Published in final edited form as:

Neurocrit Care. 2017 February ; 26(1): 58–63. doi:10.1007/s12028-016-0285-3.

Cost and utility of microbiological cultures early after intensive care unit admission for intracerebral hemorrhage

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Abstract

Background and Purpose: Fever is common among intensive care unit (ICU) patients.

Clinicians may use microbiological cultures to differentiate infectious and aseptic fever. However, their utility depends on the prevalence of infection and false positive results might adversely affect patient care. We sought to quantify the cost and utility of microbiological cultures in a cohort of ICU patients with spontaneous intracerebral hemorrhage (ICH).

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Disclosures: Dr. Hess has consulted for Philips Respironics and Bayer, received lecture honoraria from Medtronic Covidien and royalties from McGraw-Hill, Jones and Bartlett, and UpToDate. Dr. Greenberg has consulted for Hoffman La-Roche, and received payment for lectures from U of Texas-Grand Rounds. Dr. Goldstein has received consulting and research fees from CSL Behring and consulting fees from Boehringer Ingelheim.

Methods: We performed a secondary analysis of a cohort with spontaneous ICH requiring mechanical ventilation. We collected baseline data, measures of systemic inflammation, microbiological culture results for the first 48h, and daily antibiotic usage. Two physicians adjudicated true positive and false positive culture results using standard criteria. We calculated the cost per true positive result, and used logistic regression to test the association between false positive results with subsequent antibiotic exposure.

Results: Overall, 697 subjects were included. A total of 233 subjects had 432 blood cultures obtained, with one true positive (diagnostic yield 0.1%, \$22,200 per true positive), and 11 false positives. True positive urine cultures (5%) and sputum cultures (13%) were more common, but so were false positives (6% and 17%, respectively). In adjusted analysis, false positive blood and sputum results were associated with increased antibiotic exposure.

Conclusion: The yield of blood cultures early after spontaneous ICH was very low. False positive results significantly increased odds of antibiotic exposure. Our results support limiting use of blood cultures in the first days after ICU admission for spontaneous ICH.

Keywords

Intracerebral hemorrhage; critical illness; microbiology; culture; antimicrobial

Introduction

Fever is common in the intensive care unit (ICU).¹ Among patients with critical neurological illnesses, brain tissue injury causes systemic inflammation via up-regulation of tumor necrosis factor-alpha, interleukin-8 and leukotriene B-4,^{2,3} often resulting in aseptic fever. This is especially common after spontaneous intracerebral hemorrhage (ICH), where fevers develop in up to 91% of patients.⁴ Differentiating infectious from noninfectious causes of fever and the systemic inflammatory response syndrome (SIRS) can be challenging. Consensus guidelines recommend that microbiological cultures be obtained in febrile ICU patients when clinical evaluation does not strongly suggest a non-infectious cause of fever.⁵ However, contaminated (false positive) cultures are common, and might lead to increased antibiotic exposure, ICU length of stay and hospital costs.⁶

To our knowledge, the utility of obtaining microbiological cultures to screen ICU patients with ICH for infectious causes of fever has not been examined. Because non-infectious etiologies of fever and systemic inflammation are common in this population, we hypothesized that obtaining blood, urine and sputum cultures in these patients would be common in the first 48 hours after presentation and the yield for potentially clinically important pathogens would be low. We secondarily hypothesized that contaminated (false positive) cultures would be common and associated with an increase in subsequent antimicrobial exposure. In order to focus our analysis on the most severely injured patients, and those for whom the most comprehensive data was available, we analyzed those ICH patients requiring mechanical ventilation.

Methods

We performed a secondary analysis of a cohort of patients presenting to two academic medical centers with spontaneous ICH from June 1st, 2000 to November 1st, 2010. The details of the cohort are described elsewhere.⁷ Briefly, patients were included if they presented to the emergency department during the study period with spontaneous ICH severe enough to require mechanical ventilation. Patients were excluded for age <18 years; ICH secondary to head trauma, ischemic stroke with hemorrhagic transformation, brain tumor, vascular malformation or vasculitis; if they were mechanically ventilated only during an operative intervention; if they were declared brain dead or their goals of care were made comfort measures only prior to admission; or for a history of significant immunodeficiency including human immunodeficiency virus infection, cytotoxic chemotherapy within one month of admission, leukemia or common variable immunodeficiency.

