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Major advances in managing community-acquired pneumonia

Waseem Asrar Khan and Mark Woodhead*

Address: Department of Respiratory Medicine, Manchester Royal Infirmary, Manchester

* Corresponding author: Mark Woodhead (mark.woodhead@cmft.nhs.uk)

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Abstract

This article is a non-systematic review of selected recent publications in community-acquired pneumonia, including a comparison of various guidelines. Risk stratification of patients has recently been advanced by the addition of several useful biomarkers. The issue of single versus dual antibiotic treatment remains controversial and awaits a conclusive randomized controlled trial. However, in the meantime, there is a working consensus that more severe patients should receive dual therapy.

Epidemiology / risk factors

A knowledge of the risk factors for community-acquired pneumonia and those at risk of worse outcomes is important in management of the disease. Mental illness and use of benzodiazepines and angiotensin converting enzyme inhibitors have recently been highlighted as possibly having a causal link with pneumonia [1-3].

Aetiology

Aetiology worldwide

Periodic studies of community-acquired pneumonia microbial aetiology are vital to confirm whether causal pathogen frequencies have, or have not, changed to guide empirical antibiotic therapy strategies. A prospective population-based study in Spain of both inpatients and outpatients found that *Streptococcus pneumoniae* (55.7%) was the most common agent, followed by *Coxiella burnetii* (18.5%), *Mycoplasma pneumoniae* (15.9%), respiratory viruses (14.4%), Chlamydia species (10.6%) and *Legionella pneumophila* (4.4%) [4]. The microbiology of community-acquired pneumonia appears to be unchanged from that found in earlier studies. The high prevalence of C. *burnetii* has been reported in previous studies from Spain. Patients infected with conventional bacteria such as *S. pneumoniae* had a higher hospitalization rate, higher CURB65 (disease severity) scores at admission and more adverse clinical outcomes, such as severe sepsis, septic shock, ICU admission and longer length of stay compared to those with atypical and viral causes of pneumonia. Limitations in the study included an absence of sputum cultures and possible population bias.

Outpatient community-acquired pneumonia

A total of 568 outpatient community-acquired pneumonia episodes in Barcelona were recently studied [5]. Aetiology was established in a third of these cases and S. *pneumoniae* was again the most common proven pathogen, followed by mycoplasma and then legionella.

Viral causes

In another study, the data for 198 patients were analysed from a prospective cohort of community-acquired pneumonia or healthcare-associated pneumonia in a 28-bed medical intensive care unit (ICU) [6]. These were patients that were severe enough to be admitted to the intensive care unit. The breakdown was that 35% of patients had a bacterial infection and 36% had a viral infection. Of the latter, the following viruses were identified – rhino virus (23.6%), para influenza virus (20.8%), human metapneumovirus (18.1%), influenza virus (16.7%), and respiratory syncytial virus (13.9%). Mortalities of patients with bacterial, viral, and bacterial-viral co-infections were similar. Limitations of the study included a reliance on upper respiratory specimens. Lack of pharmacological therapies for most viral causes limits the value of this information at the current time.

Novel coronavirus

A recent case report in Saudi Arabia has led to the discovery of a sixth new coronavirus. The patient had pneumonia and acute respiratory distress syndrome with multi-organ dysfunction syndrome and died 11 days after admission [7]. This has also been recently referred to as the Middle East respiratory syndrome coronavirus.

Human Coronavirus-Erasmus Medical Center (HCoV-EMC) is the first human corona virus in lineage C of the betacoronavirus genus. Its closest relatives are coronaviruses HKU4 and HKU5 found in bats. Additional cases in the Middle East have raised concerns over the potential for more widespread dissemination.

Influenza viruses

Bacterial co-infection was present in 33% of 128 consecutive adult patients hospitalized with a diagnosis of influenza A (H1N1) and community-acquired pneumonia. Predictors of bacterial co-infection included underlying chronic obstructive pulmonary disease (COPD) and a higher platelet count at admission. Bacterial co-infection was not related to increased mortality [8].

