

## The Diagnostic Yield of Noninvasive Microbiologic Sputum Sampling in a Cohort of Patients with Clinically Diagnosed Hospital-Acquired Pneumonia

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The clinical predictors of positive sputum culture have not been previously reported in hospital-acquired pneumonia (HAP), and data on yield of sputum culture in this setting are scant. Current Infectious Disease Society of America guidelines for HAP recommend noninvasive sputum sampling, though the data for this practice are limited. We assessed the yield of sputum culture in HAP cases at an academic medical center from January 2007 to July 2013. HAP cases were identified by International Classification of Diseases, Ninth Revision-Clinical Modification codes for bacterial pneumonia and all cases were validated by chart review. Our cohort had 1172 hospitalizations with a HAP diagnosis. At least 1 sputum specimen was collected noninvasively and sent for bacterial culture after hospital day 2 and within 7 days of HAP diagnosis in 344 of these hospitalizations (29.4%),

with a total of 478 sputum specimens, yielding 63 (13.2%) positive, 109 (22.8%) negative, and 306 (64.0%) contaminated cultures (>10 epithelial cells per high power field). Significant predictors of a positive sputum culture were chronic lung disease (relative risk [RR] = 2.0; 95% confidence interval [CI], 1.2-3.4) and steroid use (RR = 1.8; 95% CI, 1.1-3.2). The most commonly identified organisms were Gram-negative rods not further speciated (25.9%), *Staphylococcus aureus* (21.0%), and *Pseudomonas aeruginosa* (14.8%). Because of the ease of obtaining a sputum sample combined with the prevalence of commonly drug-resistant organisms, we suggest that sputum culture in HAP is a potentially useful noninvasive diagnostic technique. *Journal of Hospital Medicine* 2018;13:34-37. Published online first October 18, 2017. © 2018 Society of Hospital Medicine

Pneumonia is a major cause of hospitalization, mortality, and healthcare cost.<sup>1,2</sup> The diagnosis involves clinical features plus radiographic evidence of infection. Hospital-acquired pneumonia (HAP) is defined by the Infectious Disease Society of America (IDSA) as a pneumonia that occurs ≥48 hours after admission and is not associated with mechanical ventilation.<sup>3</sup>

IDSA recommendations suggest that patients with suspected HAP be treated based on results of noninvasively obtained sputum cultures rather than being treated empirically.<sup>3</sup> This recommendation is graded as weak with low-quality evidence based on a lack of both evidence showing that respiratory cultures improve clinical outcomes and studies examining the yield of noninvasive collection methods.<sup>4,5</sup> However, resistant pathogens lead to a risk of inadequate empiric therapy, which is associated with increased mortal-

ity.<sup>6</sup> Culture data may provide an opportunity for escalation or de-escalation of antibiotic coverage. IDSA recommendations for microbiologic sampling are thus aimed at increasing appropriate coverage and minimizing unnecessary antibiotic exposure.

While the yield and clinical utility of sputum culture in community-acquired pneumonia has been studied extensively, data examining the yield of sputum culture in HAP (non-ventilator-associated pneumonia [non-VAP]) are sparse. In 1 small single-center study, researchers demonstrated positive sputum cultures in 17/35 (48.6%) patients with radiographically confirmed cases of HAP,<sup>7</sup> while in another study, researchers demonstrated positive sputum cultures in 57/63 (90.5%).<sup>8</sup> We aimed to identify the frequency with which sputum cultures positively identify an organism, identify predictors of positive sputum cultures, and characterize the microbiology of sputum cultures in a large cohort of HAP cases.

### METHODS

We conducted a retrospective cohort study of patients admitted to a large academic medical center in Boston, Massachusetts, from January 2007 to July 2013. All patients ≥18 years of age were eligible for inclusion. We excluded outside hospital transfers, those with a length of hospitalization <48 hours, and psychiatric admissions.

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Additional Supporting Information may be found in the online version of this article.

Received: May 1, 2017; Revised: July 11, 2017; Accepted: July 20, 2017

2018 Society of Hospital Medicine DOI 10.12788/jhm.2868

The study was approved by the institutional review board at the Beth Israel Deaconess Medical Center and granted a waiver of informed consent. Data were collected from electronic databases and supplemented by chart review.

