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Use of Procalcitonin to Guide Antibiotic Treatment of Bacterial Respiratory Infection in Elderly

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Introduction

The purpose of this critical appraisal is to determine if there is a significant difference between procalcitonin (PCT) guided treatment on antibiotic use and standard therapy in elderly patients (age 65 and older) with a suspected bacterial respiratory infection. The PICO question explored in this paper is: for elderly patients with a suspected bacterial infection, what effect does the result of a PCT test have on the determination of antibiotic use and outcome compared to patients treated empirically with antibiotics?

This topic is timely and clinically relevant because many suspected bacterial respiratory infections are treated with antibiotics empirically before clinical tests can be determined (Gernsheimer et al., 2010; Guy, 2012). Current guidelines recommend antibiotic courses of 7 to 21 days for respiratory infections, depending on illness severity and type of pathogen, but healthcare providers tend to treat elderly patients longer because of higher rates of morbidity and mortality (Christ-Crain et al., 2006). Also, because signs and symptoms of bacterial and viral infections widely overlap, older patients with these infections are more often initially treated with antibiotics, especially in the presence of coexisting illnesses.

Antimicrobial therapy must be promptly initiated with bacterial pneumonia because a delay of more than 4-8 hours is associated with increased mortality (Christ-Crain et. al, 2004). Although delay in antibiotic treatment greatly decreases the chances of survival, healthcare providers must still be judicious in their use of antibiotics because

the overuse of them in past years have caused antibiotic-resistant bacteria to become an expensive barrier to treatment (CDC, 2011).

Lower respiratory tract infections (LRTIs) - acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (COPD) or asthma, and community acquired pneumonia (CAP) - are often treated with antibiotics without evidence of clinically relevant bacterial disease and account for almost 10% of the worldwide burden of morbidity and mortality (Christ-Crain et. al, 2004). Despite their primarily viral causes, as many as 75% of all antibiotic doses are prescribed for acute respiratory-tract infections (Christ-Crain et. al, 2004). This inappropriate use of antibiotics is believed to be a main cause of the spread of antibiotic-resistant microorganisms (Christ-Crain et. al, 2004).

The PCT plasma half-life is approximately 24 hours and a rise in plasma PCT concentration is seen within 2-4 hours after infection. The rise continues until appropriate treatment is initiated, or until the infection is well controlled (Kristofferson et. al, 2008). PCT is a precursor of calcitonin and the release of PCT during infections is induced either directly by microbial toxins, indirectly by humoral factors, or the cell-mediated host response (Christ-Crain et al., 2006). The increase in plasma PCT in response to infections is faster and more specific than the increase in a C-reactive protein (CRP) or white blood cell count (WBC) tests. PCT levels also return to normal faster than those of CRP when the infection is under control, making the marker advantageous in the early diagnosis and monitoring of infection (Kristofferson et. al, 2008). Low serum PCT levels have been found to accurately predict the absence of bacteremia or sepsis in the elderly (Kristofferson et. al, 2008).

For many elderly persons, the side effects of unnecessary antibiotic

treatment can result in more harm than good, which can take a toll on their well being. Increased hospitalizations attributed to adverse drug reactions alone account for billions of dollars each year within the U.S. healthcare system. Over 140,000 of these severe reactions to antibiotics drive people to emergency rooms each year, and are not just costly, but can be toxic and even deadly. Antibacterial adverse effects account for nearly 25% of all adverse drug reactions amongst hospitalized patients (Shehab, Patel, Srinivasan, & Budnitz, 2008). According to a study published in the Journal of the American Medical Association (Lazarou, Pomeranz, & Corey, 1998), taking properly prescribed medical drugs was listed as the third leading cause of death in the U.S., presumably due to the extensive side effects of many drugs. Antibiotics were specifically listed as one of the drugs in this category. Potential adverse side effects of taking antibiotics include allergic or toxic reactions, alteration of normal bacterial flora in the gastrointestinal system and the vaginal flora, creation of super-strain resistant bacteria, and interference with other medications.

