Community Acquired Pneumonia

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Richard G. Wunderink and Mark W. Landmeier

Case Presentation

A 31 year old male with a history of diabetes mellitus type 1 and recent skin infection of the neck (for which he underwent incision and drainage and levofloxacin treatment) presented to the emergency department with a three day history of fever, cough productive of bloody sputum, and shortness of breath. He had recently returned from a trip to Asia. He was tachycardic but normotensive and had an oxygen saturation of 93 % on 3 L nasal cannula. WBC count was 21.8 K/UL with 90 % neutrophils, BUN and creatinine were 8 mg/dL and 1.0 mg/dL, respectively, and glucose >350 mg/dL. Suspicion of cavitary pneumonia on chest radiograph was confirmed by computed tomography (Fig. 20.1).

Question What would be the best empirical therapy for this patient?

Answer Ceftriaxone, azithromycin, and linezolid.

Because of additional concern for meliodosis, the patient was started on ceftazidime, azithromycin, and vancomycin. He developed progressive hypoxemia and agitation, at which time he was intubated and started on mechanical ventilation. Bronchoscopic bronchoalveolar lavage (BAL) of the right lower lobe revealed 240 WBCs with 81 % neutrophils. Sampling of a rapidly progressing pleural effusion showed a pleural fluid pH 6.95, glucose 44 mg/dL and LDH 1842 IU/L. Gram stain of both fluids revealed clusters of gram positive cocci. Chest tube drainage of the right pleural space was performed. Urinary antigen testing for S*treptocococcus pneumoniae* and fungal serologies were negative. He was empirically switched from vancomycin to linezolid. BAL and pleural fluid cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA). Serum immunoglobulins (IGs) were subsequently found to be very low and he was given IVIG. After a prolonged ICU course, he was ultimately discharged to an acute rehabilitation facility and subsequently returned to full functional status. He continues to receive intermittent outpatient IVIG.

Principles of Management

Site-of-Care Decisions

Patients admitted to the ICU with severe community-acquired pneumonia (CAP) generally fall into one of two categories: (1) those whose

R.G. Wunderink (✉) • M.W. Landmeier
Department of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: r-wunderink@northwestern.edu

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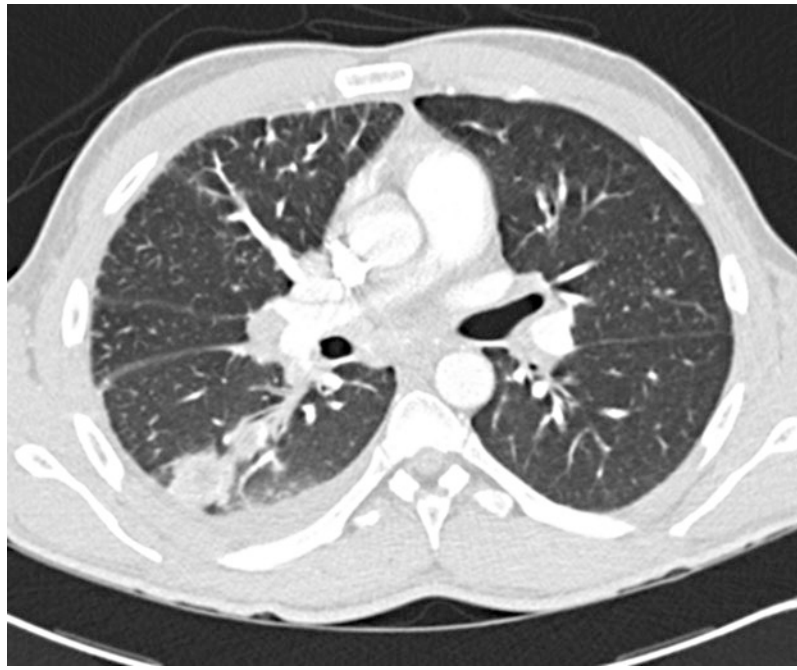

Fig. 20.1 Representative image of the CT chest upon admission

symptom severity or co-morbid conditions require ICU admission at presentation and (2) those who transfer to the ICU later because of progressive decline despite receiving inpatient therapy.