H5N1 continues to cause sporadic human infections in Egypt and South East Asia, but more alarming is the recent emergence of H7N9 as a cause of human illness [9]. Cases reported so far suggest a link with birds as the source with little or no human-to-human spread. Severe multi-organ failure with mortality of about one third is reported [10].

Severity scores

All guidelines recommend severity scoring tools in conjunction with clinical assessment in adult community-acquired pneumonia management, although controversy remains about which scoring system to use and when to use it.

PSI score

Recent systematic reviews showed that all of the standard scoring methods of the pneumonia severity index (PSI), CURB65, and CRB65 showed moderate to good accuracy in predicting 30-day mortality in these patients and risk of death [11] (see Tables 1 and 2 for more details). PSI appeared to have a significant advantage in terms of its negative likelihood ratio, therefore indicating its superior ability at identifying low risk patients.

CURB65

A higher positive predictive value than the PSI system suggests that CURB65/CRB65 may be superior for identifying high-risk patients in terms of mortality and decisions with regards to admission of high-risk patients (see Table 3 for more details).

Table 1. PSI scoring

Criteria	Points	Add/subtract points
General		
a) Age in years	1 point per year	Add
b) Gender	10 points for women	Subtract
c) Nursing home resident	10 points	Add
Past medical history		
a) Cancer	30 points	Add
b) Liver disease	20 points	Add
c) CHF	10 points	Add
d) CVA	10 points	Add
e) CKD	10 points	Add
Examination findings		
a) Altered consciousness	20 points	Add
b) Breathing rate >30 rpm	20 points	Add
c) Systolic BP <90 mmHg	20 points	Add
d) Temperature not 95-104 F(35-40 C)	15 points	Add
e) Heart rate > 125 bpm	10 points	Add
Labs: arterial blood gas (ABG)		
a) Arterial pH <7.35	30 points	Add
b) PaO2 <60 mmHg (<90% O2 SATS)	10 points	Add
Labs: Serum Chemistry		
a) Serum sodium <130 mEq/L	20 points	Add
b) Blood urea nitrogen (BUN) >64 mg/dl	20 points	Add
c) Serum glucose >250 mg/dl	10 points	Add
Labs: blood count		
a) Haematocrit <30%	10 points	Add
Other		
a) Chest Xray- pleural effusion	10 points	Add

Abbreviations: CHF, congestive heart failure; CVA, cerebrovascular accident; CKD, chronic kidney disease

Table 2. Scoring and interpretation of PSI scoring

Scoring	Interpretation
Class 1: Points 0: Mortality 0.1% (low risk)	Outpatient management
Class 2: Points <70: Mortality 0.6% (low risk)	Outpatient management
Class 3: Points 71-90: Mortality 2.8% (low risk)	Consider short observation hospital stay
Class 4: Points 91-130: Mortality 8.2% (moderate risk)	Inpatient management
Class 5: Points >130: Mortality 29.2% (high risk)	Inpatient management

Table 3. Explanation of CURB scoring

CURB scoring	Points added
Confusion of new onset (defined as an abbreviated mental test score of 8 or less)	1 point
Urea greater than 7 mmol/l	1 point
Respiratory rate of 30 breaths per minute or greater	1 point
Blood pressure less than 90 mmHg systolic or diastolic blood pressure 60 mmHg or less	1 point
Age **65** or older	1 point

The risk of death at 30 days increases as the score increases: 0 points—0.7%, 1 point—3.2%, 2 points—13.0%, 3 points—17.0%, 4 points—41.5%, 5 points—57.0%

CURB65-guided antibiotic therapy was associated with a significant decrease in broad-spectrum antibiotic use. The intervention was safe with no impact on mortality, treatment failure or clinical response [12].

CRB-65

A recent study of the CRB65 score investigated whether it was useful in patients with lower respiratory tract infection in a primary care setting but showed that it had little correlation with severe symptom duration or hospitalisation [13]. In this study, however, respiratory rate and blood pressure were infrequently measured (22.7% and 31.9% respectively), suggesting that clinical practice would have to change if this score were to be used routinely.