As drug-resistant strains of bacteria are becoming more common in communities, it is imperative that clinicians exercise antibiotic stewardship and educate patients and families to stop the spread of these bacteria. When antibiotic options are limited, providers may need to use antibiotics that are more expensive or more toxic to the patient (Frieden, 2010). If no antibiotic is effective, treatment is limited to costly long-term support care that does not treat the infection (Frieden, 2010). The patient's risk of dying from infection increases as well as potential spread to others, further extending the resistant bacteria (Frieden, 2010). The estimated cost of these resistant infections is estimated between $13.35 and $18.75 million for a single healthcare institution (Frieden,

2010).

If PCT can be shown to be a clinically significant biomarker for guiding treatment for bacterial respiratory infections, it would have important implications for clinical practice. Age-related overuse of antibiotics could be substantially reduced, which would diminish antibiotic resistance, lower medical costs for hospital systems and the patients, and result in fewer side effects of antibiotic use.

Methods

CINAHL, MEDLINE, and Google Scholar databases were used to conduct the search without any date limitations. The keywords searched were “procalcitonin” and “antibiotic”, the results of which were then narrowed using the terms “respiratory” and “infection”. The search was limited to scholarly (peer reviewed) journals, experimental studies, systematic reviews, guidelines, and clinical articles that provide expert opinions. The articles found with all databases were reviewed, using the five deemed most applicable. Criteria for determining applicability included articles discussing PCT diagnostic and treatment guidance of infection compared to standard treatment of respiratory bacterial infection. Other variables analyzed in these studies were secondary outcomes, such as antibiotic prescription at inclusion, duration of antibiotic therapy, total antibiotic exposure, length of stay in the hospital, and mortality. All studies chosen for review were random controlled trials.

Analysis

Study Characteristics

The studies chosen for this literature critical appraisal were similar in that they all examined the diagnostic value and utility of the biomarker PCT to guide treatment of bacterial respiratory infection. These studies were reviewed using the John Hopkins Nursing Evidence-Based Practice (JHNEBP) evidence rating scale, which clearly defines the strength of evidence with Levels 1 to 3, and further defines evidence of quality with a grade of A, B, or C. Using this scale, all of the studies were rated a Level 1, indicating the highest strength of evidence with the highest quality design because they are randomized controlled trials. The quality of evidence of all the studies was high and rated an A by the author of this paper. They all had consistent results with sufficient sample sizes, adequate control, and definitive conclusions. The recommendations made in these studies were based on thoughtful research and referenced scientific evidence in the literature on this topic.

All studies were published in peer review journals in English. Four of five of the studies were carried out in Switzerland (the fifth in Denmark) - the ethnic diversity of the populations in these studies was not discussed. Four of five were conducted in large hospital settings (the fifth in primary care centers), and three out of five were single-site studies (the other two were multi-centered studies). The studies' populations focused on adult patients (age ≥ 18) with respiratory tract infections, the average age ranging from 64 to 70 in four of the studies. The sample sizes varied from 208 to 458 patients with a

relatively even split between men and women in the PCT and control groups. Baseline characteristics, inclusion, and exclusion criteria were quite similar and well defined in all of the studies. All used the same rapid assay to determine PCT level, but the number of PCT tests drawn and when they were drawn varied between studies. The PCT-guided treatment algorithm referred to throughout this paper was used by all of the studies although able to be overridden if the clinician decided to treat based on clinical presentation. It was developed and published by Müeller et al. (2007) and can be found in Appendix A.

The following primary and secondary outcomes were chosen and discussed because they were found to be the most commonly reported among all of the studies.

Primary Outcome: Antibiotic Prescription at Inclusion

The Christ-Crain et al. (2004) study focused on LRTIs and found that the rate of antibiotic prescriptions foreseen by the doctor was similar in both the PCT and control groups. However, the percentage of patients who actually received antibiotics was reduced by 47% compared to the control group ($p<0.0001$). The subgroup with the greatest reduction in the number of antibiotic prescriptions were those with an acute exacerbation of COPD - prescriptions were reduced by 56% ($p=0.001$) (Christ-Crain et al., 2004).