Patients in need of mechanical ventilation or vasopressor support because of septic shock automatically require intensive care. However, the decision to admit to the ICU is more difficult when such obvious needs are not present. Early identification of patients likely to deteriorate is important as increased mortality is associated with ICU transfer for delayed respiratory failure or onset of septic shock. Pooled analysis of four prospective CAP studies, of which 138 had delayed-transfer compared to 315 direct Emergency Department (ED) to ICU admissions, demonstrated that the delayed-transfer group had higher 28-day mortality (23.4 % vs. 11.7 %, $p<0.02$) and hospital length of stay (13 days vs. 7 days, $p<0.001$) in propensity-matched analysis [1].

While some delayed transfers to the ICU represent progressive pneumonia despite appropriate treatment, many patients have subtle clinical findings upon presentation that predict a more aggressive approach will lead to improved outcomes. Using the presence of ≥3 IDSA/ATS minor criteria (Table 20.1) [2] in the ED, a before/after quality improvement project demonstrated decreased mortality (adjusted odds ratio [OR] 0.24, 95 % confidence interval [CI] 0.09–0.670, $p=0.006$), fewer delayed ICU transfers (14.8 % vs. 32 %, $p<0.001$), and minimal increase in direct admissions to the ICU when an aggressive pre-ICU assessment and resuscitation protocol was utilized [3].

The Pneumonia Severity Index (PSI) and CURB-65 Score, while useful in predicting 30-day mortality and need for hospital admission, have limited ability to predict the need for intensive respiratory monitoring or vasopressor support initially. In addition to the IDSA/ATS minor criteria, several other scores such as SMART-COP [4] generally have very good sensitivity if the threshold is set optimally. However, such scoring tools will lead to a significant increase in ICU admissions if followed rigorously, and they require prospective validation.

Table 20.1 IDSA/ATS minor[a] criteria for severe community acquired pneumonia

Respiratory rate[b] ≥ 30 breaths/min
PaO_2/FiO_2 ratio[b] ≤ 250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ≥20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36 °C)
Hypotension requiring aggressive fluid resuscitation

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[a]Other considerations include hypoglycemia (in a non-diabetic patient), acute alcoholism/withdrawal, hyponatremia, unexplained metabolic acidosis, elevated lactate level, cirrhosis and asplenia

[b]Need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or $PaO_2/FiO_2 < 250$

[c]As a result of infection alone

Diagnostic Testing

Aggressive diagnostic testing is most useful in those with severe CAP requiring ICU admission and in those with risk factors for healthcare-associated pneumonia (HCAP). In such patients, the probability of finding a pathogen resistant to usual CAP empirical therapy (e.g. *Staphylococcus aureus* or *Pseudomonas aeruginosa*) is increased, and identification of a specific pathogen can lead to tailored antimicrobials, thus decreasing cost and exposure to unnecessary medications [5].

In a patient invasively ventilated, direct access to the lower respiratory tract provides the opportunity to perform an endotracheal aspirate or bronchoalveolar lavage (BAL). Moreover, bronchoscopic BAL can be useful in those where sputum or blood cultures do not yield a pathogen. In a prospective study of 262 patients admitted with CAP, fiberoptic bronchoscopic BAL provided additional diagnostic value in 49 % of patients who could not expectorate sputum and 52 % who had treatment failure 72 h after admission [6].

Blood and sputum cultures generally have low sensitivity but should still be performed upon transfer to the ICU, even in the non-intubated patient. Growth inhibition by antibiotics decreases the diagnostic yield of both tests but less so when *S. aureus* or gram-negative bacilli are the predominant pathogen [2]. Pleural fluid sampling is necessary in a CAP patient with a large pleural effusion (either upon admission or one which develops after empirical treatment for CAP), as a complicated pleural space requires adequate drainage.