Another study of CRB65 score investigated whether the cut off age of 65 had any impact in terms of severity of patients presenting with pneumonia [14]. This study included nearly 700,000 patients hospitalised in Germany between 2008 and 2010. The age of 65 (resulting in CRB≥65) was a reasonable threshold for the assessment of the risk of death from community-acquired pneumonia in the total population, although age group 80 (CRB≥80) had the highest risk of death [14]. In patients aged less than 65 years, death prediction was best below age of 50, with excellent prediction of low-risk patients. In patients aged 65 or over with nursing home-acquired pneumonia, the optimal age group for death prediction continued to be 80 (CRB≥80).

ATS / IDSA severity criteria

The American Thoracic Society-Infectious Diseases Society of America (ATS-IDSA) rule consists of two major (mechanical ventilation or shock) and nine minor criteria. The rule is considered positive in the presence of one major or three minor criteria. A meta-analysis found the ATS minor criteria, S-community-acquired pneumonia score, and SMART-COP to have good predictive characteristics for ICU admission [15].

Biomarkers

Serum glucose

A recent predictive cohort study [16] found that an increased serum glucose level at admission to hospital and no pre-existing diabetes was a predictor of death at 28 and 90 days in 6891 patients with community-acquired pneumonia. Whether this adds to the use of a scoring system and whether blood glucose management alters the outcome in community-acquired pneumonia is not known. Although the PSI scoring system includes serum glucose, this paper investigated serum glucose as an independent risk factor in predicting death in patients with community-acquired pneumonia.

Procalcitonin

A systematic review of procalcitonin as a prognostic marker in community-acquired pneumonia found that complications during admission, severity of disease and death within a month correlated with high levels of procalcitonin but no definite cut off level was found. Procalcitonin with a cut-off point of 0.15 ng/ml was the best predictor for bacterial aetiology and to select patients eligible for outpatient care in another study [17]. They suggested that levels of procalcitonin and C reactive protein positively correlate with increasing severity of community-acquired pneumonia and may have a role in disease prediction, perhaps in patients with low CURB65 scores [18]. Limitations of the study included study heterogeneity and risk of publication bias. Using a procalcitonin algorithm on antibiotic guidance reduced antibiotic use without increased complications. Good compliance with the procalcitonin algorithm was possible in real-life conditions but had to be reinforced by other measures to achieve an optimal benefit [19]. Limitations here included observational design and unclear diagnostic criteria.

Pro-adrenomedullin

Another recent study showed that increased pro-adrenomedullin (proADM) levels closely correlated with increased severity scores and showed a predictive power in both long and short term complications in patients with community-acquired pneumonia, especially when used in conjunction with PSI and CURB65. An admission proADM level of 0.646 nmol correlated in such a fashion that 92% of the 139 patients in PSI classes 4 and 5 would have been correctly classified [20]. This was a single hospital study and serial biomarkers were not used throughout the study. Another study also reflected that proADM may be helpful in individual risk stratification of community-acquired pneumonia patients with a high PSI score in the Emergency Department, allowing better identification of patients at risk of death [21].

IL-6, IL-10 and lipopolysaccharide-binding protein

The highest levels of IL-6, IL-10 and lipopolysaccharide-binding protein (LBP) correlated best with a CURB65 score of 3 and 4 and the accuracy of CURB65 was greatly enhanced by the use of IL-6 levels [22]. These are best used as a predictor of severity of community-acquired pneumonia rather than prognosis.

Serum cortisol

Serum cortisol level predicts mortality and critical disease independently of clinical scores and inflammatory biomarkers. A recent study showed that increased serum cortisol level was associated with the development of critical disease and increased 30-day-mortality in

hospitalised community-acquired pneumonia-patients. Serum cortisol level improved the predictive power of the CRB65 score and showed independent prognostic significance [23]. The main limitation of the study was that controlling for the time point of blood sampling could not be done, so diurnal concentration changes may have influenced the results.