We performed a structured chart review using REDCap.⁸ Trained clinical research coordinators abstracted clinical data under the supervision of a physician. Data in the original study were collected until the patient met one of the following endpoints: death, transfer out of the ICU, hospital day 5, or development of acute respiratory distress syndrome (the outcome of interest in the initial study). We recorded baseline clinical characteristics on all patients including age, sex and date and site presentation, as well as disease-specific markers of severity including Glasgow Coma Scale score (GCS), hematoma size, hematoma location and presence of intraventricular hemorrhage, which we used to calculate each patient's ICH Score.⁹ We abstracted clinical data in the emergency department and for each ICU day from electronic records and nursing flow sheets including vital sign, vasopressor administration, white blood cell (WBC) counts, and microbiology culture data for all blood, urine and sputum cultures that were obtained. Cultures were obtained at the discretion of the treating physician when deemed appropriate, but no specific protocol guided attainment of cultures. For the present study, only cultures obtained in the first 48h of admission were analyzed. A board certified attending radiologist reviewed all chest imaging to adjudicate the presence of infiltrates consistent with pneumonia. We calculated the daily burden of systemic inflammatory response syndrome (SIRS) by assigning points based on standard criteria (heart rate >90, respiratory rate >20 or PaCO₂ <35mmHg, temperature >38°C, or <36°C, and WBC count <4×10³/μL or >12×10³/μL).

We defined fever as a core temperature >38.3°C based on consensus guidelines, and also examined those patients with temperatures >38.9°C, which has a higher sensitivity for infectious etiologies of fever in a general ICU population.^{5,10,11} The results of all blood, urine and sputum cultures were reviewed by two physicians, one specializing in critical care and one in infectious disease. In adjudicating the results of positive blood cultures, we considered all fungi, Gram-positive cocci and Gram-negative rods to be pathogens if they grew from multiple blood culture bottles or also grew from urine or sputum cultures. We considered blood cultures with common contaminate species (i.e. skin flora) in a single bottle to be false positives. Urine cultures were considered positive if they grew at least 10,000 colony forming units (CFUs) of a uropathogen including *Escherichia coli*, *Enterobacter*, *Staphylococcus*, or *Enterococcus*.¹² Based on 2015 ventilator-associated pneumonia guidelines from the Centers for Disease Control and Prevention, we considered

purulent sputum cultures to be positive, defined as bacterial growth with abundant or 4+ polymorphonucleocytes with no, rare or occasional epithelial cells.¹³ We calculated kappa scores to assess inter-rater reliability in adjudicating culture results.

To evaluate the impact of cultures on downstream antibiotic exposure, we abstracted daily antibiotic usage for the first 5 days of hospitalization for all subjects. Based on institutional practice at the time, we considered post-procedural antimicrobials targeting gram positives (e.g. cefazolin or vancomycin administered after external ventricular drain or craniectomy) to be prophylactic. All other parenteral antimicrobials were considered to be active treatment.

Statistical methods

We used descriptive statistics to examine population characteristics and the rate of true, positive, false positive and negative culture results. We summarized demographic and clinical characteristics using median with interquartile range for continuous variables and proportions for categorical variables. We calculated the cost of each culture to be \$50 per culture and an additional \$50 for speciation and sensitivities for cultures with any growth, an estimate based on the average cost during the study period at our institutional laboratory. We summed these costs and divided by the number of true positive results to obtain an estimated cost per true positive result.

To assess the impact of contaminated (false positive) culture results on antibiotic exposure, we first used logistic regression to test the unadjusted association of biologically plausible baseline and clinical covariates with antibiotic exposure, then constructed separate adjusted models for each culture site including covariates with an unadjusted $p < 0.10$. It was our initial intent to adjust for presence of central venous and Foley catheters in our analysis, but in this cohort these were almost universally present, preventing their inclusion in statistical models. We calculated Hosmer-Lemeshow statistics to test the goodness of fit of these adjusted model.

Results

During the 10-year study period, 697 subjects presented and met inclusion and exclusion criteria. Median age was 71 years (interquartile range 59 – 79 years) and 53% were male (Table 1). The vast majority of subjects (628 (90%)) met at least 2 SIRS criteria in the first 48 hours after presentation, and 221 (35%) were febrile at a threshold of $\geq 38.3^{\circ}\text{C}$ (Table 2). Roughly a quarter (169 (24%)) of subjects received vasopressors.

A total of 233 subjects had 432 blood cultures obtained during the first 2 days, with one true positive culture (diagnostic yield 0.1%), 11 contaminated culture results and a cost of \$22,200 per positive culture (Table 3). Signs of systemic inflammation and vasopressor dependence were associated with increased odds of blood culture obtainment, but year of presentation was not (Supplemental Table 1). The positive blood culture that met criteria to be considered a true positive was obtained in an afebrile subject and grew *Enterococcus* in 1 of 4 blood culture bottles, with negative sputum and urine cultures, prompting linezolid to be added to her empiric antibiotic regimen. A source for this positive blood culture was never

identified. The true positive rate for urine cultures (5%) and sputum cultures (13%) was higher than for blood cultures, but so were false positives (6% and 17%, respectively). The adjudication process for culture results had excellent inter-rater reliability (kappa = 1.0, 0.90 and 0.97 for blood, urine and sputum, respectively).