Urinary antigen testing has reasonable sensitivity and excellent specificity for detecting *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. The test can stay positive for over 3 days in patients with *S. pneumoniae* and for weeks with *L. pneumophila* [2]. Although antibiotic sensitivity data cannot be obtained, the test is qualitatively important to verify that an antibiotic regimen adequately covers such pathogens.

Viral testing is important, especially in the appropriate season. A positive influenza test in a critically-ill patient should be an impetus for antiviral therapy, which can hasten disease resolution and decrease spread.

Microbial Culprits

Microorganisms responsible for CAP in the ICU mirror those of the outpatient setting, with the addition of gram-negative pathogens and MRSA. A review of 9 studies of patients with CAP admitted to the ICU showed that the most common typical bacterial pathogens were *S. pneumoniae*, *L. pneumophila*, *Haemophilus influenzae*, aerobic gram-negative bacilli, and *S. aureus* [7]. The relative frequency of atypical pathogens in the ICU setting is unclear because of heterogeneity in diagnostic technique but is approximately 20 % [2]. Respiratory viruses, either as a pure or co-infection, can be detected in up to 49 % of severe pneumonias. Common culprits include parainfluenza virus, human metapneumovirus, influenza A and B, respiratory syncytial virus, and adenovirus [8, 9]. Much less common viral pathogens include coronaviruses, such as the SARS virus and Middle East respiratory syndrome coronavirus (MERS-CoV), parechoviruses, and enteroviruses.

Epidemiologic risk factors are helpful to suggest less common etiologies (Table 20.2). Structural lung disease (e.g. COPD with repeated exacerbations or bronchiectasis), prior hospitalization and healthcare exposure pose an increased risk of *Pseudomonas*, chronic alcoholism is a risk for other gram-negative pathogens (*Klebsiella pneumoniae* or *Acinetobacter* species), and end-stage renal disease, injection drug use, prior influenza infection, and prior treatment with fluoroquinolones pose an increased risk of *S. aureus* [2].

Empirical Versus Pathogen-Directed Therapy

With severe CAP, timely diagnosis and adequate empirical antimicrobial therapy are paramount. Retrospective analysis of 2731 adult patients with septic shock, the majority of whom had a pulmonary primary site of infection, demonstrated that each hour delay in initiation of appropriate antibiotic therapy after the onset of hypotension was associated with a mean decrease in survival of 7.6% [10]. Consideration of the

Table 20.2 Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* species, *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti* (Q fever)
HIV infection (CD4 > 200)	*S. pneumoniae*, *H. influenzae*, *M. tuberculosis*
HIV infection (CD4 < 200)	The pathogens listed for early infection plus *Pneumocystis jirovecii*, *Cryptococcus*, *Histoplasma*, *Aspergillus*, atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa*, *H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to/residence in southwestern United States	*Coccidioides* species, *Hantavirus*
Travel to/residence in Southeast and East Asia	*Burkholderia pseudomallei*, avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae*, *Staphylococcus aureus*, *H. influenzae*
Cough >2 weeks with whoop or post tussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa*, *Burkholderia cepacia*, *S. aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis*, *S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae*, *H. influenzae*, *S. aureus*

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CA-MRSA community-acquired methicillin-resistant *Staphylococcus aureus*, *COPD* chronic obstructive pulmonary disease, *SARS* severe acute respiratory syndrome

need to alter an empirical regimen to cover specific (and perhaps drug-resistant) organisms is a major consideration when a patient is transferred to the ICU while already on standard empirical antimicrobial coverage for CAP.

