

Richard G. Wunderink

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 3 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 21.8k/ μ L 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.

The patient was initially admitted to a general medicine unit. Because of concern for melioidosis based on travel history, the patient was started on ceftazidime, azithromycin, and vancomycin. He developed progressive hypoxemia and agitation, requiring intubation and 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 *Streptococcus pneumoniae* and fungal serologies were negative. He was empirically switched from vancomycin to



Fig. 20.1 Representative image of the CT chest upon admission

linezolid. BAL and pleural fluid cultures subsequently grew methicillin-resistant *Staphylococcus aureus* (MRSA). Serum immunoglobulins (IGs) were found to be very low and he was given intravenous IG. After a prolonged ICU course, he was ultimately transferred to an acute rehabilitation facility and was subsequently discharged to home. 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 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.

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

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 commonly used 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 [2]. In addition to IDSA/ATS minor criteria, several other scores have been developed and generally have good sensitivity if the threshold is set optimally. However, all such scoring tools lead to significant increases in ICU admissions if followed rigorously.

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

^bNeed for noninvasive ventilation can substitute for a respiratory rate > 30 breaths/min or PaO₂/FiO₂ < 250

^cAs a result of infection alone

Microbial Etiologies

Microorganisms responsible for CAP in the ICU mirror those of the outpatient setting, with the addition of Gram-negative pathogens and MRSA. In nine studies of CAP patients admitted to the ICU showed that the most common typical bacterial pathogens were *S. pneumoniae*, *L. pneumophila*, *Haemophilus influenzae*, Enterobacteriaceae, and *S. aureus* [4]. The relative frequency of atypical pathogens in the ICU setting is unclear because of heterogeneity in diagnostic technique and testing frequency but can be up to 20% [2]. Respiratory viruses, either as a pure or co-infection, can be detected in up to 49% of severe pneumonias. Common culprits in adults include influenza A and B, parainfluenza virus, human metapneumovirus, respiratory syncytial virus, and adenovirus [5, 6]. Much less common viral pathogens include coronaviruses, such as the SARS virus, hantaviruses, parechoviruses, and enteroviruses.

Epidemiologic risk factors are potentially helpful to suggest less common etiologies (Table 20.2). Unfortunately, the sensitivity of these risk factors is so low that empirical antibiotic treatment is usually not warranted; rather, enhanced diagnostic testing to exclude these etiologies is the most prudent response.

Diagnostic Testing

Aggressive diagnostic testing is useful in patients with severe CAP requiring ICU admission. In such patients, the probability of finding a pathogen resistant to usual CAP empirical therapy (e.g. MRSA) is increased, and identification of a specific pathogen can lead to tailored antimicrobials, thus decreasing cost and exposure to unnecessary medications [7].

In a patient invasively ventilated, direct access to the lower respiratory tract provides the opportunity to perform higher yield endotracheal aspirate or bronchoalveolar lavage (BAL) cultures. In a prospective study of 262 patients admitted with CAP, 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 [8].

Blood and sputum cultures have low sensitivity but should still be performed upon transfer to the ICU, even in non-intubated patients. Growth inhibition by prior antibiotics decreases the diagnostic yield of both types of culture but less so when MRSA or Gram-negative bacilli are the etiology [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 remains

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

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

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

positive for over 3 days in patients with *S. pneumoniae* and for weeks with *L. pneumophila* [2]. Although antibiotic sensitivity data cannot be obtained, isolates of these pathogens resistant to usual therapy are actually uncommon and ther-

apy can be appropriately modified to specifically cover either pathogen.

Viral testing is important as viruses are increasing recognized as an important cause of SCAP, particularly in immunocompromised patients. The standard for viral diagnosis is polymerase chain reaction (PCR), often in a multiplex panel. A positive influenza test in a critically-ill patient should be an impetus for antiviral therapy, which can hasten disease resolution and decrease spread. The benefit of a positive assay for viruses other than influenza remains unclear: few have treatment options and antibiotics are rarely held for a viral detection only, given the low sensitivity of testing for bacterial etiologies.

