacterial pathogens in CAP [8, 18], the important roles of viruses as the cause, especially of Influenza group during seasonal outbreaks, RSV, metapneumoviruses [18], and recently coronaviruses, have evolved [5, 33••]. Most cases of severe CAP are caused by S. pneumonia. Gram-negative, organisms, COVID-SARS-2, or have polymicrobial etiology [20]. When MDR organisms cause pneumonia, gram negatives such as Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii, and hospital-acquired MRSA variety are the usual culprits [16, 29]. Pseudomonas aeruginosa is much more common in North America than in Europe and K. pneumoniae is much more prevalent in Asia [29] calling for caution when applying results from studies done in different regions. Multiple pathogens are identified in up to 13% of cases of pneumonia [17, 29]. When viral particles are detected in the nasopharynx or sputum of patients with pneumonia along with a bacterial pathogen, it is not always clear whether this represents a colonization, acute infection, or co-infection [17]. It is well known that viral particles can persist in airways for weeks after the symptoms of infection have resolved [18]. Interestingly it appears that many respiratory viruses, especially Influenza, parainfluenza, and RSV, can modulate ACE receptors in upper airways predisposing the patient to subsequent SARS-COV-2 infection [5]. While aspiration is thought to be an important cause of CAP, the exact mechanism involved is unknown as up to 45% of population is documented to aspirate during sleep without any consequences [32••]. Recent studies question the importance of anaerobic bacteria as pathogens in aspiration community-acquired pneumonia, while Gram-negative bacteria are isolated more commonly in this patient population [32••]. Timely and appropriate emergency department diagnosis, management, and disposition can reduce mortality and morbidity in patients with pneumonia [1, 4, 11].

Conclusion

Rapid diagnosis of pneumonia enables appropriate triage of patients based on expected course and early symptomatic and etiologic treatment to improve clinical outcomes.

Diagnosis Update

Diagnosing pneumonia which is defined as an acute infection of the alveolar lung tissue [3] is often straightforward in young, otherwise healthy individuals based on history of present illness and physical examination [3, 15]. It has been shown in a study from pre-COVID era that otherwise healthy adults with respiratory complaints, normal vital signs, and normal lung exam have a chance of CAP less than 1% during that visit [15]. Older, immunocompromised patients are more likely to have an atypical presentation, such as an isolated altered mental status, with up to 65% lacking the triad of cough, fever, and shortness of breath [3], leading to delays in diagnosis. Isolated abdominal pain, chest pain, hemoptysis, or vomiting can all be chief presenting complaint in a patient harboring pneumonia [1, 8]. Radiographic demonstration of lung infiltrate by some means is highly desirable to rule out other mimicking conditions and distinguish pneumonia from bronchitis [8]. The status of plain two-view chest radiography which has been a gold standard for decades in identifying an infiltrate in the lungs has been increasingly challenged as both false positive and false negatives are common [3, 10]. Field diagnostic accuracy of CXR in diagnosis of pneumonia is estimated at 65% and ED physicians long understood that CXR findings may be delayed or absent in a patient with the disease [3, 21]. While chest CT may be the new gold standard in pneumonia diagnosis [21], its routine use for this purpose is problematic given associated ionizing radiation, cost, and time it takes to complete. As CT is much more sensitive and specific in detecting lung infiltrates, several concerns now arise. Firstly, is it possible that some patients will be overtreated as prior studies of antibiotics’ risks and benefits were based on evaluating chest X-rays? Secondly, since some of what was called pneumonia was not, then these patients may not have benefited from receiving antibiotic courses [18]. Reassuringly, recent small study suggests that the groups diagnosed by CT and X-ray behave similarly in terms of complications and the need for admission [17]. In addition to being more sensitive and specific, CT can better delineate the pathology allowing the radiologist to comment on causative organism, more so than based on CXR [3, 33••]. Chest sonography for diagnosing pneumonia or looking for an alternative diagnosis is an attractive modality in the emergency department, given its portability and high accuracy reported in recent studies reaching 97% [10, 21], and the ability of an emergency physician to rapidly learn the procedure [25]. It can help to detect certain pneumonia mimics, such as pneumothorax and pericardial effusion and clue in the clinician to the others, such as when McConnell’s sign is noted in large pulmonary embolism, or bilateral pleural effusions are seen in congestive heart failure. On the other hand, as bedside ultrasound performance inevitably entails close and prolonged staff exposure to a patient with respiratory complaints, the potential of SARS-COV-2 transmission should be kept in mind. A variety of blood tests is obtained in sicker and complicated patients worked up for pneumonia. Attempts to establish a specific biomarker, such as C-reactive protein or procalcitonin to rapidly identify
patients not needing aggressive therapy, have not worked so far and it is not recommended to guide antibiotics therapy based on procalcitonin level [19••]. Interestingly, elderly pneumonia patients with decreased total blood cholesterol showed increased mortality in a recent study [14]. Patients admitted to the hospital with pneumonia commonly develop cardiovascular complications [24, 31••] so cardiac biomarkers may be helpful in a select group. For pneumonia mimics, please see Table 2.

