Diagnostic Microbiology and Infectious Disease 86 (2016) 102–107

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

# The potential of molecular diagnostics and serum procalcitonin levels to change the antibiotic management of community-acquired pneumonia

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ARTICLE INFO

*Article history:*
Received 19 April 2016
Received in revised form 7 June 2016
Accepted 8 June 2016
Available online 15 June 2016

*Keywords:*
Community-acquired pneumonia

ABSTRACT

Two diagnostic bundles were compared in 127 evaluable patients admitted with community-acquired pneumonia (CAP). Diagnostic modalities in all patients included cultures of sputum (if obtainable) and blood, urine for detection of the antigens of *Streptococcus pneumoniae* and *Legionella pneumophila*, and nasal swabs for PCR probes for *S. pneumoniae* and *Staphylococcus aureus*. At least one procalcitonin level was measured in all patients. For virus detection, patients were randomized to either a 5-virus, lab-generated PCR panel or the broader and faster FilmArray PCR panel.

Overall, an etiologic diagnosis was established in 71% of the patients. A respiratory virus was detected in 39%. The potential for improved antibiotic stewardship was evident in 25 patients with only detectable respiratory virus and normal levels of PCT.



## 1. Introduction

Community-acquired pneumonia (CAP) is a common and potentially lethal infectious disease that requires concomitant attempts to determine a microbial etiology and the prompt initiation of broad spectrum empiric antibacterials (Mandell et al., 2007).

Our study was designed to: optimize the rapid detection of pathogenic bacteria and/or viruses; use normal serum procalcitonin (PCT) levels to exclude the presence of invasive bacteria; provide the microbiologic and PCT data to clinicians within 48 hours or less of admission; and determine if physician providers would respond to the data provided by switching from empiric to either no therapy (non-influenza viral illness) or a directed specific antimicrobial regimen.

The protocol described herein is the same used during January to March, 2014 (Gelfer et al., 2015), enrolling an additional 127 patients during the 2014-2015 winter months.

## 2. Materials and methods

### 2.1. Study conduct and design

#### 2.1.1. Study conduct

This study was conducted as a non-blinded cluster randomization trial at a 480 bed community-teaching hospital in Portland Oregon (Providence Portland Medical Center-PPMC). The project was approved by both the Institutional Review Board (IRB) and the Privacy Board of PPMC. Only de-identified chart data was collected; the IRB indicated no need for informed consent.

Prior to study initiation, the investigators reviewed the study protocol with Emergency Department nurses, physicians, hospitalists, residents, and clerks.

A diagnosis of CAP requiring admission made by ED physicians prompted enrollment in the study. The ED physician ordered protocol-mandated diagnostic "bundles" which were initiated by ED nurses, who also ordered empiric antibiotic therapy. ED unit clerks notified investigators of a new patient. The protocol neither dictated nor suggested antibiotic management to either the ED or inpatient physicians.

Providers learned of test results via the electronic medical record (EMR), with two exceptions. Providers were notified immediately of positive blood cultures or identification of influenza.

#### 2.1.2. Study design

A common core of diagnostic tests was applied to all patients in the study: i.e., two blood cultures, sputum culture and sensitivity, serum PCT level, urine antigen testing for *Legionella pneumophila,* serogroup 1 and *Streptococcus pneumoniae*, nasal swabs for PCR detection of the lyt gene of *S. pneumoniae* and *Staphylococcus aureus. S. aureus* PCR (BD Max Staph SR) was purchased from Becton-Dickinson.

PCT levels were determined using an immunoassay (bioMerieux) performed on a Vidas system. The protocol called for only one baseline PCT serum level; providers ordered additional PCT levels at their discretion. PCT results included an interpretative algorithm modeled after a widely-used used European format (Schuetz et al., 2012, 2013). Values below 0.1 ng/mL were interpreted as "bacterial etiology very unlikely"; values >0.25–0.5 ng/mL as "bacterial etiology likely"; and values >0.5 ng/mL as "bacterial etiology very likely". The algorithm suggests

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http://dx.doi.org/10.1016/j.diagmicrobio.2016.06.008
0732-8893/

a repeat PCT level in 4-6 hours in those patients with levels ≤ 0.25 ng/mL and possible evolving bacterial infection.

In addition to the common bundle, patients were cluster-randomized in one week blocks to undergo additional diagnostic testing with either the PPMC laboratory-generated respiratory pathogen PCR panel (Standard) or a commercial multiplex PCR panel (FilmArray), from Biofire (Salt Lake City, UT).The Standard panel probes for influenza A and B, adenovirus, human metapneumovirus, respiratory syncytial virus, and rhinovirus. Specimens were run daily at least 6 days per week; results were available within 12-48 hours. On alternate weeks, nasaopharyngeal (NP) swabs were processed with FilmArray, that probes for five types of influenza, four types of parainfluenza, rhinovirus/enterovirus, adenovirus, human metapneumovirus, four types of coronavirus, respiratory syncytial virus, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Bordetella pertussis*.

*2.1.3. Data collection*

The authors extracted data from the patients' EMR, using an assigned study number and database file (Filemaker, Pro 13). Data extraction began at enrollment, continued periodically during hospitalization, and was completed post-discharge. All data entry was verified by two or three of the authors.