Despite aggressive culture and other routine diagnostic testing, the majority of cases of CAP [9], including SCAP, remain without a definitive etiology. Even when research techniques are routinely used, increased numbers of the usual pathogens are detected, rather than resistant or rare pathogens. PCR testing for usual bacteria is emerging as an option for intubated patients with CAP. PCR is becoming the standard for *Mycoplasma* and *Chlamydomphila*. Recent studies have demonstrated that a MRSA PCR is highly sensitive and avoidance of anti-MRSA treatment is safe when a BAL sample is PCR negative [10]. Multiplex bacterial PCR panels have been approved by the FDA but clinical studies of treatment based on results of these tests is still needed.

Antibiotic Treatment

With severe CAP, timely diagnosis and adequate empirical antimicrobial therapy are paramount. Similar to data from septic shock [11], appropriate antibiotic treatment within 3 h of admission is associated with significantly lower mortality for severe CAP [12].

Adequate coverage of *S. pneumoniae*, methicillin-susceptible *S. aureus* (MSSA) and *L. pneumophila* is crucial and adequate in the absence of risk factors for drug-resistant pathogens. Combination antibiotics with a beta-lactam (ceftriaxone, cefotaxime, or ampicillin-sulbactam) and either a macrolide or fluoroquinolone are strongly recommended [2]. A prospective randomized controlled trial (RCT) in non-ICU inpatients demonstrated improved clinical outcomes for beta-lactam combination therapy compared to monotherapy with the identical beta-lactam [13], confirming multiple observational and retrospective studies showing better clinical outcomes and mortality with combination therapy, especially for bacteremic pneumococcal pneumonia [2].

For MRSA pneumonia, linezolid is superior to vancomycin, particularly if a toxin-secreting community-acquired strain is the culprit [14]. A double-blind RCT comparing linezolid to dose-adjusted vancomycin for treatment of proven MRSA nosocomial pneumonia demonstrated

eradication of MRSA and clinical cure were statistically better with linezolid, with less nephrotoxicity [15]. For MSSA, beta-lactam therapy is still the treatment of choice.

Parapneumonic Effusions

For a CAP-related pleural effusion, chemistry and culture of thoracentesis fluid distinguishes between uncomplicated parapneumonic effusion (UPPE), complicated parapneumonic effusion (CPPE) or empyema [12]. 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 [16, 17]. In contrast, UPPEs are usually exudates with pleural fluid pH > 7.28 and normal glucose. As UPPEs are reactive, they should resolve with appropriate antibiotic therapy.

Optimal therapy for CPPE and empyema hinges on the combination of adequate antibiotic coverage and pleural drainage. If loculations develop, an RCT of intrapleural DNase with concomitant tissue plasminogen activator in patients with empyema showed a lower rate of surgical referral and hospital length of stay than placebo or each agent alone [18]. Lysis of adhesions or decortication via video-assisted thoracoscopic surgery or thoracotomy may be necessary if less invasive measures fail.

Evidence Contour

Several aspects of severe CAP management remain controversial, including the assessment of risk for multidrug resistant (MDR) pathogens, other assessment tools, and adjunctive treatments.

Risk of Multidrug Resistant (MDR) Pathogens

Broad spectrum empirical antibiotic therapy for severe CAP hinges on the risk for drug resistant organisms, such as *Pseudomonas* and MRSA. Several ICU studies suggest this risk is < 5% of patients. Previously, the healthcare-associated pneumonia (HCAP) category was used to identify patients who develop pneumonia outside the hospital yet were at risk for resistant pathogens usually associated with nosocomial pneumonia [19]. HCAP criteria were not originally developed for pneumonia and their use has resulted in significant overtreatment with broad spectrum antibiotics and an associated increased mortality [19, 20]. Conversely, ignoring risk factors is associated with undertreatment and adverse outcomes [7]. 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 [20]. MRSA risk factors were slightly different but overlapped. Importantly, two or more risk factors are required before the frequency of MDR pathogens justifies empirical broad-spectrum therapy, resulting in far less use while still identifying the majority who would need broad-spectrum therapy. New CAP guidelines will offer an alternative to the HCAP criteria but these will also need validation.

