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The clinical impact of the detection of potential etiologic pathogens of community-acquired pneumonia

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ABSTRACT

The etiology of community-acquired pneumonia (CAP) is determined in less than half of the patients based on cultures of sputum and blood plus testing urine for the antigens of *Streptococcus pneumoniae* and *Legionella pneumophila*. This study added nasal polymerase chain reaction (PCR) probes for *S. pneumoniae*, *Staphylococcus aureus*, and respiratory viruses. Serum procalcitonin (PCT) levels were measured. Pathogens were identified in 78% of the patients. For detection of viruses, patients were randomized to either a 5-virus laboratory-generated PCR bundle or the 17-virus FilmArray PCR platform. The FilmArray PCR platform detected more viruses than the laboratory-generated bundle and did so in less than 2 hours. There were fewer days of antibiotic therapy, $P = 0.003$, in CAP patients with viral infections and a low serum PCT levels.

1. Introduction

Clinical guidelines call for the early initiation of empiric antibiotic therapy for patients with community-acquired pneumonia (CAP) Mandell et al., 2007. If admitted via the emergency department (ED), it is recommended that antibacterial therapy starts in the ED (Mandell et al., 2007). De-escalation or discontinuation is recommended when the results of microbiologic tests are available. However, the diagnostic yield from cultures of sputum and blood plus probing urine for the antigen of *Streptococcus pneumoniae* and *Legionella pneumophila* is under 50% (Musher et al., 2013). Further, the results of traditional diagnostics (e.g., sputum culture) are not available for days. As a result, the often broad multidrug empiric antibiotic regimen is often prolonged.

Some physicians may not be willing to discontinue empiric antibiotics despite identification of a potential viral pathogen. Providers oft times express fear that a concomitant invasive bacterial pathogen could be present and will be found later in the sputum culture. To address this issue, our protocol included at least 1 baseline serum procalcitonin (PCT) level. It is generally accepted that serum PCT levels do not increase substantively in pure viral respiratory tract infections (Becker et al., 2008; Gilbert, 2011). In addition, PCT levels may help interpret culture data. *S. pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae* may be in the airway of chronic obstructive pulmonary disease patients. PCT levels do not increase unless the latter are causing invasive infection (Falsey et al., 2012).

Our study was designed to address 3 questions. First, can expansion of the traditional diagnostic test bundle substantively increase the detection of potential etiologic organisms? Second, can molecular diagnostics provide clinicians with actionable data in hours rather than days? Lastly, will providers respond to rapid diagnostic data with adjustments of empiric antibiotic treatment regimens?

2. Materials and methods

2.1. Study conduct and design

2.1.1. Study conduct

This study was conducted as a nonblinded cluster randomization trial at a 480-bed community teaching hospital in Portland Oregon (Providence Portland Medical Center [PPMC]). Prior to initiation of the study, the research project was approved by both the Institutional Review Board (IRB) and the Privacy Board of PPMC. As only deidentified chart data were collected, the IRB indicated no need for informed consent. A study information form was available for enrolled patients.

Prior to study initiation, the investigators reviewed the study protocol with ED nurses, physicians, and clerks (health unit coordinators). Similar meetings were conducted for hospitalists and residents.

The diagnosis of CAP was made by ED physicians. If the ED physician determined the need for hospitalization, the patient was enrolled in the study. The ED physician used the hospital's electronic medical record (EMR) to order protocol-mandated diagnostic "bundles" and instructed the health unit coordinator to notify the investigators of a new patient. The ED physician initiated empiric antibiotic therapy; the protocol did not dictate or suggest antibiotic management to either the ED or inpatient physicians. The diagnostic test bundle (see below) was initiated by the ED nursing staff.

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For the vast majority of patients, providers learned of test results via posting in the EMR. There were 2 exceptions. As per hospital policy, providers were immediately notified directly (usually through nursing unit nurses or clerks) of positive blood cultures or identification of influenza. The inpatient physician providers were not officially notified the patient was in the study, although through the prestudy educational sessions, they were aware a hospital-wide CAP diagnostic study investigation was in process. Further, the test bundles ordered in the ED indicated study participation.

2.1.2. Study design

A common core diagnostic test bundle was applied to all patients in the study: i.e., 2 blood cultures; sputum culture and sensitivity; serum PCT level; and urine antigen testing for *L. pneumophila*, serogroup 1, and *S. pneumoniae*. All patients had nasal swabs for polymerase chain reaction (PCR) detection of the lyt gene of *S. pneumoniae* and the mecA and nuc genes of *Staphylococcus aureus*. The PCR for *S. pneumoniae* is an in-house laboratory-generated test available for a number of years as a supplement to the *S. pneumoniae* urine antigen. The PCR for *S. aureus* was purchased from Becton-Dickinson (BD Max Staph SR).