In the absence of risk factors for HCAP or drug-resistant pathogens, adequate coverage of *S. pneumoniae* and *L. pneumophila* is crucial. Combination antibiotics with a beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) and either a macrolide or fluoroquinolone is recommended. A recent prospective randomized trial demonstrated improved clinical outcomes for combination therapy compared to beta-lactam monotherapy, confirming multiple observational studies showing better clinical outcomes and decreased mortality with combination therapy, especially for bacteremic pneumococcal pneumonia [2].

For suspected *Pseudomonas* CAP, dual therapy is required and can take the form of one of three initial combinations:

1. anti-pneumococcal anti-pseudomonas beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus fluoroquinolone (ciprofloxacin or levofloxacin), or
2. beta-lactam plus an aminoglycoside and azithromycin, or
3. beta-lactam plus an aminoglycoside and an anti-pneumococcal fluoroquinolone

For MRSA pneumonia linezolid is superior to vancomycin, particularly if a toxin-secreting community-acquired strain is the culprit [2]. A randomized double-blind trial comparing linezolid to dose-adjusted vancomycin for treatment of MRSA-proven HAP or HCAP demonstrated eradication of MRSA and clinical cure were statistically better with linezolid, and linezolid had less incidence of nephrotoxicity [11]. In the setting of methicillin-susceptible S. *aureus*, beta-lactam therapy is still the treatment of choice.

Parapneumonic Effusions

In the presence of a CAP-related pleural effusion, thoracentesis can distinguish between uncomplicated parapneumonic effusion (UPPE), complicated parapneumonic effusion (CPPE) or empyema [12]. Frank pus or a positive pleural fluid gram stain or culture indicate an infected pleural space and need for immediate drainage. However, pleural fluid gram stain and culture can be negative in CPPE or empyema. In such situations, pleural fluid chemistry is the most efficient way to assess the effusion [12]. A meta-analysis showed pleural fluid pH to have the highest diagnostic accuracy in detecting a complicated effusion, followed by glucose and lactate dehydrogenase (LDH) [13]. While optimal thresholds are still a matter of debate, a pH <7.28, glucose <40 mg/dL and/or LDH level >1000 IU/L suggests CPPE or empyema and the necessity for pleural drainage to achieve a good outcome [12, 14].

If the pleural space is not evacuated in CPPE, fibrinous adhesions develop, and neutrophils and bacteria accumulate leading to empyema. Optimal therapy for CPPE and empyema hinges on adequate antibiotic coverage and pleural drainage [15]. If pleural loculations develop, multiple thoracostomy tubes may be needed along with intrapleural instillation of fibrinolytic agents [12]. A randomized controlled trial of intrapleural DNase with concomitant tissue plasminogen activator (TPA) in patients with empyema showed a lower rate of surgical referral and hospital length of stay compared with placebo and individual agents alone [16]. Lysis of adhesions or decortication via video-assisted thoracoscopic surgery (VATS) or thoracotomy may be necessary if less invasive measures fail. The timing of surgical referral and type of surgical maneuver, though, largely depend on the patient and severity of illness.

In contrast, uncomplicated parapneumonic effusions are usually exudates with pleural fluid pH >7.28 and normal glucose. As these effusions are reactive, they should resolve with continued antibiotic therapy.

Evidence Contour

Several aspects of severe CAP management remain without consensus, including the assessment of risk for multidrug resistant (MDR) pathogens, adjuvant assessment tools, and treatments.

