

## Respiratory Review of 2012: Pneumonia

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Pneumonia is the cause of significant morbidity and mortality, despite advances in diagnosis and antibacterial treatment. Pneumonia is often misdiagnosed and mistreated up until recently. Recent classification of pneumonia consists of community-acquired pneumonia, health care-associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia. The etiology, risk factors, and treatment are different among them. This article briefly introduces new concepts and ideas in biomarkers, diagnosis, treatment, prognosis, and prevention of pneumonia during the past 2 years. One of the most frequent subjects of recent papers was those about pandemic H1N1 in 2009.

**Key Words:** Pneumonia; Diagnosis; Therapeutics; Prognosis; Prevention and Control

### Introduction

Pneumonia is still the leading disease of infectious cause despite many efforts in diminishing of morbidity and mortality. In the past, pneumonia was usually classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP). Nowadays, a new category of pneumonia-termed health care-associated pneumonia (HCAP) was proposed because some outpatients had potential of multidrug-resistant (MDR) pathogens same as HAP. However, some challenge for this concept for HCAP has emerged. Numerous papers about novel biomarkers, diagnostic technology, classification, antimicrobial agents, treatment, prognosis, and vaccines were published for the past 2 years. In this article, several recent clinical studies about novel bio-

markers, prevention and treatment of CAP, epidemiology for HCAP and HAP, and ventilator associated tracheobronchitis (VAT), will be discussed.

### Community Acquired Pneumonia (CAP)

CAP is a common and potentially serious illness that is associated with high morbidity and mortality. Only half of the cases had an etiology microorganism identified. Bacteria are the most common identifiable cause, and among them, *Streptococcus pneumoniae* is the single most common bacterium responsible. Antibiotic therapy is usually begun empirically, because the causative organism is not identified in a proportion of patients<sup>1</sup>. Mortality of pneumonia in Korea is about 9.4 persons per 100,000 in 2006, which is the highest among mortality due to infectious diseases<sup>2</sup>.

#### 1. Biomarker

1) Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. Bello S, et al.<sup>3</sup> Eur Respir J 2012;39:1144-55

Biomarkers are useful in community-acquired pneumonia (CAP). Recently, midregional (MR) proadrenomedullin

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Received: Jun, 26, 2012

Revised: Jul, 2, 2012

Accepted: Jul, 6, 2012

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(proADM) has been shown to be of potential prognostic use. We sought to determine whether this prognostic role depends on the cause of CAP. We conducted a prospective cohort study of immunocompetent patients with CAP. Pneumonia Severity Index (PSI) and CURB-65 score (confusion (abbreviated mental test score of  $\leq 8$ ), urea  $\geq 7$  mol/L, respiratory rate  $\geq 30$  breaths/min, blood pressure  $< 90$  mmHg systolic or  $< 60$  mmHg diastolic, and age  $\geq 65$  yrs), blood C-reactive protein, procalcitonin, MR-proADM, and microbiological studies were systematically performed. Patients were grouped as bacterial, viral/atypical and mixed CAP, and were followed up at 30, 90 and 180 days, and 1 yr. We recruited 228 CAP patients. Identification of at least one pathogen was achieved in 155 (68%) patients. MR-proADM levels closely correlated with increasing severity scores, and showed an important predictive power for complications and short- and long-term mortality (1 yr). Its addition to PSI and CURB-65 significantly improved their prognostic accuracy. A MR-proADM cutoff of 0.646 nmol/L identified 92% of patients scored as PSI classes IV and V as high risk. MRproADM outcome prediction power was not affected by different aetiologies. MR-proADM has high short- and long-term prognostic accuracy, and increases the accuracy of clinical scores. The prognostic value of MR-proADM is not modified by different possible CAP aetiologies.