The Christ-Crain et al. study, published in 2006, focused on CAP and found one-fifth of patients had already received antibiotics at the time of the study. Upon admission, a PCT level was drawn and then a treatment algorithm was followed to determine whether or not to continue antibiotic therapy. Antibiotics were withheld or discontinued

in 15% of the patients in the PCT group ($p<0.001$) and 3% of those were discharged to home the day of admission after follow up PCT tests within 6 to 24 hours of admission. They continued to be followed and received PCT tests on Days 4, 6, 8, 10, 14, and 21. Antibiotics were started in five patients based on PCT levels that rose above 0.25 µg/L at the initial follow-up after 6 hours. The patients who had their antibiotics withheld on admission based on low PCT levels all had favorable outcomes.

The population of study by Stolz et al. (2007) was patients with exacerbations of COPD. PCT guidance significantly reduced antibiotic prescriptions by 44% ($p<0.0001$). This finding was not as significant when compared to the 56% reduction in the COPD subgroup of the 2004 Christ-Crain et al. study, but still demonstrates antibiotic use could be greatly and safely reduced in this specific population.

The only study included that examined PCT guided therapy in primary care centers was done by Briel et al. (2008). This study found a significant 72% overall reduction in antibiotic use. In the COPD or asthma exacerbations and CAP subgroups, antibiotic prescriptions were reduced by about 40% but the largest reduction in antibiotic prescriptions was in the upper respiratory tract infections and acute bronchitis groups, where an 80% reduction in antibiotic prescriptions was found.

The final study reviewed (Kristofferson et al. 2008) attempted to reproduce results found by Christ-Crain et al. in their 2004 study that explored PCT guided therapy in LRTIs. Kristofferson et al. wanted to try to generalize the results by making their study multi-centered and also followed a treatment algorithm using only one PCT test done as soon as possible upon admission. There was a low rate of adherence to guidelines by physicians: 44% or 42/103 cases were treated with antibiotics despite a serum PCT below

0.25 µg/L. Reasons given for this by the physicians were the clinical presentation of the patient (47%) and delay in the test result (41%). In light of this, there was no difference in antibiotic prescription rates between the PCT and control group.

Duration of Antibiotic Therapy

Little clinical significance was found between the standard and PCT groups regarding duration of antibiotic therapy in the 2004 LRTIs study (Christ-Crain et al.) (12.8 vs. 10.9 days respectively; p=0.03). However, the 2006 CAP study (Christ-Crain et al.) found a more significant decrease in duration of antibiotic treatment (55% reduction) with a median of 5 days in the PCT group, compared to a median of 12 days in the standard therapy group (p<0.001).

The Stolz et al. study (2007) did not list antibiotic duration as a primary or secondary outcome, whereas the Briel et al. study (2008) reported a mean duration of antibiotic treatment of 6.2 days in the PCT group and 7.1 days with standard therapy (95% confidence interval [CI], 0.4-1.7 days). Antibiotic treatment during hospitalization in the Kristofferson et al. (2008) study was of significantly longer duration in the control group. The mean duration of treatment was reduced by 25% (95% CI 7-38%) in the PCT group as compared to the control group (p=0.007).

Antibiotic Exposure

Antibiotic use per 1,000 days of follow-up was a primary endpoint in the 2004 Christ-Crain study where the relative risk of antibiotic exposure was calculated and found to be 0.39 (CI 0.36-0.42, p<0.0001) in the PCT group and absolute risk reduction was

50% (95% CI 47-53, p<0.0001). This equates to 39 fewer antibiotic courses per 100 patients with LRTIs. This study adds to the literature that withholding antibiotic treatment with PCT-guided therapy was safe and did not compromise outcomes (Christ-Crain et al., 2004). Christ-Crain et al. (2006) also found that PCT guidance reduced the total rate of antibiotic exposure (relative risk, 0.52; 95% CI, 0.48-0.55; p<0.001).