Risk of Multidrug Resistant (MDR) Pathogens

Empirical antibiotic therapy for severe CAP hinges on the risk for drug resistant organisms. Over the last decade HCAP has been used to describe the entity wherein patients develop pneumonia outside the hospital yet have pathogens usually associated with HAP or VAP, such as MDR gram-negative bacilli and MRSA. Criteria for HCAP and the resultant number of patients who should get broad-spectrum empirical therapy remain subject to debate. Using any risk factor for drug-resistant pathogens (DRP) leads to antibiotic overtreatment, while ignoring risk factors is associated with undertreatment and adverse outcomes [5]. In a prospective observational study, Shindo et al. found six independent risk factors for pathogens resistant to the usual CAP antibiotics: (1) hospitalization ≥ 2 days during the previous 90 days, (2) antibiotic use during the previous 90 days, (3) non-ambulatory status, (4) tube feedings, (5) immunocompromised status, and (6) use of gastric acid suppression medications [17]. Presence of three or more risk factors should prompt a physician to consider broad-spectrum antibiotic therapy, as the frequency of drug resistant pathogens may be as high as 43 %. These criteria work equally well as the previous definition of HCAP, and a strategy for initial antibiotic selection based on these risk factors may result in far less empirical broad-spectrum therapy while still identifying the majority who need it.

Drugs to Suppress Toxin with MRSA

A community-acquired MRSA (CA-MRSA) clone, distinct from that usually causing HCAP, HAP or VAP, has emerged as a cause of pneumonia with striking necrotizing features. Methicillin resistance results from a different staphylococcal cassette chromosome type (SCCmec type IV), which also includes a gene encoding Panton-Valentine leukocidin (PVL) and other exotoxins. Presence of PVL may explain the associated neutropenia while other exotoxins, such as alpha-hemolysin, may result in the characteristic severe pulmonary hemorrhage of both the MRSA and MSSA infections [18]. Antibiotic therapy that also suppresses toxin production provides better outcomes and improved survival, as illustrated in a retrospective study of PVL-positive CAP [19]. Clindamycin and linezolid have been shown to suppress in-vitro formation of PVL, alpha-hemolysin, and toxic shock syndrome toxin 1, whereas vancomycin and beta-lactams have no effect [18]. The benefit of clindamycin combined with a beta-lactam for MSSA CAP is unclear, with a recent prospective analysis demonstrating that nearly 18 % of CA-MRSA isolates were clindamycin resistant; whether antibiotic growth inhibition detected by MIC-susceptibility tests correlates with toxin-suppression activity, though, is unclear [20, 21]. While the preferred treatment for PVL-positive MSSA CAP is still unclear, linezolid appears the most reasonable choice for CA-MRSA CAP in light of its potential to suppress exotoxin and offer faster eradication of other MRSA clones. The rapid bactericidal activity of ceftaroline, a cephalosporin with MRSA activity, may obviate the need to suppress exotoxin production, but data are still very limited.

Procalcitonin

Procalcitonin (PCT), a peptide released in response to bacterial infection but suppressed by interferons induced by viral infections, has the potential to distinguish between bacterial and viral causes of pneumonia and potentially guide antibiotic decisions. In a prospective study of CAP, clinicians were encouraged (PCT level >0.25 mcg/L) or discouraged (PCT level <0.1 mcg/L) from using antibiotics based on procalcitonin cutoffs. PCT guidance reduced total antibiotic exposure, antibiotic prescriptions on admission, and antibiotic treatment duration without adversely affecting clinical outcomes [22]. Further analysis has shown that persistently elevated PCT levels are associated with adverse outcomes such as the development of pneumonia complications and death [23]. A similar benefit on shortening antibiotic duration with a PCT-driven protocol has been found

in several studies of severe sepsis. Despite these studies, PCT has not been FDA approved for this indication in the US.

Corticosteroids

Death in CAP may result from either failure to eradicate the microorganism or from inappropriate (and perhaps exaggerated) host response to the infection. This has led investigators to attempt modulation of the inflammatory response in severe CAP with corticosteroids.

While a small prospective study [24] and several retrospective studies [25] support corticosteroid administration in severe CAP, a larger randomized double-blinded trial evaluating the efficacy of prednisolone to placebo in patients with severe CAP (PSI IV or V) failed to show a beneficial effect of corticosteroids [26]. Conversely, in a highly selected group of patients with very high C-reactive protein levels on admission, use of corticosteroids was associated with less treatment failure [27].

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