**2) Comments:** Clinical severity scores, the Pneumonia Severity Index (PSI)<sup>4</sup>, and CURB-65 score<sup>5</sup>, are the most frequently used tools for evaluating CAP-associated risk of mortality. Traditionally biomarkers of infection for diagnostic and prognostic purposes have widely been used such as white blood cell count and C-reactive protein (CRP) but their prediction of risk in CAP is limited. Recently hormone such as procalcitonin has increasing evidence for better diagnosis and guiding antibiotic therapy, and assessing severity<sup>6</sup>. Also, MR-proADM has been shown to be potential biomarker to predict severe complication, mortality and risk stratification of clinical scores<sup>7</sup>. In this study by Bello et al.<sup>3</sup>, MR-proADM levels showed considerable prognostic value with/without clinical severity scores such as PSI and CURB-65 in-

dependently of etiology of CAP. Although this study didn't show that MR-proADM discriminated the etiology of CAP, ProADM could be used for the identification of patients with a high risk of mortality that be needed a more rapid initiation of appropriate therapy.

## 2. Prevention

1) **Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine.** Smith KJ, et al.<sup>8</sup> JAMA 2012;307:804-12

**Context** The cost-effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) compared with 23-valent pneumococcal polysaccharide vaccine (PPSV23) among US adults is unclear.

**Objective** To estimate the cost-effectiveness of PCV13 vaccination strategies in adults.

**Design, Setting, and Participants** A Markov state-transition model, lifetime time horizon, societal perspective. Simulations were performed in hypothetical cohorts of US 50-year-olds. Vaccination strategies and effectiveness estimates were developed by a Delphi expert panel; indirect (herd immunity) effects resulting from childhood PCV13 vaccination were extrapolated based on observed PCV7 effects. Data sources for model parameters included Centers for Disease Control and Prevention Active Bacterial Core surveillance, National Hospital Discharge Survey and Nationwide Inpatient Sample data, and the National Health Interview Survey.

**Main Outcome Measures** Pneumococcal disease cases prevented and incremental costs per quality-adjusted life-year (QALY) gained.

**Results** In the base case scenario, administration of PCV13 as a substitute for PPSV23 in current recommendations (ie, vaccination at age 65 years and at younger ages if comorbidities are present) cost \$28 900 per QALY gained compared with no vaccination and was more cost-effective than the currently recommended PPSV23 strategy. Routine PCV13 at ages 50 and 65 years cost \$45 100 per QALY compared with PCV13 substituted in current recommendations. Adding PPSV23 at age 75 years to PCV13 at ages

50 and 65 years gained 0.00002 QALYs, costing \$496 000 per QALY gained. Results were robust in sensitivity analyses and alternative scenarios, except when low PCV13 effectiveness against nonbacteremic pneumococcal pneumonia was assumed or when greater childhood vaccination indirect effects were modeled. In these cases, PPSV23 as currently recommended was favored.

**Conclusion** Overall, PCV13 vaccination was favored compared with PPSV23, but the analysis was sensitive to assumptions about PCV13 effectiveness against nonbacteremic pneumococcal pneumonia and the magnitude of potential indirect effects from childhood PCV13 on pneumococcal serotype distribution.

**2) Comments:** Current recommendations by US Advisory Committee on Immunization Practices (ACIP) are for immunization of persons 2 years and older with conditions at increased risk of serious pneumococcal infections and all persons 65 years and older with 23-valent pneumococcal polysaccharide vaccine (PPSV23)<sup>9</sup>. Although most studies show that PPSV23 has at least moderate effectiveness in preventing invasive pneumococcal disease (IPD), its effectiveness in preventing nonbacteremic pneumococcal pneumonia (NPP), which is at least 10 times more common than IPD, appears to be limited. In 2000, 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for routine childhood immunization. In 2010, PCV13 replaced PCV7 for routine childhood immunization. Also PCV13 has recently been approved by the Food and Drug Administration for use among adults aged 50 years and older<sup>10</sup>. However, the effectiveness of PCV13 in preventing NPP in adults is unclear and clinical trials are ongoing. Routine childhood vaccination with PCV13 might have potential further indirect effects in adults. This study by Smith et al.<sup>8</sup> suggests that PCV13 instead of PPSV23 for routine immunization of adults, favor in prevention against pneumococcal disease in an economically reasonable fashion. But they need two assumptions. First, PCV13 would be effective in preventing NPP in adults and secondly herd immunity effect from childhood PCV13 would not been greater. In the future, improve-

ments in vaccines against pneumococci and increased rates of immunization in community will bring reductions in the incidence of pneumococcal disease.