The Stolz et al. study (2007) found similar results in the COPD population: antibiotic exposure was reduced (relative risk, 0.56; 95% CI, 0.43 to 0.73; p<0.0001) compared to standard therapy. This study also followed patients longer than the others and found the PCT guidance at the index exacerbation allowed a significant sustained reduction in total antibiotic exposure for up to 6 months (relative risk, 0.76; 95% CI, 0.64 to 0.92; p=0.004).

Total antibiotic exposure was not explored in the Briel et al. (2008) or the Kristofferson et al. (2008) studies.

Secondary Outcomes: Length of Stay in Hospital

There was not a significant reduction in the length of hospital stay noted in any of the studies. Christ-Crain et al. (2004) reported length of stay as a mean of 10.7 +/- 8.9 days in the PCT group and 11.2 +/- 10.6 days in the control group. Length of hospitalization the CAP study by Christ-Crain et al. (2006) was similar between the two groups with a mean of 12.0 +/- 9.1 days in the PCT group and 13.0 +/- 9.0 days in the control group.

Kristofferson et al. (2008) also reported no difference in length of hospitalization between the two groups with LRTIs, except in the subgroup of patients with COPD. The

mean length of stay was 4.8 days (95% CI 3.8-6.1) vs. 7.1 days (95% CI 5.9-8.5) in the PCT and control groups, respectively (p=0.009).

The Stolz et al. study did not address length of stay as an endpoint and Briel et al. (2008) only studied respiratory infections in primary care settings so no hospitalizations were reported.

Mortality

All of the studies reported the mortality and accounted for the cause. Christ-Crain (2004) reported four deaths in the standard group – two were due to sepsis, one from myocardial infarct, and one from an unknown cause after discharge. The researchers emphasized that none of the four deaths in the PCT group were from delaying or withholding antimicrobial treatment – two were due to myocardial infarction, one from acute renal failure, one from a gastrointestinal bleed, and one from suicide (Christ-Crain et al., 2004).

There were more reported deaths in the Christ-Crain et al. (2006) study, 18 in the PCT group and 20 in the control group. On admission, patients who died during the course of the study were noted to have significantly higher levels of PCT when compared to those patients who survived (median: 0.7 [0.4-3.0] and 0.45 [0.2-2.0] µg/L, respectively; p=0.02). C-reactive protein (CRP) levels and leukocyte counts were similar in patients who died and in patients who survived. All 18 patients who died in the PCT group were treated with antibiotics upon admission according to the PCT-guided algorithm and high PCT levels exceeding 0.25 µg/L.

Stolz et al. (2007) reported a total of 14 deaths throughout the course of their study – 5 in the PCT group and 9 in the control group. Four of these patients died of COPD-related respiratory failure, eight from medical conditions other than COPD, and in two the cause of death remains unknown.

Mortality was low in the Briel et al. study (2008) but the study took place in a primary care setting. Only one patient died of herpes simplex pneumonia in the standard therapy group, however, other serious adverse events were reported. One patient in the PCT group had exudative tonsillitis and developed a peri-tonsillary abscess and underwent surgery. Four patients were hospitalized with pneumonia within 28 days of baseline. By day 28 symptoms were completely resolved in all but two patients. One in the PCT group developed a septic syndrome, and the other patient, in the control group, had a relapse of pneumonia.

A total of three patients in the Kristofferson et al. (2008) study died during hospitalization. Two were in the PCT group – one due to cancer, the other due to respiratory failure. The one patient in the control group died from multi-organ failure.

Additional Significant Findings

These findings were unique to each study but still demonstrated significance. The Christ-Crain et al. (2004) study reviewed antibiotic costs per patient and found that in the PCT group, mean antimicrobial costs per patient were reduced by 52% in all patients with LRTIs ($p<0.0001$) and by 36% in those with acute exacerbations of COPD ($p=0.012$). They also discovered that in the standard group, the odds of being treated with antibiotics increased by 6.5% with every additional year of age (95% CI 3.4-9.8,

$p<0.0001$. This age/treatment with antibiotics relationship could not be found in the PCT group (95% CI -1.2-2.4, p=0.53) (Christ-Crain et al., 2004).