### Hospital-Acquired Pneumonia

We defined HAP as pneumonia occurring at least 48 hours after admission, consistent with American Thoracic Society and IDSA criteria.<sup>3</sup> To identify cases, we reviewed the charts of all admissions identified as having a discharge *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code for bacterial pneumonia (481, 482, 483, 485, 486, 507), indicated as not “present-on-admission.” We validated that the treating clinician had clinically diagnosed pneumonia and initiated antibiotics for this purpose by performing chart review. We reviewed the radiologist interpretation of radiographs surrounding the date of the clinical diagnosis of pneumonia to confirm the presence of a new opacity. Uncertain cases (with respect to either the presence of pneumonia or the timing of the diagnosis) were reviewed by a second member of the study team and, in the case of disagreement, adjudicated by a third member of the study team. Only the first clinically validated HAP per hospitalization was included in the analysis. To focus on HAP rather than VAP, we excluded hospitalizations in which the date of a procedure code for mechanical ventilation preceded the date of pneumonia diagnosis.

### Microbiology

In our analysis, we used sputum samples obtained from expectorated or induced samples to evaluate the yield of noninvasive sputum sampling, as recommended by the IDSA. We included sputum samples collected  $\geq 48$  hours after admission and within 7 days of the clinical diagnosis of HAP. Sputum samples with  $>10$  epithelial cells per high-power field (hpf) were considered to be contaminated. Among noncontaminated samples, positive sputum cultures were defined as those with a microbiologic diagnosis other than “oral flora,” while those with no growth or growth of oral flora or only yeast were considered to be negative. The hospital’s microbiology laboratory does not routinely provide species identification for Gram-negative rods (GNRs) growing on culture in the presence of growth of  $\geq 3$  other colony types. We considered such GNRs (not further speciated) to represent a positive culture result in our analysis given that colonization versus pathogenicity is a clinical distinction and, as such, these results may impact antibiotic choice.

### Statistical Analysis

Data were analyzed by using SAS software, version 9.3. We used a 2-sided  $P$  value of  $<.05$  to indicate statistical significance for all comparisons. We used the  $\chi^2$  test and the non-parametric median test for unadjusted comparisons.

To identify predictors of a positive (versus negative or contaminated) sputum culture among patients with HAP, we used a generalized estimating equation model with a Poisson distribution error term, log link, and first-order autoregressive correlation structure to account for multiple sputum specimens

per patient. We combined culture negative and contaminated samples to highlight the clinical utility of sputum culture in a real-world setting. Potential predictors chosen based on clinical grounds included all variables listed in Table 1. We defined comorbidities specified in Table 1 via ICD-9-CM secondary diagnosis codes and diagnosis related groups (DRGs) using Healthcare Cost and Utilization Project Comorbidity Software, version 3.7, based on the work of Elixhauser et al.<sup>9,10</sup>; dialysis use was defined by an ICD-9-CM procedure code of 39.95; inpatient steroid use was defined by a hospital pharmacy charge for a systemic steroid in the 7 days preceding the sputum sample.

## RESULTS

There were 230,635 hospitalizations of patients  $\geq 18$  years of age from January 2007 to July 2013. After excluding outside hospital transfers ( $n = 14,422$ ), hospitalizations  $<48$  hours in duration ( $n = 59,774$ ), and psychiatric hospitalizations ( $n = 9887$ ), there were 146,552 hospitalizations in the cohort.

Pneumonia occurred  $\geq 48$  hours after admission in 1688 hospitalizations. Excluding hospitalizations where pneumonia occurred after mechanical ventilation ( $n = 516$ ) resulted in 1172 hospitalizations with (non-VAP) HAP. At least 1 sputum specimen was collected noninvasively and sent for bacterial culture after hospital day 2 and within 7 days of HAP diagnosis in 344 of these hospitalizations (29.4%), with a total of 478 sputum specimens (398 expectorated, 80 induced). Hospitalizations of patients with noninvasive sputum sampling were more likely to be male (63.1% vs 50.9%;  $P = .001$ ) and to have chronic lung disease (24.4% vs 17.5%,  $P = .01$ ) but were otherwise similar to hospitalizations without noninvasive sampling (Supplemental Table 1).

Of these 478 specimens, there were 63 (13.2%) positive cultures and 109 (22.8%) negative cultures, while 306 (64.0%) were considered contaminated. Table 1 displays the cohort characteristics overall and stratified by sputum culture result. For positive cultures, the median number of days between specimen collection and culture finalization was 3 (25th-75th percentile 2-4). On review of the gram stains accompanying these cultures, there were  $>25$  polymorphonuclear cells per hpf in 77.8% of positive cultures and 59.4% of negative cultures ( $P = .02$ ).