PCT levels were determined using an immunoassay developed by Brahms, marketed by bioMérieux, and performed on a Vidas system. An interpretative algorithm was provided with the PCR results. The protocol called for only 1 baseline PCT serum level. Some providers ordered additional levels at their discretion.

PCT results included an interpretative algorithm modeled after the format used in multiple European studies (Schuetz et al., 2012, 2013). Values below 0.1 ng/mL were interpreted as "bacterial etiology very unlikely"; values of >0.25–0.5 ng/mL, as "bacterial etiology likely"; and values of >0.5 ng/mL, as "bacterial etiology very likely". The algorithm suggests repeat PCT levels in 4–6 hours in those patients with levels ≤0.25 ng/mL and a clinical picture compatible with an evolving bacterial infection.

In addition to the common bundle, patients were cluster randomized in 1-week blocks to undergo additional diagnostic testing with either the PPMC laboratory-generated respiratory pathogen PCR panel (standard) or a commercial faster and broader multiplex PCR panel (FilmArray).

The PPMC laboratory-generated PCR panel probes for influenza A and B, adenovirus, human metapneumovirus, respiratory syncytial virus, and rhinovirus. Specimens are run once a day at least 6 days per week. Results are generally available within 12–48 hours.

On alternate weeks, nasopharyngeal (NP) swabs were processed with a FilmArray multiplex PCR panel (Biofire, Salt Lake City, UT, USA). The FilmArray panel can detect the nucleic acid of 5 types of influenza, 4 types of parainfluenza, rhinovirus/enterovirus, adenovirus, human metapneumovirus, 4 types of coronavirus, respiratory syncytial virus, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*.

The FilmArray assay takes 60 minutes: the total time from specimen collection to reporting of results in the EMR is roughly 2 hours.

2.1.3. Data collection

A panel of internal medicine residents (see Acknowledgment) extracted data from the patients' EMR. Patients were assigned a study number, and a database file (Filemaker, Pro 13) was established. Data extraction began at enrollment, continued periodically during hospitalization, and was completed postdischarge. All data entry was checked and verified by 2 or 3 of the authors.

In addition, the infectious disease pharmacists entered all data referable to use of antibiotics and/or anti-influenza therapy. Using a standardized list of the purchase expense of individual antibiotics, 1 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. The days of antibiotic therapy and length of antibiotic therapy 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. Postdiagnosis, the ED physician enrolled the patient and initiated the appropriate order set.

Patients were required to be 18 years of age or older.

Patients were excluded if it was not possible to obtain an NP swab or if it was decided to withhold antibiotics and initiate comfort care management.

Postenrollment, patients were excluded and hence nonevaluable if 2 sites of infection were present: e.g., CAP plus a non-CAP infection.

2.3. Final clinical categorization

The final database for each enrolled patient was reviewed by 2 of the investigators (JL and DNG) for the purpose of final categorization as per the definitions below. In the event of disagreement, the case was adjudicated by a third investigator (GG). The criteria for the assigned final clinical diagnosis were as follows:

2.3.1. Uninfected

Postadmission clinical, laboratory, and imaging studies document an alternative noninfectious diagnosis. Congestive heart failure is an example.

2.3.2. Bacterial pneumonia

Proven: presence of a bacterial pathogen in sputum, blood, or pleural fluid. Also accepted was presence of *S. pneumoniae* by NP swab PCR and/or a positive *S. pneumoniae* urine antigen in a patient with a clinical syndrome of pneumonia in the absence of other detected pathogens.

Presumptive: The presence of multifocal pulmonary infiltrates and detection of *S. pneumoniae* or S. *aureus* by PCR of a nasal swab in patients with a clinical syndrome of pneumonia and in whom it was not possible to obtain sputum or a bronchoalveolar lavage specimen.

In the presence of clinical pneumonia, a serum PCT level of ≥0.25 ng/mL was accepted as presumptive evidence of bacterial pneumonia in the absence of detection of a bacterial pathogen. A common example is the patient with documented aspiration. The 0.25 ng/mL "cut-off" used is based on a large number of European trials of PCT levels in patients with a variety of lower respiratory tract infections (Schuetz et al., 2012, 2013).

2.3.3. Viral pneumonia

Identification of the presence of adenovirus, coronavirus, human metapneumovirus, parainfluenza, respiratory syncytial virus, or rhinovirus by 1 of the PCR probes and a compatible clinical syndrome.

2.3.4. Coinfected

Patients were considered coinfected if diagnostic data demonstrated the presence of both a viral and a bacterial pathogen. If a respiratory virus was detected and the serum PCT was above 0.5 ng/mL and/or a bacterial pathogen was found in the sputum culture, the patient was assumed to have a dual infection with the identified virus and bacteria.

The detected bacterial and viral pathogens are identified as "potential" etiologic agents. No seroconversion studies were performed to document invasive disease.

2.4. Determination of protocol adherence of patient data

Each patient file was reviewed by 3 investigators (GG, JL, and DG). A patient was considered evaluable only if all protocol-required