Overall 278 patients (40%) received non-prophylactic antibiotics. Younger age, male sex, fever, greater number of SIRS criteria met, and radiographic infiltrates on chest imaging were all associated with antibiotic exposure (Table 4). In unadjusted analysis, false positive blood culture results were associated with a 4-fold increase in the odds of antibiotic exposure, and false positive sputum cultures were associated with a >3-fold increase in the odds of antibiotic exposure. Both of these associations remained statistically significant in adjusted models (Table 5). Hosmer-Lemeshow test statistics for these adjusted indicated good fit.

Discussion

Our main findings are that microbiological cultures were obtained commonly in the first 48 hours after presentation of critically ill subjects with spontaneous ICH. The yield of blood cultures for true bacteremia was exceedingly low, the total cost per true positive culture was substantial, and the false positive (contaminated) blood culture results were independently associated with a significant increase in subsequent antibiotic exposure. This is of clinical importance, since unnecessary antibiotic exposure increases the risk of developing resistant infections and medication-related adverse events.¹⁴

The rate of true positive sputum and urine cultures was higher, reflecting the higher prevalence of pulmonary and urinary infections compared to bacteremia in the cohort. This is consistent with previous studies that report aspiration pneumonitis and pneumonia occur in up to 20% of patients with ICH, often early after ictus.¹⁵ Similarly, the urinary tract is the most common site of infection in patients hospitalized after ICH;¹⁶ however, as we focused on the first 2 hospital days, it is likely that most positive urine cultures represented asymptomatic bacteriuria or infection present on admission.

Consideration of our study design suggests important caveats regarding its generalizability. By including only subjects with spontaneous ICH, we excluded those with hemorrhage secondary to mycotic aneurysm or septic embolus. Although rare, accounting for just 2 of 1013 ICH cases in the largest available cohort study,¹⁷ accurately identifying these etiologies of ICH is clinically important. Our results do not imply that blood cultures are of limited utility if ICH secondary to an underlying infectious process is considered possible. Similarly, we included only mechanically ventilated patients treated at academic medical centers, so caution is advisable generalizing our results outside this setting. However, we speculate that the patients we included are likely to be at equal or higher risk of infection than the overall ICH population given their overall APACHE-II scores, mechanical ventilation and rates of vasopressor dependence, which would only inflate our estimation of the utility of obtaining cultures. Additionally, cultures were obtained at the discretion of the treating clinical team rather than at random or systematically. If clinical suspicion for the presence of infection was better than random chance, this would have led us to over-estimate

the utility of cultures. Conversely, we may have failed to detect true infection in patients where cultures were not obtained, obtained at a referring facility prior to transfer to one of our centers, or in patients who received antibiotics prior to transfer that were not captured in our chart review and may have partially sterilized their cultures.

A limitation of our study is our reliance on microbiological culture results, particularly in the case of sputum and urine cultures. Although we treated the presence of purulent sputum cultures or uropathogens as positive test results, these findings do not necessarily imply active infection. Differentiating asymptomatic bacteriuria and respiratory tract colonization from acute infection is challenging and relies on multiple clinical features in addition to culture results.^{18,19} Although our inter-rater reliability was excellent, by adjudicating true positive cultures without considering other clinical features, we may have misclassified some false positive results as true positives and thereby over-estimated the diagnostic yield of these tests. Another limitation inherent to all observational studies is our ability to assert association but not causality in the relationship between false positive culture results and subsequent antibiotic exposure. Finally, our estimates of the direct costs of cultures do not include the potentially considerable downstream costs of false positive culture results. These are best characterized for false positive (contaminated) blood cultures, and are likely in excess of \$10,000 per patient with false positive results.²⁰ Thus, our estimated direct cost calculations may substantially underestimate the true costs associated with indiscriminant microbiological testing.

In conclusion, although fever, vasopressor dependence and systemic inflammation were common in this cohort, bacteremia and the diagnostic yield of blood cultures was low leading us to question their clinical utility. Moreover, false positive results significantly increased the risk of antibiotic exposure. We believe our results support limiting use of blood cultures in the first 2 days after ICU admission for spontaneous ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding: This work was supported by grants from the Emergency Medicine Foundation/ Emergency Medicine Resident's Association, the Department of Emergency Medicine at Brigham and Women's Hospital, and the National Institutes of Health (R01NS073344, R01NS059727, 5K23NS059774 and 5K12HL109068).

