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Procalcitonin Test Availability: A Survey of Acute Care Hospitals in Massachusetts

To the Editor:

Limiting unnecessary antibiotic use is a major public health goal (1, 2). Procalcitonin (PCT) is a biomarker of bacterial infection that can enhance identification of patients in whom antibiotics can be safely withheld or duration shortened (3, 4). Multiple randomized controlled trials have demonstrated that PCT-based algorithms can substantially reduce antibiotic exposure without increasing mortality or infection-related complications (5–9). These have led to clinical practice guidelines suggesting use of PCT to guide antibiotic duration for patients with sepsis or suspected infection (1, 10, 11).

Despite promise for reducing antibiotic use in randomized trials, recent observational studies examining the effectiveness of PCT in routine clinical practice suggest PCT has not consistently led to reduced antibiotic use (12, 13). The reasons the benefits of PCT for antimicrobial stewardship have not successfully translated from clinical trials are unclear. To impact clinical decision-making and shorten antibiotic duration, the results of PCT testing must be rapidly available. Thus, one possible explanation for failure to translate trial results into clinical practice is that PCT test results may not be as rapidly available in routine clinical practice as in clinical trials. The purpose of our study was to determine the availability and timeliness of PCT test results at acute care hospitals in Massachusetts.

Methods

Study design. We conducted a survey of all acute care short-stay hospitals in the state of Massachusetts in August, 2016 to determine PCT assay availability, whether testing is performed on site or at an outside laboratory, and turnaround time. This study was reviewed by the institutional review board of the University of Massachusetts Medical School and determined not to be human subjects research.

Data collection. We contacted the laboratory of all acute care hospitals in Massachusetts by telephone and asked to speak with the

individual who could best answer our inquiry regarding PCT testing. We then asked the following questions: (1) “Is PCT testing available at specified hospital?” (2) “Is the testing performed on site, or are specimens sent to an outside laboratory?” (3) “If performed on site, what is the expected turnaround time for result availability?” and (4) “If specimens are sent to an outside laboratory, which laboratory is used?” We contacted each outside laboratory from question 4 to determine the processing time for the PCT assay.

We hypothesized that hospital characteristics might be associated with the availability of PCT test results. For example, for-profit hospitals may be more likely to perform PCT testing at a send-out laboratory for cost-savings reasons, or hospitals with higher quality ratings (e.g., Centers for Medicare and Medicaid Services [CMS] stars) may be more likely to offer evidence-based testing. Therefore, we collected descriptive data about each hospital (hospital size, profit status, teaching status, affiliation with multihospital system, and star rating) using publicly available information from the CMS Hospital Compare website (<https://www.medicare.gov/hospitalcompare/search.html>) and from the Massachusetts Center for Health Information and Analysis hospital profile website (<http://www.chiamass.gov/massachusetts-hospitals/>).

Data analysis. We computed descriptive statistics, including the number and percentage of hospitals with PCT testing available on site, not available, or performed at an outside laboratory. We compared differences in hospital characteristics on the basis of PCT testing availability using chi-square and *t* test. All statistical analyses were performed using SPSS version 24.

Results

All 61 of the 61 (100%) acute care hospitals in Massachusetts responded to our survey. PCT analysis was performed on site at 9 hospitals (14.8%), whereas 48 hospitals (78.7%) sent specimens to outside laboratories for PCT testing, and 4 hospitals (6.6%) did not offer testing at all. The turnaround time for PCT assays performed on site was less than 1 to 2 hours at eight of the nine hospitals that performed on-site analysis (13.1% of all hospitals). At one hospital with on-site testing, PCT turnaround time was less than 1 hour for tests performed during the day, but specimens received during the second and third shift took as long as 16 hours due to batching. The turnaround time for PCT assays performed at the 48 hospitals that used outside laboratories varied from 2 to 7 days, including time for transportation.

Hospitals with on-site PCT testing may be more likely to be nonprofit (100 vs. 80.8%, respectively; *P* = 0.15) and have lower mean CMS star ratings (2.89 vs. 3.23; *P* = 0.15) than hospitals where PCT testing was not available or was performed by outside

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hospitals, although the statistical power of these comparisons was limited by the small number of hospitals with on-site PCT testing. Hospitals where PCT was not performed on site or was unavailable were more likely to be affiliated with a multihospital health system than hospitals where PCT testing was performed on site (82.7 vs. 11.1%; $P < 0.0001$), as shown in Table 1.

Comment

Fewer than 20% of acute care hospitals in Massachusetts performed PCT testing on site. This finding is striking given the difference in turnaround time for PCT testing performed on site (<2 hours for most samples) as compared with testing at outside laboratories (2–7 d). In most of the randomized controlled trials demonstrating reduced antibiotic exposure with use of a PCT-based antibiotic algorithm (5–8), PCT testing was performed on site, 7 d/wk, with results available to treating clinicians within 3 hours. By comparison, with turnaround times measured in days as compared with hours at the majority of Massachusetts hospitals, the benefits of PCT-based algorithms on antibiotic initiation and duration is likely to be minimal, as found in recent observational studies (12, 13). Given the increased duration of antibiotics with PCT use in one observational study (12), it is also possible that clinicians may inadvertently prolong antibiotics courses while awaiting PCT results at hospitals with long turnaround times.

