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

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Abstract

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 IDSA guidelines for HAP recommend non-invasive 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 1/2007–7/2013. HAP cases were identified by ICD-9 codes for bacterial pneumonia and all cases were validated by chart review. Our cohort had 1,172 hospitalizations with a HAP diagnosis. At least 1 sputum specimen was collected non-invasively 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/hpf). Significant predictors of a positive sputum culture were chronic lung disease (RR 2.0, 95% confidence interval 1.2–3.4) and steroid use (RR 1.8, 95% confidence interval 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%). The ease of obtaining a sputum sample combined with the prevalence of commonly drug-resistant organisms suggests that sputum culture in HAP is a potentially useful non-invasive diagnostic technique.

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Keywords

hospital-acquired pneumonia; nosocomial pneumonia; sputum culture; sputum sample; microbiology; diagnostic yield

INTRODUCTION:

Pneumonia is a major cause of hospitalization, mortality, and healthcare cost [1,2]. 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, not associated with mechanical ventilation [3].

IDSA recommendations suggest that patients with suspected HAP be treated based on results of noninvasively obtained sputum cultures rather than being treated empirically [4]. 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 non-invasive collection methods [5, 6]. However, resistant pathogens lead to risk of inadequate empiric therapy, which is associated with increased mortality [7]. 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 (CAP) has been studied extensively, data examining the yield of sputum culture in HAP (non-VAP) are sparse. One small single-center study demonstrated positive sputum cultures in 17/35 (48.6%) patients with radiographically confirmed cases of HAP [8], while another demonstrated positive sputum cultures in 57/63 (90.5%) [9]. 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 1/2007–7/2013. 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.

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

HAP:

We defined HAP as pneumonia occurring at least 48 hours after admission, consistent with ATS and IDSA criteria [10]. 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 presence of pneumonia or timing of 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:

Our analysis used sputum samples obtained from expectorated or induced samples to evaluate the yield of non-invasive sputum sampling, as recommended by the IDSA. We included sputum samples collected 48 hours after admission and within 7 days of the clinical diagnosis of HAP. Sputum samples with >10 epithelial cells/hpf were considered to be contaminated. Among non-contaminated 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 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 using SAS software, version 9.3. We used a two-sided p -value of <0.05 to indicate statistical significance for all comparisons. We used the Chi-square 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 auto-regressive 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 DRGs using Healthcare Cost and Utilization Project Comorbidity Software, version 3.7, based on the work of Elixhauser *et al.* [11, 12]; 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 18 years of age from 1/2007–7/2013. After excluding outside hospital transfers ($n = 14,422$), hospitalizations < 48 hours in duration ($n = 59,774$), and psychiatric hospitalizations ($n = 9,887$), there were 146,552 hospitalizations in the cohort.

Pneumonia occurred 48 hours after admission in 1,688 hospitalizations. Excluding hospitalizations where pneumonia occurred after mechanical ventilation ($n=516$) resulted in 1,172 hospitalizations with (non-VAP) HAP. At least 1 sputum specimen was collected non-invasively 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 with non-invasive sputum sampling were more likely to be male (63.1% vs. 50.9%, $p=0.001$) and to have chronic lung disease (24.4% vs. 17.5%, $p=0.01$), but were otherwise similar to hospitalizations without non-invasive 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/hpf in 77.8% of positive cultures and 59.4% of negative cultures ($p=0.02$).

The top three 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 adjusted analysis (Table 1), the significant predictors of a positive sputum culture were chronic lung disease (RR 2.0, 95% confidence interval 1.2–3.4) and steroid use (RR 1.8, 95% confidence interval 1.1–3.2).

DISCUSSION:

Our study is the first to assess the predictors of positive sputum culture among patients with HAP (non-VAP) who had sputum samples obtained non-invasively, and is larger than prior studies reporting 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 non-invasive 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 [13]. 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. Future studies should examine barriers to guideline-concordant care.

We considered a culture result of GNRs (not further speciated) as positive in our analysis since 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%).

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, our study 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 have resulted in incomplete capture of HAP cases.

In conclusion, our study provides 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. 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, suggests that sputum culture in HAP is a useful diagnostic tool with the potential to inform antibiotic escalation or de-escalation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Cohort characteristics, overall and stratified by sputum culture result, and adjusted association between each characteristic and sputum culture positivity.

Characteristic	Overall	Positive Culture	Negative / Contaminated Culture	Adjusted relative risk* [95% CI]
	n=478	n=63	n=415	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 sample obtained – 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
ICU	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]
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]

* Adjusted relative risk determined using a generalized estimating equation model with a Poisson distribution error term, log link, and first-order auto-regressive correlation structure controlling for all characteristics simultaneously as independent variables

Table 2:

Microbiology of positive sputum cultures.

	n *	% of isolated organisms
Organism		
Gram-negative rods (not further speciated) **	21	25.9
Staph aureus	17	21.0
Pseudomonas aeruginosa	12	14.8
Haemophilus influenzae	5	6.2
Klebsiella pneumoniae	5	6.2
Escherichia coli	3	3.7
Streptococcus pneumoniae	3	3.7
Moraxella catarrhalis	3	3.7
Beta streptococci (not group A)	3	3.7
Enterobacter cloacae	3	3.7
Serratia marcescens	2	2.5
Klebsiella oxytoca	1	1.2
Enterobacter aerogenes	1	1.2
Stenotrophomonas maltophilia	1	1.2
Mycobacterium avium complex	1	1.2

* Number of speciated organisms (n=81) adds up to more than total number of positive cultures (n=63) because some cultures grew multiple organisms.

** Not further speciated due to presence of 3 other bacterial types growing on culture, based on our microbiology laboratory protocol.