### Recognition of Severe CAP in the Emergency Department

Pneumonia is a leading cause of death in the USA from infectious disease with mortality in admitted patients at approximately 6% [3], with most death occurring in the elderly and those with comorbidities. In a group of patients with CAP, the disease rapidly and at times suddenly progresses to a life-threatening organ dysfunction [20] typically manifesting as either respiratory failure or septic shock [27]. It is recommended that established clinical guidelines are used in the emergency department to help decide treatment and disposition [2], but adherence to established guidelines varies quite widely among individual practitioners [4]. The American Thoracic Society and Infectious Diseases Society of America defined major and minor criteria for ICU admission in patients with pneumonia. Major criteria are straightforward and include the need for mechanical ventilation and/or pressors support. Minor criteria originally included tachypnea, hypoxia, altered mental status, hypothermia, hypotension, multilobar infiltrates, acute kidney injury, leukopenia, and thrombocytopenia, with age greater than sixty-five and lactic acidosis suggested as additional important variables [27, 30]. Severe CAP can be defined when either one of the major or three minor criteria are present [8, 19••]. Of note, including patients that require mechanical ventilation or vasopressors on admission in a prediction tool for ICU versus non-ICU admission makes the prediction tool less relevant to the ED doc [30]. In a recent study, when pneumonia patients with tachycardia, tachypnea, hypotension, hypothermia, or newly altered mental status documented on admission went to a non-ICU setting, their mortality was almost 50% higher than patients directly admitted to ICU [8, 30]. SMART-COP is another validated tool to assess the need for ICU admission that adds PaO2, serum pH, and serum albumin to the calculation [19••]. Other tools to help the clinician recognize severe CAP in need of inpatient care but not to guide ICU admission include Pneumonia Severity Index (PSI) and CURB65 (confusion, blood urea nitrogen, blood pressure, age greater than 65) tool. PSI use is favored in current guidelines over CURB65 in determining the need for admission, although it also may underestimate disease severity in younger patients [9, 19••]. There have been attempts to incorporate various biomarkers, such as procalcitonin and C-reactive protein into the decision instruments to predict negative outcomes of patients with pneumonia [6]. The authors of a recent Korean study found that combining procalcitonin level with pneumonia severity index was better at predicting short-term mortality than PCI alone [6]. There are studies looking at using machine-learning models, using data and algorithms helping computer programs to improve over-time to predict mortality of patients with pneumonia in the emergency department [26]. Since pneumonia caused by MDRO organisms, such as *P. aeruginosa*, extended-spectrum beta-lactamase-producing Enterobacteriaceae, or MRSA tends to have a severe course, but is relatively rare, there is an interest in identifying patients at risk for this malady. For the gram negatives, the residence in a nursing home, immune-suppressive therapy, history of colonization of infection with the pathogens, systemic antibiotic therapy, or hospitalization for longer than 2 days in the past 3 months, tube feeding, severe chronic lung disease, or tracheostomy increase the risk [22, 23, 30]. For MRSA pneumonia, any cerebrovascular disease, dementia, prior MRSA colonization or infection, hospital admission within the past 30 days, or hemodialysis increase the risk [30]. MDcalc web site lists Shorr rule for identifying patients with the risk of healthcare-associated MRSA pneumonia that also incorporates age older than 79 or younger than 30, and presence of diabetes mellitus but only in female patients. Community-acquired MRSA pneumonia is rare but tends to have a malignant course. Rapid progression of radiographic findings of pneumonia, gross hemopty-sis, evidence of lung necrosis, presence of toxic shock, or scalded skin syndrome, especially in a patient after recent influenza infection or history of MRSA skin lesions, are all features suggesting this disease [18]. Both young, otherwise healthy patients and debilitated