### 3. Treatment

1) Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomized, double-blind, placebo-controlled trial. Meijvis SC, et al.<sup>11</sup> *Lancet* 2011;377:2023-30

**Background** Whether addition of corticosteroids to antibiotic treatment benefits patients with community-acquired pneumonia who are not in intensive care units is unclear. We aimed to assess effect of addition of dexamethasone on length of stay in this group, which might result in earlier resolution of pneumonia through dampening of systemic inflammation.

**Methods** In our double-blind, placebo-controlled trial, we randomly assigned adults aged 18 years or older with confirmed community-acquired pneumonia who presented to emergency departments of two teaching hospitals in the Netherlands to receive intravenous dexamethasone (5 mg once a day) or placebo for 4 days from admission. Patients were ineligible if they were immunocompromised, needed immediate transfer to an intensive-care unit, or were already receiving corticosteroids or immunosuppressive drugs. We randomly allocated patients on a one-to-one basis to treatment groups with a computerised randomization allocation sequence in blocks of 20. The primary outcome was length of hospital stay in all enrolled patients. This study is registered with ClinicalTrials.gov, number NCT00471640.

**Findings** Between November, 2007, and September, 2010, we enrolled 304 patients and randomly allocated 153 to the placebo group and 151 to the dexamethasone group. 143 (47%) of 304 enrolled patients had pneumonia of pneumonia severity index class 4-5 (79 [52%] patients in the dexamethasone group and 64 [42%] controls). Median length of stay was 6.5 days (IQR 5.0-9.0) in the dexamethasone group compared with 7.5 days (5.3-11.5) in the placebo group (95% CI of difference in medians 0-2 days; p=0.0480). In-hospital mortality and severe adverse events

were infrequent and rates did not differ between groups, although 67 (44%) of 151 patients in the dexamethasone group had hyperglycaemia compared with 35 (23%) of 153 controls ( $p < 0.0001$ ).

**Interpretation** Dexamethasone can reduce length of hospital stay when added to antibiotic treatment in non-immunocompromised patients with community-acquired pneumonia.

2) **Comments:** Early diagnosis and rapid initiation of appropriate antibiotics is most important in treatment for CAP<sup>12</sup>. There are many studies to use corticosteroid in severe pneumonia and sepsis because dexamethasone is lowering of the cytokine response. But recent guideline for sepsis recommend not to use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine function isn't intact or patients has corticosteroid history<sup>13</sup>. The effect of corticosteroids in addition to antibiotics in patients with CAP who are admitted to general ward is unclear. In this article, the authors suggested the early use of dexamethasone in immunocompetent patients could reduce the length of hospital stay and costs despite increase of hyperglycemia.

### Hospital-Acquired Pneumonia (HAP)

HAP, VAP, and HCAP remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide-range of preventive measures. HAP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission, VAP refers to pneumonia that arises more than 48~72 hours after endotracheal intubation, HCAP includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic<sup>14</sup>.

### 1. Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. Ewig S, et al.<sup>15</sup> Thorax 2012;67:132-8

**Objective** To determine differences in aetiologies, initial antimicrobial treatment choices and outcomes in patients with nursing-home-acquired pneumonia (NHAP) compared with patients with community-acquired pneumonia (CAP), which is a controversial issue.

**Methods** Data from the prospective multicenter Competence Network for Community-acquired pneumonia (CAPNETZ) database were analysed for hospitalized patients aged  $\geq 65$  years with CAP or NHAP. Potential differences in baseline characteristics, comorbidities, physical examination findings, severity at presentation, initial laboratory investigations, blood gases, microbial investigations, aetiologies, antimicrobial treatment and outcomes were determined between the two groups.