Infectious diseases pharmacists entered data referable to use of antibacterial and/or anti-influenza therapy. Using a standardized list of the purchase expense of individual antibiotics, one investigator (DNG) determined the days of, and expense of, antimicrobial therapy. On any given day, empiric therapy with 3 different antibiotics, regardless of the number of doses, was defined as 3 days of therapy (DOT). The length, or number of days, of therapy (LOT), regardless of the number of drugs administered each day, was also calculated. Results were normalized to 1000 hospital patient-days.

*2.2. Inclusion and exclusion criteria*

Inclusion required an ED diagnosis of CAP of sufficient severity to require hospitalization in a patient 18 years of age or older. Patients were excluded if it was not possible to obtain a NP swab or if antibiotics were withheld and comfort care initiated. Post-enrollment, patients were excluded if two sites of infection were present: e.g., CAP plus a non-CAP infection, if patients were placed on comfort care with discontinuation of anti-infectives, or if there was a failure to collect the protocol-mandated diagnostic tests. Patients unable to provide an acceptable sputum for culture were not excluded.

*2.3. Final clinical categorization*

The final database for each enrolled patient was reviewed by two of the investigators (JL and DNG) for the purpose of final categorization as per the definitions below. In the event of disagreement, adjudication was by a third investigator (GG). The criteria for the assigned final clinical diagnosis were:

*2.3.1. Uninfected; no evidence of CAP*

Post-admission clinical, laboratory and imaging studies document an alternative non-infectious diagnosis: e.g., congestive heart failure.

*2.3.2. Bacterial pneumonia*

Proven: Pulmonary infiltrates and a bacterial pathogen in sputum, blood, or pleural fluid; a positive *S. pneumoniae* NP swab PCR and/or *S. pneumoniae* urine antigen was accepted as bacterial pneumonia.

Presumptive: Multifocal pulmonary infiltrates and detection of *S. pneumoniae* or S. *aureus* by PCR of a nasal swab in patients in whom it was not possible to obtain sputum or a bronchoalveolar lavage specimen. Elevation of the serum procalcitonin was used as evidence of bacterial invasion as opposed to asymptomatic colonization.

In the presence of clinical pneumonia, a serum procalcitonin level of ≥0.25 ng/mL was accepted as presumptive evidence of bacterial pneumonia in the absence of detection of a bacterial pathogen; e.g., the patient with documented aspiration.

*2.3.3. Viral pneumonia*

Presumptive: Identification of the presence of adenovirus, coronavirus, human metapneumovirus, influenza, parainfluenza, respiratory syncytial virus, or rhinovirus by one of the PCR probes and a compatible clinical syndrome. In distinction to potential bacterial pathogens like *S. aureus* and *S. pneumoniae*, asymptomatic nasal colonization by respiratory viral pathogens is a rare occurrence.

*2.3.4. Bacterial-viral co-infected*

Presumptive: Respiratory virus detected and either serum PCT was above 0.5 ng/mL, and/or a bacterial pathogen found in a sputum culture, by urine antigen, or PCR. Bacterial and viral pathogens were identified as "potential" etiologic agents as no seroconversion studies were performed.

*2.4. Determination of protocol adherence of patient data*

Each patient file was reviewed by three investigators (GG, JL, DG). A patient was considered evaluable only if all protocol-required diagnostic studies were performed, except for sputum culture if no sputum could be obtained. Each patient file was reviewed to determine if the patient's pneumonia diagnosis was, in hindsight, correct. Of those patients with a clinical pneumonia syndrome, the investigators classified the etiology of the pneumonia in one of 4 ways: viral, bacterial, or a combination of viral and bacterial, or, when no pathogen was found, clinical pneumonia of unclear etiology. If a respiratory virus was detected, an associated bacterial infection was deemed present if a bacterial pathogen was identified by culture PCR or urine antigens, or if the serum PCT concentration was >0.5 ng/mL.

*2.5. Statistics*

For comparisons between the two diagnostic methods, *t* test or Wilcoxon test was performed for continuous variables, and chi-square test or Fisher's Exact test was performed for categorical variables. Kruskal-Wallis test or one-way ANOVA test was used for comparisons among the three distinct etiology groups (viral, bacterial, or a combination of viral and bacterial).

## 3. Results

From December 4, 2014, to March 6, 2015, the ED admitted 211 patients with a diagnosis of CAP (Fig. 1). Of the 99 patients randomized to the Standard group, 31 patients were non-evaluable, due to inadequate evidence of pneumonia in 26, incomplete diagnostics in 3, and transition to comfort care within a day in 2 patients. Inadequate evidence of pneumonia was attributable to patients with bronchitis or COPD exacerbation (8), sepsis from another source (7), CHF (5), cystic fibrosis (2), metastatic cancer (2), MAI (1) and chemical aspiration (1). Of the remaining 68 evaluable patients, 1 or more pathogens were identified in 47 (69%).

Of the 111 patients randomized to the FilmArray group, 52 patients were non-evaluable, due to inadequate evidence of pneumonia in 40, incomplete diagnostics in 3, and transition to comfort care in 9 patients within a day. Inadequate evidence of pneumonia was attributable to patients with bronchitis or COPD exacerbation (13), sepsis from another source (12), CHF (6), metastatic cancer (6), asthma, pulmonary embolism, or chemical aspiration (1 each). Of the remaining 59 evaluable patients, 1 or more pathogens were identified in 43 (73%).

Non-evaluable patients were otherwise similar to those evaluable with respect to demographics, comorbidities, and other features listed in Table 1.