old people seem to be at risk. While early identification of these patients enables appropriate therapy and improves outcomes, inappropriately broad inclusion actually leads to worse outcomes and breeds more MDRO [12, 23]. All of these rules were developed for assessment of patients with CAP of bacterial etiology and are not for use in patients with severe viral CAP where currently some recommendations for the level of care exist only for patients with COVID-19. Viral pneumonia, depending on the causative organism, commonly has a different set of risk factors for severe disease development, such as pregnancy for influenza viruses or obesity for COVID-SARS-2 and in pre-COVID studies up to 30% of patients admitted for viral CAP went to ICU [29]. Certain common clinical situations, for example pneumonia complicated by acute heart failure, are not
| Condition                | Common features with pneumonia | Differences                                                                 | Comments                                                                 |
|-------------------------|--------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Bronchitis              | Very similar but usually less  | No identifiable infiltrate                                                   | Not life-threatening and usually does not require antibiotic administration |
|                         | severe clinical syndrome       |                                                                             |                                                                           |
| Pulmonary embolus       | Dyspnea, chest pain, fever     | High-grade fever, productive cough, and crackles on exam are less common,    | Life-threatening and requires expeditious diagnosis                        |
|                         |                                | while CXR is usually abnormal but uncommonly shows an infiltrate             |                                                                           |
| Congestive heart failure| Dyspnea, cough, crackles on exam | Orthopnea and high blood pressure are more common with CHF, while fever is less common | Pneumonia is a well-described risk factor for an exacerbation of known CHF or causing a de novo presentation of CHF so the two commonly co-exist [3]■■ |
| Septic emboli           | Fever, chills, chest pain      | Risk factors for endocarditis, specific appearance on advanced imaging such as chest CT | Blood cultures are crucial for appropriate diagnosis and management in this category |
| Pneumothorax/           | Dyspnea, cough, chest pain     | Fever is uncommon, unless another source exists                              | CXR may need careful scrutinization, bedside US can be very helpful        |
| Neoplasm                | Dyspnea, cough, chest pain, mass can be mistaken for an infiltrate          | Indolent course, fever is less common                                      | Can be complicated and unmasked by developing pneumonia                    |
| Interstitial lung disease| Dyspnea, cough, fever          | High fever, acute onset, and localized infiltrates are less common           | Especially with cryptogenic organizing pneumonia the differentiation is difficult, treatment is with corticosteroids |
| Pertussis               | Cough, dyspnea                 | Prolonged course, fever is usually absent, CXR normal or nonspecific        | Uncommon in the US                                                         |
| Drug or chemical-induced pneumonitis | Dyspnea, cough | Fever and isolated infiltrate are less common                              | Symptoms may be delayed by weeks from drug administration depending on the agent |
| Unstable angina         | Dyspnea, chest pain, diaphoresis | Fever and typical infiltrates are less common, pulmonary edema and EKG abnormalities may be present | Pneumonia can trigger acute coronary syndrome [3]■■ |
| Pericardial tamponade   | Dyspnea, chest pain, hypotension | Fever is less common except in purulent effusion, no infiltrate on CXR      | Chest sonography can help identify this condition rapidly if cardiac windows are obtained |
| Pulmonary tuberculosis  | Dyspnea, fever                 | Hemoptysis, protean constitutional symptoms, travel or exposure history     | Predilection of upper lobe involvement on chest X-ray                      |