The top 3 bacterial organisms cultured from sputum samples were GNRs not further speciated (25.9%), *Staphylococcus aureus* (21.0%), and *Pseudomonas aeruginosa* (14.8%). The frequencies of isolated microorganisms are presented in Table 2.

In an adjusted analysis (Table 1), the significant predictors of a positive sputum culture were chronic lung disease (relative risk [RR] = 2.0; 95% confidence interval [CI], 1.2-3.4) and steroid use (RR = 1.8; 95% CI, 1.1-3.2).

## DISCUSSION

To our knowledge, our study is the first to assess the predictors of positive sputum culture among patients with HAP (non-VAP) who had sputum samples obtained noninvasively, and this study is larger than prior studies in which research-

**TABLE 1. Cohort Characteristics, Overall and Stratified By Sputum Culture Result, and Adjusted Association Between Each Characteristic And Sputum Culture Positivity**

| Characteristic  | Overall<br>n = 478 | Positive Culture<br>n = 63 | Negative or Contaminated<br>Culture<br>n = 415 | Adjusted Relative Risk <sup>a</sup><br>[95% CI]<br>n = 478 |
|---|--------------------|----------------------------|--|--|
| Age in years – median (25th-75th percentile)                                    | 68.0 (56-75)       | 68.0 (60.0-75.0)           | 68.0 (55.0-75.0)                               | 1.0 [1.0-1.0]  |
| Gender  |                    |                            |  |  |
| Female  | 166 (34.7%)        | 26 (41.3)                  | 140 (33.7)                                     | Reference  |
| Male  | 312 (65.3%)        | 37 (58.7)                  | 275 (66.3)                                     | 0.9 [0.5-1.5]  |
| Hospital day on which the sample was obtained—<br>median (25th-75th percentile) | 7.0 (5-12)         | 8.0 (5.0-14.0)             | 7.0 (5.0-12.0)                                 | 1.0 [1.0-1.0]  |
| Collection method   |                    |                            |  |  |
| Expectorated  | 398 (83.3%)        | 56 (88.9)                  | 342 (82.4)                                     | Reference  |
| Induced   | 80 (16.7%)         | 7 (11.1)                   | 73 (17.6)                                      | 0.7 [0.3-1.5]  |
| Patient Location  |                    |                            |  |  |
| Ward  | 375 (78.5%)        | 46 (73.0)                  | 329 (79.3)                                     | Reference  |
| Intensive Care Unit   | 103 (21.6%)        | 17 (27.0)                  | 86 (20.7)                                      | 1.3 [0.8-2.3]  |
| Service   |                    |                            |  |  |
| Surgical  | 149 (31.2%)        | 23 (36.5)                  | 126 (30.4)                                     | Reference  |
| Medical   | 329 (68.8%)        | 40 (63.5)                  | 289 (69.6)                                     | 0.6 [0.4-1.2]  |
| Comorbidities   |                    |                            |  |  |
| Congestive Heart Failure  | 92 (19.3%)         | 14 (22.2)                  | 78 (18.8)                                      | 1.2 [0.6-2.3]  |
| Chronic Lung Disease  | 113 (23.6%)        | 26 (41.3)                  | 87 (21.0)                                      | 2.0 [1.2-3.4] <sup>b</sup>                                 |
| Diabetes Mellitus   | 124 (25.9%)        | 17 (27.0)                  | 107 (25.8)                                     | 0.9 [0.5-1.7]  |
| Chronic Liver Disease   | 37 (7.7%)          | 6 (9.5)                    | 31 (7.5)                                       | 1.5 [0.7-3.2]  |
| Dialysis  | 39 (8.2%)          | 8 (12.7)                   | 31 (7.5)                                       | 1.6 [0.8-3.2]  |
| Steroid Use   | 117 (24.5%)        | 22 (34.9)                  | 95 (22.9)                                      | 1.8 [1.1-3.2] <sup>b</sup>                                 |

<sup>a</sup>Adjusted relative risk determined using a generalized estimating equation model with a Poisson distribution error term, log link, and first-order autoregressive correlation structure controlling for all characteristics simultaneously as independent variables.

<sup>b</sup>Numbers represent statistically significant associations between comorbidities and sputum culture positivity.