**Results** Patients with NHAP presented with more severe pneumonia as assessed by CRB-65 (confusion, respiratory rate, blood pressure, 65 years and older) score than patients with CAP but received the same frequency of mechanical ventilation and less antimicrobial combination treatment. There were no clinically relevant differences in aetiology, with *Streptococcus pneumoniae* the most important pathogen in both groups, and potential multi-drug-resistant pathogens were very rare ( $< 5\%$ ). Only *Staphylococcus aureus* was more frequent in the NHAP group ( $n=12$ , 2.3% of the total population, 3.1% of those with microbial sampling compared with 0.7% and 0.8% in the CAP group, respectively). Short-term and long-term mortality in the NHAP group was higher than in the CAP group for patients aged  $\geq 65$  years (26.6% vs 7.2% and 43.8% vs 14.6%, respectively). However, there was no association between excess mortality and potential multi-drug-resistant pathogens.

**Conclusions** Excess mortality in patients with NHAP cannot be attributed to a different microbial pattern but appears to result from increased comorbidities, and consequently, pneumonia is frequently considered and managed as a terminal event.

1) **Comments:** NHAP is associated with higher mortality than CAP. Data from the USA showed an excess of MDR pathogens in patients with HCAP and the guideline of HAP in 2005 included HCAP as HAP<sup>14</sup>. But recent studies has revealed this higher mortality rate in HCAP was not related to different etiologies including potential MDR pathogens and inadequate use of initial antibiotics but underlying condition<sup>16</sup>. NHAP is a main subclass of HCAP. Therefore this article by using data from the prospective multicenter Competence Network for Community-acquired pneumonia (CAPNETZ) database in German for hospitalized patients aged  $\geq 65$  years with CAP or NHAP for 8 years showed that excess mortality didn't associate with potential multidrug-resistant pathogens but patient's functional status and treatment restriction. Similarly, other article conducted in UK for patients with HCAP revealed that increased mortality was primarily related to patient's underlying factors rather than MDR pathogens<sup>17</sup>. The other European cohort study demonstrated that antibiotic resistance little influenced on the overall effect of HCAP in patients admitted to intensive care unit<sup>18</sup>.

## 2. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia, Chung DR, et al.<sup>19</sup> Am J Respir Crit Care Med 2011;184:1409-17

**Rationale:** Hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) remain important causes of morbidity and mortality. Increasing antimicrobial resistance has aroused the concern of the failure of antibiotic treatment.

**Objectives:** To determine the distribution of the bacterial isolates of HAP and VAP, their antimicrobial resistance patterns, and impact of discordant antibiotic therapy on clinical outcome in Asian countries.

**Methods:** A prospective surveillance study was conducted in 73 hospitals in 10 Asian countries from 2008-2009. A total of 2,554 cases with HAP or VAP in adults were enrolled and 2,445 bacterial isolates were collected from 1,897 cases. Clinical characteristics and antimicrobial resistance profiles were analyzed.

**Measurement and Main Results:** Major bacterial isolates from HAP and VAP cases in Asian countries were *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Imipenem resistance rates of *Acinetobacter* and *P. aeruginosa* were 67.3% and 27.2%, respectively. Multidrug-resistant rates were 82% and 42.8%, and extensively drug-resistant rates were 51.1% and 4.9%. Multidrug-resistant rate of *K. pneumoniae* was 44.7%. Oxacillin resistance rate of *S. aureus* was 82.1%. All-cause mortality rate was 38.9%. Discordant initial empirical antimicrobial therapy increased the likelihood of pneumonia-related mortality (odds ratio, 1.542; 95% confidence interval, 1.127-2.110).

**Conclusions:** *Acinetobacter* spp., *P. aeruginosa*, *S. aureus*, and *K. pneumoniae* are the most frequent isolates from adults with HAP or VAP in Asian countries. These isolates are highly resistant to major antimicrobial agents, which could limit the therapeutic options in the clinical practice. Discordant initial empirical antimicrobial therapy significantly increases the likelihood of pneumonia-related mortality.