*It is important to realize that even if the diagnosis of pneumonia is a certain diagnosis, the above conditions may co-exist and vice versa and pneumonia can complicate the clinical course of these ailments*
covered by existing guidelines [24]. Importantly, none of the mentioned decision instruments has been shown to be better than an experienced clinician judgment and should supplement not replace the one [30].

**Treatment of CAP Update**

Once the diagnosis of pneumonia is established, the focus of the clinician shifts to choosing an appropriate treatment. Antibacterial and/or anti-viral agents are chosen as appropriate and various disease-modifying, supportive, or symptomatic measures may be needed. If complications develop or comorbidities are exacerbated, those need to be managed as well. In the ED, the initial antibiotic treatment of bacterial pneumonia is empiric in majority of cases. Antibiotic resistance has been impacting available choices for pneumonia treatment worldwide for a long time [1]. But the problem of resistance is especially difficult for Gram-negative pathogens. Limiting broad-spectrum antibiotic use and developing new agents are the two main ways that the medical community is using trying to stay ahead of the game. Amoxicillin in high-dose monotherapy is now considered the treatment of choice for a patient with mild pneumonia and no comorbidities, while in a patient with comorbidities who is appropriate for outpatient management, amoxicillin/clavulanic acid is recommended [8]. These recommendations seem to be based on a study by Postma et al. that showed similar outcomes in patient with beta-lactam monotherapy or beta-lactam/macrolide combination or respiratory fluoroquinolone [30]. A total of 25% of patients enrolled in that study did not have a confirmatory chest X-ray however [30]. Neither amoxicillin nor amoxicillin/clavulanate combination is effective against the atypical organisms, so if there is a concern for atypical being the culprit, an addition of a macrolide or possibly doxycycline is needed. Alternatively, a respiratory fluoroquinolone can be used as monotherapy. When fluoroquinolones are chosen, a careful risk–benefit and drug-drug interaction assessment should be performed especially in patients at risk for tendinopathy, cardiac, or neurologic complications. Macrolide monotherapy is problematic due to emerging *S. pneumonia* resistance [8, 18], but it is unique among antibiotics in suppressing exotoxin production by *S. pneumonia* and has beneficial host immunomodulatory effects, making it an important agent in sicker, admitted patients. It can still be used as monotherapy if local resistance is less than 25% according to the new pneumonia guidelines [19••]. Oral cephalosporins are no longer recommended for treatment of pneumonia [8]. Non-ICU pneumonia patients that are admitted are usually treated with a combination b-lactam and macrolide or respiratory fluoroquinolone. Broader spectrum agents may be needed if risk factors for Gram-negative pathogens or MRSA exist and local hospital epidemiological data indicate their prevalence [8, 22]. Patients who are admitted to ICU need broad-spectrum antibiotic coverage unless clear clinical or epidemiological signs allow for pneumonia etiology to be established early [22]. Most patients diagnosed with severe viral pneumonia get at least a short course of antibiotics [8, 30]. Specific anti-viral treatment exists for influenza, and arguably SARS-COV-2 disease. Supportive care of patients with pneumonia typically revolves around management of respiratory failure and septic shock. Pneumonia is the most frequent cause of acute respiratory distress syndrome [27] and early and frequent assessments of oxygenation are mandatory in sicker patients [1]. Non-invasive ventilation (NIV) is usually the first step in pneumonia patients with respiratory failure either as a bridge to endotracheal intubation or as a more permanent solution. Especially the use of high-flow nasal cannula oxygen therapy, while not novel, became more common in this COVID-19 pandemic. It should be noted, however, that patients who continue needing either high-flow nasal cannula or BIPAP for support are at high risk of failure of this therapy approaching 50% [11] and require frequent re-assessment. Intubation should not be delayed if respiratory failure is worsening [27] mandating an ICU level of care for this group of patients even if they initially appear relatively stable on NIV and hemodynamic support requirement is a strong predictor of NIV failure [11, 27]. Pneumonia is also the most common cause of sepsis [27] and can present in septic shock requiring fluid resuscitation and pressors support as appropriate. Corticosteroids are no longer recommended in treatment of pneumonia except as needed to treat refractory septic shock [17] or another complication where they are clearly beneficial, such as acute concomitant COPD exacerbation. There have been some retrospective studies suggesting a reduction in acute cardiovascular complications with prophylactic antiplatelet therapy in patients with pneumonia [31••] with clopidogrel and ticagrelor more effective than aspirin [18]. For new antibiotics that have been either approved for treatment of pneumonia or are in late clinical trials, see Table 3.
| Antibiotic name | Spectrum of activity and indications | Comments |