Note: Abbreviations: ICU, intensive care unit.

ers reported on sputum culture yield in HAP. Sputum samples were obtained in 29.4% cases of clinically diagnosed HAP. Although 87% of specimens obtained were culture-negative or contaminated, 13% yielded a bacterial organism. Although we do not report the antibiotic sensitivity patterns of the isolated organisms, the organisms identified frequently demonstrate antibiotic resistance, highlighting the potential for both antibiotic escalation and de-escalation based on sputum culture. In a multivariable model, presence of chronic lung disease and steroid use in the preceding week were both significantly associated with culture positivity.

The retrospective nature of the study raises the possibility of selection bias from systematic differences between the 29.4% of patients with HAP who had sputum collected and those who did not. Patients with sputum cultures were similar to patients without cultures in most measured characteristics, but we are unable to know what the yield of noninvasive sputum culture would have been had all patients with HAP been sampled. As such, our findings reflect the yield of sputum culture among patients with HAP for whom cultures were successfully obtained. It is not clear why only 29.4% of HAP patients received IDSA guideline-concordant care, but similar rates of culture

use are reported elsewhere.<sup>7</sup> While physician decision-making could have contributed to this finding, it is also possible that many sick, hospitalized patients are simply unable to produce sputum for analysis. In future studies, researchers should examine barriers to guideline-concordant care.

We considered a culture result of GNRs (not further speciated) as positive in our analysis because this result indicates growth of mixed bacterial types, the pathogenicity of which is a clinical determination. Physicians may request speciation and antibiotic sensitivities and, as such, these results have the potential to impact antibiotic choice. Had we considered such cultures to be negative or contaminated, the rate of culture positivity would have been only slightly reduced from 63/478 (13.2%) to 50/478 (10.5%).

The strengths of our study include the chart-based validation of administratively identified cases of pneumonia and a large cohort. There are also limitations. The single-center nature of the study has implications for pretest probability and generalizability. Additionally, in our study, we did not examine outcomes among patients treated empirically versus those treated based on sputum culture results. Finally, our reliance on administrative codes to identify cases of HAP for subsequent validation could

TABLE 2. Microbiology of Positive Sputum Cultures.

| Organism  | n <sup>a</sup> | % of Isolated Organisms |
|---|----------------|-------------------------|
| Gram-negative rods (not further speciated) <sup>b</sup> | 21             | 25.9                    |
| <i>Staphylococcus aureus</i>                            | 17             | 21.0                    |
| <i>Pseudomonas aeruginosa</i>                           | 12             | 14.8                    |
| <i>Haemophilus influenzae</i>                           | 5              | 6.2                     |
| <i>Klebsiella pneumoniae</i>                            | 5              | 6.2                     |
| <i>Escherichia coli</i>                                 | 3              | 3.7                     |
| <i>Streptococcus pneumoniae</i>                         | 3              | 3.7                     |
| <i>Moraxella catarrhalis</i>                            | 3              | 3.7                     |
| Beta streptococci (not group A)                         | 3              | 3.7                     |
| <i>Enterobacter cloacae</i>                             | 3              | 3.7                     |
| <i>Serratia marcescens</i>                              | 2              | 2.5                     |
| <i>Klebsiella oxytoca</i>                               | 1              | 1.2                     |
| <i>Enterobacter aerogenes</i>                           | 1              | 1.2                     |
| <i>Stenotrophomonas maltophilia</i>                     | 1              | 1.2                     |
| <i>Mycobacterium avium complex</i>                      | 1              | 1.2                     |

<sup>a</sup>Number of speciated organisms (n = 81) adds up to more than total number of positive cultures (n = 63) because some cultures grew multiple organisms. <sup>b</sup>Not further speciated because of the presence of  $\geq 3$  other bacterial types growing on culture, based on our microbiology laboratory protocol.

have resulted in incomplete capture of HAP cases.

In conclusion, in our study, we provide an estimate of the diagnostic yield of sputum culture in a large cohort with chart-validated HAP, a description of HAP microbiology, and predictors of positive sputum culture. Thirteen percent of patients who had sputum culture testing received a microbiologic diagnosis. Because of the relative ease of obtaining a sputum sample and the microbiologic distribution in our study (representing

a mix of commonly drug-resistant pathogens and more typical community-acquired pathogens), we suggest that sputum culture in HAP is a useful diagnostic tool with the potential to inform antibiotic escalation or de-escalation.

## Acknowledgments

Dr. Herzig was funded by grant number K23AG042459 from the National Institute on Aging. Dr. Marcantonio was funded by grant number K24AG035075 from the National Institute on Aging. The funding organizations had no involvement in any aspect of the study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosure: No conflicts of interest apply for any of the authors.

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