1) **Comments:** Increasing antimicrobial resistance increased the failure rate of antibiotic treatment for HAP and VAP. The resistant pattern is different in each area. In Asia, the distribution of the bacterial isolates of HAP and VAP and their antimicrobial resistance patterns were not well known. This prospective surveillance study, conducted in 73 hospitals in 10 Asian countries including Korea, China, Hong Kong, Taiwan, Thailand, Philippines, Malaysia, Singapore, Indonesia, and India from 2008~2009, showed the distribution of the bacterial isolates of HAP and VAP and their antimicrobial resistance patterns in Asia. Asian countries had *Acinetobacter* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* and high multidrug resistance. Relatively, *Acinetobacter* spp. isolated 4.8% and 5.6% each from patients with HAP in the United States and Europe<sup>20</sup>. Interestingly, in Korea, *S. aureus* was the most frequent isolate in both HAP (30.7%) and VAP (26.6%), followed by *P. aeruginosa* (14.3% and 14.1% in HAP and VAP, respectively) and *Acinetobacter*

spp. (10% and 15.6%). Similar with previous study, discordant initial empirical antimicrobial therapy is important variable in pneumonia-related mortality. Therefore, the authors suggest that new distinct therapeutic guidelines for HAP and VAP are needed separately in Asia.

### 3. Ventilator-associated tracheobronchitis in a mixed surgical and medical ICU population, Dallas J, et al.<sup>21</sup> Chest 2011;139:513-8

*Background:* Ventilator-associated tracheobronchitis (VAT) is considered an intermediate condition between bacterial airway colonization and ventilator-associated pneumonia (VAP). The purpose of this prospective cohort study was to further characterize VAT in terms of incidence, etiology, and impact on patient outcomes.

*Methods:* Patients intubated for > 48 h in the surgical and medical ICUs of Barnes-Jewish Hospital were screened daily for the development of VAT and VAP over 1 year. Patients were followed until hospital discharge or death, and patient demographics, causative pathogens, and clinical outcomes were recorded.

*Results:* A total of 28 patients with VAT and 83 with VAP were identified corresponding to frequencies of 1.4% and 4.0%, respectively. VAP was more common in surgical than medical ICU patients (5.3% vs 2.3%;  $P < .001$ ), but the occurrence of VAT was similar between surgical and medical patients (1.3% vs 1.5%;  $P = .845$ ). VAT progressed to VAP in nine patients (32.1%) despite antibiotic therapy. There was no significant difference in hospital mortality between patients with VAP and VAT (19.3% vs 21.4%;  $P = .789$ ). VAT was caused by a multidrug-resistant (MDR) pathogen in nine cases (32.1%).

*Conclusion:* VAT occurs less commonly than VAP but at a similar incidence in medical and surgical ICU patients. VAT frequently progressed to VAP, and patients diagnosed with VAT had similar outcomes to those diagnosed with VAP, suggesting that antimicrobial therapy is appropriate for VAT. VAT is also frequently caused by MDR organisms, and this should be taken into account when choosing antimicrobial therapy.

1) **Comments:** VAT is a new disease concept as an intermediate condition between bacterial airway colonization and VAP<sup>22</sup>. There is controversy whether VAP is a simple colonization or precursor of VAP. There are not many studies about VAT to define the diagnosis criteria or to characterize its incidence and outcomes. This prospective cohort study defined VAT as the presence of all of the following in a patient intubated with endotracheal tube and receiving mechanical ventilation for >48 hours: body temperature >38.3°C or <36.0°C, new or increased purulent tracheal secretions, positive culture of tracheal secretions at a concentration of  $\geq 10^5$  cfu/mL, and no new or progressive infiltrate on portable chest radiograph. Although incidence of VAT in this study, which was 1.4%, was much lower than that of a previous randomized study where the incidence of VAT was 10.6%, this study by Dallas et al.<sup>21</sup> demonstrated VAT could progress to VAP and further suggested the use of antibiotics treatment and identification of multidrug resistant pathogens in VAT. Further studies are necessary to determine patients with VAT who would need antimicrobial therapy and optimal duration of antibiotic treatment.

## Summary

In recent two years, new biomarkers and vaccination were introduced, corticosteroid as adjuvant therapy in non-immunocompromised patients with CAP was favored, and weighed that high mortality of HCAP was not associated MDR pathogens. Consensus on new guidelines for HAP and VAP in Asia and further studies on VAT were suggested.

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