Management

Guidelines

See Table 4 for a comparison of selected features in National and International community-acquired pneumonia Guidelines, drawn from [24-26].

Risk stratification and admission to ICU

ATS/IDSA

These guidelines make it quite clear that severity illness scores such as CURB65 and PSI should be used to identify patients for outpatient management. Physicians are advised to take into account factors such as availability of outpatient support resources. CURB65 scores ≥2 suggest hospital admission. Direct admission to ICU should be made upon factors such as septic shock requiring vasopressor support and /or respiratory failure requiring intubation and ventilation.

British thoracic society

The British Thoracic Society (BTS) guidelines are quite clear that the scoring system of CURB65 in conjunction with clinical assessment is the main requirement in deciding point of care admission of community-acquired pneumonia patients. Those with a score of CURB65 0 or 1 can be managed quite safely as outpatients. Patients with CURB65 score of 2 should be considered for hospital admission, as there is a significant increase in mortality with this group. Those with CURB65 scores of 3 and above should be reviewed by senior clinicians, and patients with CURB65 scores of 4 and above should be seriously considered for ICU admission. Persistent hypoxia, progressive hypercapnoea, shock or reduced consciousness are indications for transfer to critical care.

European respiratory society / european society of clinical microbiology and infectious diseases

These guidelines make it very clear that the decision to hospitalise community-acquired pneumonia patients is a clinical decision. A CRB score of 1 or more (except if age ≥65 is the only criterion met) suggests that hospitalisation should be considered. Factors such as acute respiratory failure, septic shock and decompensated comorbidities should be considered for early referral to intensive care.

Antibiotics – dual vs single

There has always been a debate with regards to the value of single (B-lactam or macrolide) versus dual (B-lactam plus macrolide) antibiotic therapy – a question that has never been addressed by a good-quality randomised controlled trial.

Although there are some differences in the antibiotics recommended for first-line treatment in the Guidelines (Table 4) there is consensus that patients with more severe community-acquired pneumonia should be given dual therapy. A total of 23 studies with approximately 137,000 patients were included in a recent meta-analysis of the efficacy of macrolides in patients hospitalised with community-acquired pneumonia [27]. Macrolide-based regimens were associated with a significant 22% reduction in mortality compared to non-macrolides.

Table 4. Recommended community-acquired pneumonia therapy and management from published international guidelines

	BTS guidelines [24]	ATS/IDSA guidelines [25]	ERS/ESCMID guidelines [26]
Low severity patients*	Use CURB65 score with clinical judgement Treat with oral amoxicillin or (doxycycline or clarithromycin if hypersensitive).	Use CURB65 or PSI score to guide Outpatient treatment Stratify by risk for drug resistant *S. pneumoniae* Low risk: Treat with macrolide or doxycycline High risk: Treat with respiratory fluoroquinolone or b-lactam+macrolide	Use CRB65 to guide Outpatient treatment Treat with one of: aminopenicillin ± macrolide Aminopenicillin/b-lactamase inhibitor ± macrolide Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone ± macrolide Levofloxacin Moxifloxacin Penicillin g ± macrolide
Moderate/high severity patients*	CURB65 score 3 or more consider ICU Treat with β-lactam plus macrolide iv	Consider ICU for sepsis or >2 minor severity criteria Increased Comorbidities or prior antimicrobials (within 3 months) treat with respiratory fluoroquinolone or beta lactam plus macrolide iv	Consider ICU for respiratory failure or sepsis or >2 minor severity criteria Stratify by risk for *Pseudomonas aeruginosa* Non-antipseudomonal treat with cephalosporin III + macrolide Or Moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III

*These are not necessarily the terms used in the guidelines but give a broad translation of what the guidelines state.

However, this benefit did not extend to randomised controlled trials or patients that received guideline-concordant antibiotics (also found in a study of community-acquired pneumonia patients with severe sepsis [26]). Guideline-concordance may be more important than choice of antibiotic when treating community-acquired pneumonia [28].