Christ-Crain et al. (2006) also found significance in the median antibiotic costs per patient. The median costs of antibiotics in the PCT group were $100 per patient, compared with $190 per patient in the control group. In the PCT group, the biomarker was measured an average of 3.5 times per patient. After that cost, the use of PCT for antibiotic stewardship in patients with CAP would become cost-effective below $25 per analysis.

The primary outcome of the Stolz et al. (2007) study was the antibiotic exposure at the index exacerbation and the subsequent antibiotic requirement for COPD exacerbation within 6 months. Secondary outcomes unique to this study were lung function, exacerbation rate, and time to next exacerbation. They found that the absolute risk reduction of 31.5% in antibiotic exposure implied that for on in every four patients admitted for an exacerbation of COPD, on course of antibiotics can be prevented (number-needed-to-treat, 3.2; 95% CI, 2.3-5.3). PCT-guided therapy did not result in an increase of exacerbation rate, a decrease in time to next exacerbation or a more rapid decline in lung function. This may allow for a more sustained reduction in antibiotic use for the treatment of COPD both short-term and long-term.

Briel et al. (2008) is the only study that follows patients in a primary care setting. The primary outcome was the measurement of days with restricted activities from infection. Both groups reported a mean of 8.7 days with restricted daily activities with no significant loss of time due to illness reported in the PCT group compared to the control group. In addition to no difference in outcome, the PCT group reduced antibiotic

prescriptions by 72% and duration of antibiotics was, on average, 1 day shorter than standard therapy.

Kristofferson et al. (2008) attempted to generalize the Christ-Crain et al. (2004) study's results to more than one center. In contrast to that study, they obtained only a single PCT measurement upon admission and assessed the physicians' willingness to use PCT in routine clinical decision-making. Despite low adherence to guidelines by physicians, they were still able to demonstrate a 25% reduction in antibiotic use without adverse effects.

Some ethical issues that should be noted are that an author of the Christ-Cain et al. (2004) study served as a consultant and was paid by the manufacturer of the assay used to determine level of PCT in the study, to do research, lecture, and attend meetings. Two researchers in the Christ-Cain et al. (2006) study had received grants, lecture fees, and compensation for advisory board activities from the manufacturer of the PCT assay they promote and have used in their studies. Both studies had favorable outcomes for use of PCT to guide antibiotic treatment. The Stolz et al. (2007) study had a researcher that had served as a consultant and received payments from the same manufacturer of the assay used in the study. The same researcher was one of the authors in the Briel et al. (2008) study. Kristofferson et al. (2008) reports none of the authors has or has ever had any affiliation with the manufacturer of the PCT assay or any of the funding sources.

Synthesis

Based on extensive review of these studies, all have determined that PCT can currently be used safely and reliably in clinical practice to guide antibiotic therapy

treating respiratory infections in the elderly. Although none of the studies found a significant reduction in the length of hospital stays, there was a trend of reduced mortality. The studies reviewed found that PCT-guided therapy can substantially reduce antibiotic use, exposure, and duration in this population without adverse effects.

Limiting antibiotics is necessary to decrease cases of antibiotic resistant infection. It is also more cost effective than standard therapy for both hospitals and patients. This approach allows the clinician to customize antibiotic treatment to each patient by using an objective and reliable biomarker.

These studies reveal a topic that is clinically relevant because of the impact reduced cost of treatment and less antibiotic use would have on societal health as a whole. There is potential for this test to significantly improve patient health care outcomes, especially in those who could benefit from less expensive treatment of infection, namely the elderly. Replicated studies should be done in other parts of the world, paying attention to uniformity with assays and similarity in study design.

Recommendations

The studies reviewed in this paper overwhelmingly advocate the use of PCT for antibiotic guidance for respiratory infections in the elderly. However, implementation must move beyond the question of whether or not PCT tests should be used and the issue of how to incorporate the test into routine clinical decision-making needs to be addressed.