For most hospital characteristics, we did not find significant differences between hospitals where PCT testing was performed on site as compared with hospitals where it was unavailable or performed at an outside laboratory. Unexpectedly, hospitals that performed PCT testing on site were less likely to be part of a multihospital health system. This finding raises the possibility that decision-making about laboratory test processes may be made centrally, with less opportunity for input from frontline clinicians,

at hospitals that are part of a larger system. However, it should be noted that the hospital comparison is an exploratory analysis, limited by small sample size, and these findings should be considered hypothesis generating rather than definitive.

This study has several limitations. Due to the single-state sample, we were unable to assess geographic differences in PCT test performance, and therefore our findings may not be generalizable to all U.S. hospitals. We did not have information about PCT testing rates and were therefore unable to assess for association between on-site availability and usage. Finally, we did not assess other potential barriers that may also contribute to the limited impact of PCT in reducing antibiotic use in routine clinical practice. Such factors may include clinician knowledge of PCT, comfort with antibiotic deescalation, acceptance of PCT-based antibiotic algorithms, as well as institutional normative antibiotic prescribing practices and local antibiotic stewardship programs. However, in the absence of timely PCT test result availability, these barriers are expected to be of lesser consequence.

Despite these limitations, our findings demonstrate that PCT testing in routine clinical practice is not available to clinicians in a manner that would be expected to yield timely results or favorably impact antibiotic prescribing in the majority of hospitals in Massachusetts. Ensuring timely and widely available PCT test results is an important first step toward reaching the currently unrealized (12, 13) potential benefits of PCT-based algorithms for antibiotic stewardship outside of clinical trials.

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Table 1. Hospital characteristics on the basis of procalcitonin test processing and availability

Hospital Characteristic	Procalcitonin Assay Processing		P Value
	In House (n = 9)	Send out or Not Available (n = 52)	
Nonteaching status, n (%)	7 (77.8)	36 (69.2)	0.60
Size, n (%)			0.59
Small (<250 beds)	6 (66.7)	35 (67.3)	
Medium (250–424 beds)	1 (11.1)	11 (21.2)	
Large (≥425 beds)	2 (22.2)	6 (11.5)	
Size, No. of beds, median (IQR)	230 (129–443)	161 (76–284)	0.50
Nonprofit status, n (%)	9 (100)	42 (80.8)	0.15
Affiliated with multihospital system, n (%)	1 (11.1)	43 (82.7)	<0.0001
CMS star rating, mean (SD)	2.89 (0.60)	3.23 (0.73)	0.15

Definition of abbreviations: CMS = Centers for Medicare and Medicaid Services; IQR = interquartile range

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Epithelial Mesenchymal Transition in Chronic Obstructive Pulmonary Disease, a Precursor for Epithelial Cancers: Understanding and Translation to Early Therapy

To the Editor:

We read with interest the recent editorial by Nichole T. Tanner and colleagues, published in the *AnnalsATS*, considering the lethal association between chronic obstructive pulmonary disease (COPD) and lung cancer that highlighted the potential causal role of epithelial mesenchymal transition (EMT) in this link (1). Understanding these mechanisms is much needed for translation to early, and potentially even preventative, therapy. It is encouraging and reassuring that leading clinical respiratory journals are now recognizing this, as it has been difficult to obtain data on such a novel concept published in high-profile journals.

Human epidemiological studies strongly suggest that patients receiving high-dose inhaled corticosteroids have an appreciable (50%) reduction in the risk for lung cancer (2). We have hypothesized that EMT might be the process through which this effect of inhaled corticosteroids occurs. Thus, in a proof-of-concept randomized controlled trial, we reported that inhaled fluticasone propionate delivered in high doses over the course of 6 months did suppress airway epithelial activation and EMT-related changes in large airways of patients with COPD (3). This was the first study to report anti-EMT effects of inhaled corticosteroids in COPD. If this hypothesis is indeed correct, it has major implications for treating/preventing both obstructive airway fibrosis and lung cancer, although a more safe drug than steroids in these doses would be ideal for long-term use.

We were the first to report that EMT is an active process in both small and large airways of smokers and patients with COPD and was related to reduced lung function in COPD (4, 5). Several

other groups have since confirmed these findings. In the large airways, we found that active EMT is present and is associated with hypervascularity of the reticular basement membrane. This gives the typical appearance of active type 3 EMT, which is considered a premalignant condition. It is important to note that it is large airways where most of the squamous cell carcinomas occur, and type 3 EMT could be central to this. The other key pathology associated with COPD is small airway or peribronchiolar fibrosis and obliteration, and this could potentially be related to active type 2 EMT at this site, but fibrosis in general is also associated with malignancy (5).

Very recently, we also reported active EMT in the leading edge of invasive nonsmall cell lung cancer, both squamous and adenocarcinoma cell types, with the aggressiveness of the tumors being strongly related to the activity of their EMT (6). Further, EMT activity within the tumors closely related to EMT activity in nontumor-affected airway wall epithelium. This work suggests that the level of EMT activity in the airway wall, even in large airways amenable to bronchoscopic biopsy, could potentially be used as a marker for smokers most likely to develop both COPD and lung cancer.

In summary, we appreciate that major journals are beginning to recognize that epithelial activation and basal cell reprogramming with EMT (and epithelially related vessel changes) may represent fundamentally important aspects of COPD pathology, including the severe sequelae of airway fibrosis and cancer development. Indeed, we may now be getting into a position that allows an integrated understanding of this airway disease, with the potential to be translated into a new paradigm for earlier or even preventive therapy, attacking fundamental disease mechanisms rather than symptoms and clinical exacerbations in later-stage patients.

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