Both studies point towards the need for good adherence to hospital prescribing guidelines. A very careful study conducted in 2007 came to a verdict that the benefit of dual therapy versus single therapy cannot be reliably assessed in observational studies, since the propensity to prescribe these regimens differs markedly [29]. Taking this into account may skew the results of previous studies comparing single and dual therapy.

A total of 5240 patients were included in an audit of adult community-acquired pneumonia management in the UK [30]. The death rate was high at 24%. Patients treated with dual therapy had a significantly lower death rate in both moderate- and high-severity groups compared with β-lactam therapy alone.

As in other studies, the propensity to prescribe could not be corrected for. The concordance of findings with other cohort studies may suggest a real result, but randomized controlled trial results are required to confirm this.

Corticosteroids

These have often been an intervention of last resort in the failing patient. Studies in meningitis and pneumocystis pneumonia support their role in infection control but, until recently, studies in community-acquired pneumonia were absent. The conflicting results from studies in sepsis confirmed the need for community-acquired pneumonia-specific studies, preferably randomised controlled trials. A recent double blind, placebo-controlled randomized controlled trial using 40 mg prednisolone for 7 days as the intervention found that there were no beneficial effects of adjunctive corticosteroids in patients hospitalized with community-acquired pneumonia. Other outcomes of the study showed that clinical cure was equal in both groups at Day 7 [31]. A similar study using dexamethasone for 3 days did find a reduced hospital stay of one day in the steroid-treated patients, but a large number of exclusions and lack of control for other factors limiting length of stay limited the usefulness of this study [32]. The only other randomised controlled trial evaluating patients with community-acquired pneumonia admitted to ICU found a reduction in mortality using hydrocortisone [33]. The small patient number and absence of any deaths in the intervention arm mean that these findings cannot be generalised unless reproduced in other studies. A role for steroids in patients with community-acquired pneumonia is yet to be proved.

Process of care – choice of quality indicators

Pay for performance programs are being adopted internationally to try and improve patient outcomes with limited evidence of their effectiveness. One reason for this may be lack of robust evidence to support the quality indicators used [34]. Conversely, in a US study of 2076 patients, there was no association with either individual or combinations of quality indicator compliance and mortality [35]. In a study of 30-day inpatient mortality amongst 143,435 adults admitted with pneumonia, heart failure, or acute myocardial infarction to 24 UK hospitals covered by a pay-for-performance program [36], an association between use of the program and significant mortality reduction was found when compared to other UK hospitals not using the pay-for-performance program. Of the three included conditions, however, only pneumonia was found to have an association with mortality reduction in the pay-for-performance group [36].

Not only are the quality measures controversial but so are the methods of implementation. A randomized controlled trial investigated the implementation of a three-step strategy of early mobilisation, objective criteria for switching to oral therapy and for deciding on hospital discharge, and showed interesting results [37]. The use of a three-step critical pathway was safe and effective in reducing the duration of intravenous antibiotic therapy and length of hospital stay for community-acquired pneumonia patients and this did not adversely affect patient outcomes [37]. The jury is still out with regards to performance-related programmes but there is a need to develop further randomised controlled trials.

Summary and future directions

The last few years have seen some major advances in the management of community-acquired pneumonia. Risk stratification of patients has recently been advanced by the addition of several useful biomarkers. The issue of single versus dual antibiotic treatment remains controversial and awaits a conclusive randomized controlled trial. However, in the meantime, there is a working consensus that more severe patients should receive dual therapy.

Abbreviations

ATS-IDSA, American Thoracic Society-Infectious Diseases Society of America; BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; HCoV-EMC, Human Coronavirus-Erasmus Medical Center; ICU, intensive care unit; LBP, lipopolysaccharide-binding protein; proADM, pro-adrenomedullin; PSI, pneumonia severity index.

Disclosure

"The authors declare that they have no disclosures."

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