|-----------------|-------------------------------------|----------|
| Omadacycline    | Bacterial CAP, skin and skin structure infections. Activity against MRSA, MSSA, *S. pneumoniae*, vancomycin-resistant enterococcus, *Legionella*, *Mycoplasma*, and *Chlamydia* | A tetracycline that overcomes resistance to older tetracyclines. Has IV and oral formulations (should be taken on empty stomach) |
| Ceftaroline     | Bacterial CAP, skin and skin structure infections. Active against MRSA in addition to MSSA, *S. pneumonia*, many Gram negatives. No activity against extensively resistant Gram-negative bacteria limited activity against most non-fermentative Gram-negative bacilli (such as *P. aeruginosa*) and anaerobes | Severe myelosuppression reported with therapy exceeding 7 days. Reports of MRSA strains resistant to ceftaroline limit its usefulness |
| Nemonoxacin     | Novel quinolone with activity against MRSA, vancomycin-resistant pathogens, and *Nocardia* spp., in addition to the usual quinolone spectrum. Poor activity against *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Mycobacterium tuberculosis* | In phase III trials; already reached market in many countries. Does not seem to prolong QTc interval |
| Delafloxacin    | Novel quinolone. Bacterial CAP, skin and skin structure infections. Activity against *S. pneumoniae*, MSSA, *Klebsiella pneumoniae*, *E. coli*, *P. aeruginosa*, *H. influenzae* and *parainfluenzae*, *Mycoplasma*, *Chlamydia*, and *Legionella* | Standard black box warning for quinolones including precautions in myasthenia gravis patients [7]. Approved for MRSA skin and soft tissue infections but not for MRSA pneumonia |
| Lefamulin       | Bacterial CAP caused by *S. pneumoniae*, MSSA, *Haemophiles influenzae*, *Legionella*, *Mycoplasma*, and *Chlamydia* | First pleuromutilin for oral or parenteral use in humans, unique mechanism of action potentially can overcome resistance to other antibiotics. Active against MRSA in vitro. Also active against *Neisseria* spp., including against extensively drug-resistant *N. gonorrhea*. Prolongs QTc interval Not studied in severe infections |
| Tedizolid       | Activity against MRSA, vancomycin-resistant enterococci, including some linezolid-resistant strains. Approved for bacterial skin and soft tissue infections, studies show good penetration into lung tissue | Novel oxazolidinone, available in IV and oral forms. Lower risk of side effects compared to linezolid and less drug-drug interactions, specifically lowering chances of serotoninergic and adrenergic toxicity via monoamine oxidase pathway |
| Cefiderocol     | Treatment of hospital-acquired and ventilator-associated pneumonia caused by MDR Gram-negative organisms, including *P. aeruginosa* and carbapenem-resistant *Acinetobacter* infections | Novel modified cephalosporin. When compared with meropenem, all-cause mortality was higher in cefiderocol group for unclear reasons |
| Ceftolozane-tazobactam | Use for treatment of pneumonia is off-label in the USA. Active against extended-spectrum b-lactamase-producing Enterobacteriaceae | Combination of a novel cephalosporin with the β-lactamase inhibitor. *K. pneumoniae* carbapenemase and metallo-b-lactamase-producing Gram-negative bacteria are resistant to this agent. It is less active in patients with reduced creatinine clearance |
| Plazomicin      | Approved for complicated UTI. Has enhanced activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*. Activity against *P. aeruginosa* is similar to older aminoglycosides. In vitro activity against MRSA. Not approved for treatment of sepsis ion in the USA due to lack of data | Aminoglycosides can cause neuromuscular blockade making their use dangerous in patients with myasthenia gravis |
| Imipenem/cilastatin/relebactam | Active against MDR Gram-negative bacteria, including *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae*. It is approved for the treatment of hospital-acquired and ventilator-associated pneumonia in patients with limited or no alternative treatment options | New carbapenem/β-lactamase inhibitor combination. Ineffective against excluding metallo-β-lactamase-producing Enterobacteriaceae and carbapenem-resistant *Acinetobacter baumannii*. CNS side effects including confusional state and seizures. Drug-drug interactions with valproic acid resulting in rapidly decreasing valproate levels and potential for breakthrough seizures |
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Compliance with Ethical Standards

Competing Interests The author declares no competing interests.

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| Antibiotic name | Spectrum of activity and indications | Comments |
|-----------------|------------------------------------|----------|
| Meropenem/vaborbactam | Approved for the treatment of hospital-acquired and ventilator-associated pneumonia in Europe. | Gram-negative coverage extended-spectrum beta-lactamase-producing organisms and K. pneumoniae carbapenemase. |
| Eravacycline | Broad-spectrum activity against Gram-positive, Gram-negative organisms, and anaerobes, including extended-spectrum beta-lactamase-producing organisms, carbapenem-resistant Enterobacteriaceae, and MDR A. baumannii. | It readily penetrates lung tissue. |

Table 3 (continued)
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