Drugs to Suppress Toxin Production

Almost 20% of SCAP patients with documented *S. pneumoniae* die despite no antibiotic resistance [21]. So clearly, antibiotic resistance and/or unusual pathogens are not the major cause of the persistent high SCAP mortality. One explanation is toxin production by more common pathogens, in particular *Staphylococcus* and *Streptococcus* sp.

Gram positive bacteria often produce exotoxins as a component of their pathogenesis. The *S. aureus* Panton-Valentine leukocidin (PVL) exotoxin is a classic example. Presence of PVL may explain the associated neutropenia while other exotoxins, such as α -hemolysin, may result in the characteristic severe pulmonary hemorrhage of both the MRSA and MSSA infections. A community-acquired MRSA (CA-MRSA) clone, distinct from that usually causing nosocomial pneumonia, has emerged as a cause of pneumonia with striking necrotizing features [7]. Antibiotic therapy that also suppresses toxin production provides better outcomes and improved survival, as illustrated in a retrospective study of PVL-positive CAP [14]. Clindamycin and linezolid suppress in vitro formation of PVL, α -hemolysin, and toxic shock syndrome toxin-1, whereas vancomycin and beta-lactams have no effect. The benefit of clindamycin in MSSA isolates resistant by susceptibility testing is unclear, since the correlation of susceptibility with toxin-suppression activity is uncertain. While 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 greater eradication in other MRSA clones.

S. pneumoniae exotoxin production may partially explain the long-standing controversy about the need for macrolide combination therapy, especially for bacteremic or severe CAP cases. Host immunomodulation or concomitant atypical bacterial co-infection have been postulated as the major mechanisms. However, macrolides also suppress production of pneumolysin, a potent exotoxin involved in many of the manifestations of severe pneumococcal disease [22]. This phenomenon may also explain why a macrolide combined

with a fluoroquinolone is also synergistic despite overlapping antibacterial spectrums.

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 [23]. However, the majority of viral pneumonias severe enough to require ICU admission have elevated PCT levels. Whether this reflects occult bacterial superinfection or the pro-inflammatory response to severe viral pneumonia overcoming the interferon suppression is unclear. Persistently elevated PCT levels are associated with adverse outcomes such as the development of pneumonia complications and death [24].

Corticosteroids

Since failure to eradicate a bacterial cause is unusual, death in CAP may result from an inappropriate, perhaps exaggerated, host response to the infection. Investigators have therefore attempted to modulate the inflammatory response in SCAP with corticosteroids. While several small or retrospective studies support corticosteroid administration in SCAP, a larger double-blinded RCT in patients with SCAP (defined as PSI IV or V) failed to show a beneficial effect of corticosteroids [25]. Conversely, in a highly selected group of SCAP patients with very high C-reactive protein levels on admission, use of corticosteroids was associated with less treatment failure [26]. Caution with corticosteroid use is warranted with known influenza pneumonia since worse outcomes have been reported in these cases.

Inappropriate host response can also be immunosuppression, sometimes occult as illustrated by our case. SCAP should warrant consideration of altered host immunity, especially with a family history of death from infection.

Extracorporeal Membrane Oxygenation (ECMO)

Use of ECMO is an emerging issue in SCAP management. ECMO use underwent a resurgence with the 2009 H1N1 influenza pandemic. Recent studies of ECMO include disproportionate numbers of pneumonia compared to other causes of ARDS [27]. The preponderance of pneumonia in ECMO series may be because alveoli filled with a pneumonic infiltrate are less amenable to improvement by higher level PEEP and recruitment maneuvers, including prone positioning.

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