An important note regarding validity is that each of these studies used the same kind of rapid assay to determine PCT level. The sensitivity and specificity of the assay is key to determining an accurate serum PCT level. Improvements in the quality of assays

have increased sensitivity, decreased the time it takes to perform, and lowered the cost of the test. Because these studies used the most sensitive assay, they had more statistically significant outcomes.

While it would be useful to have a reliable method for detecting all bacterial infections, these studies provide good data to support the use of PCT as a guide to antibiotic therapy in elderly patients with respiratory infections. There is promising research currently being done on this topic and with more consistent results, the determination of whether or not to use the PCT test as a gold standard will be made. The ability to generalize these results to diverse, marginalized populations will help improve overall patient satisfaction, safety, and health care outcomes.

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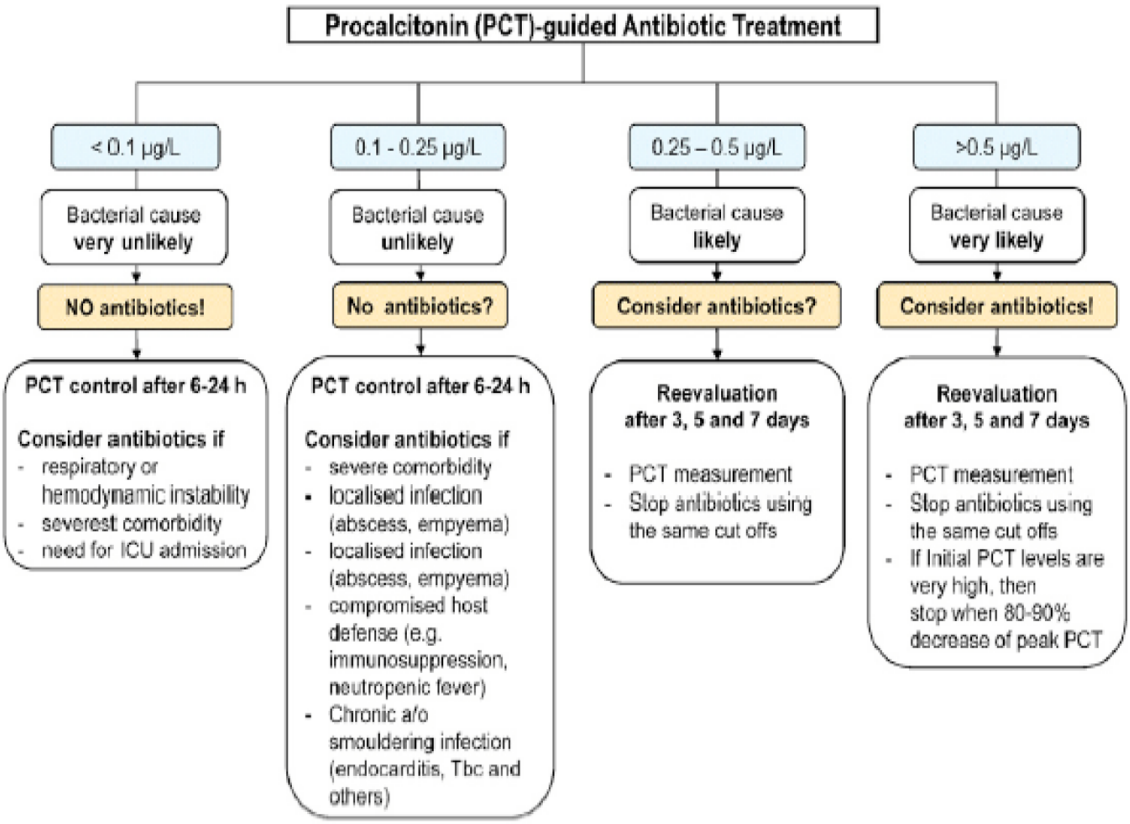
Appendix B: Procalcitonin algorithm



Proposed algorithm for procalcitonin (PCT)-guided antibiotic therapy

(Müller et al., 2007)