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Table 1 –

Baseline population characteristics and severity of illness on presentation

Baseline Characteristic	Overall cohort (n = 697)
Age, years	71 [59 – 79]
Male sex	368 (53)
GCS	7 [4 – 11]
APACHE-II	20 [16 – 25]
ICH score	3 [2 – 4]
ICH volume, mL	
<30	253 (42)
30 to 60	121(20)
60 to 90	74 (13)
90	102 (17)
Intraventricular hemorrhage	136(22)
Infratentorial hemorrhage	43 (7)
Initial WBC count, 10 ³ /μL	11.4 [9.0 – 14.8]
Initial Temperature, °C	35.7 [36.2 – 36.8]
Heart rate, beats per minute	80 [68 – 94]
Mean arterial pressure, mmHg	114 [97 – 133]

Data are presented as median with interquartile range or number with corresponding percentage.

Abbreviations – GCS – Glasgow Coma Scale; APACHE-II – Acute Physiology and Chronic Health Evaluation - II; ICH – Intracerebral hemorrhage; WBC – white blood cell.

Table 2 –

Patient characteristics during the first two hospital days

Characteristic	Day 1 (n = 697)	Day 2 (n = 591)	Cumulative (n = 697)
Maximum temperature			
38.3°C	139 (20)	159 (27)	221 (32)
38.9 °C	84 (12)	77 (13)	125 (18)
Maximum WBC > 12×10 ³ /μL	390 (56)	300 (51)	485 (70)
Bandemia >10%	19 (3)	12 (2)	31 (4)
Maximum SIRS criteria met			
0	29 (4)	33 (6)	7 (1)
1	132 (19)	99 (17)	62 (9)
2	267 (38)	192 (32)	214 (31)
3	208 (30)	187 (32)	287 (41)
4	61 (9)	80 (14)	127 (18)
Vasopressor dependence	99 (14)	144 (24)	169 (24)
Infiltrate on chest imaging	35 (5)	38 (6)	91 (13)

Data are presented number with corresponding percentage.

Abbreviations: WBC – White blood cell count; SIRS – Systemic inflammatory response syndrome.

Table 3 –

Daily microbiological culture acquisition and results

Microbiology cultures	Day 1 (n = 697)	Day 2 (n = 591)	Cumulative (n = 697)	Estimated <u>direct</u> costs
Blood				
Patients tested	125 (18)	131(22)	233 (33)	Total:
Total cultures obtained	214	218	432	\$22,200
True positive	1 (0.1)	0 (0)	1 (0.1)	Per true positive:
False positive (contaminant)	6 (1)	5 (0)	11 (2)	\$22,200
Urine				
Patients tested	154 (22)	134(23)	261 (37)	Total:
Total cultures obtained	160	137	297	\$18,750
True positive	21 (3)	15 (2)	36 (5)	Per true positive:
False positive (contaminant)	22 (3)	20 (3)	42 (6)	\$521
Sputum				
Patients tested	100 (14)	146(25)	227 (33)	Total:
Total cultures obtained	101	148	249	\$23,000
True positive	43 (6)	52 (7)	92 (13)	Per true positive:
False positive (contaminant)	44 (6)	76 (11)	119 (17)	\$250

Data are presented number with corresponding percentage.

Table 4 –

Factors associated with subsequent antibiotic exposure after intracerebral hemorrhage

Characteristic	Unadjusted odds ratio (95%CI)	P value
Age, per decade	0.83 (0.74 – 0.93)	0.001
Male sex	2.17 (1.49 – 2.97)	<0.001
Temperature		
>38.3 °C	1.92 (1.40 – 2.65)	<0.001
>38.9 °C	1.49 (1.03 – 2.17)	0.04
WBC > 12k/dL	1.19 (0.81 – 1.54)	0.49
Bandemia >10%	1.90 (0.90 – 4.01)	0.09
Number of SIRS criteria met	1.38 (1.16 – 1.64)	<0.001
Infiltrates on chest imaging	3.62 (2.06 – 6.39)	<0.001
Microbiology results		
Blood – true positive	Unable *	--
Blood – false positive	4.09 (1.08 – 15.55)	0.04
Sputum – true positive	2.97 (1.88 – 4.67)	<0.001
Sputum – false positive	3.27 (2.17– 4.94)	<0.001
Urine – true positive	3.65 (1.76 – 7.54)	<0.001
Urine – false positive	1.54 (0.82 – 2.88)	0.18

* Only one subject in this category, precluding regression.

Abbreviations: WBC – White blood cell count; SIRS – Systemic inflammatory response syndrome.

Table 5 –

Adjusted associations between false positive culture results and subsequent antibiotic exposure after intracerebral hemorrhage

False positive culture site	Adjusted odds ratio* (95%CI)	P value
Blood	4.04 (1.02 – 16.05)	0.04
Sputum	2.80 (1.80 – 4.36)	<0.001
Urine	1.68 (0.87 – 3.24)	0.12
Any false positive	2.77 (1.86 – 4.12)	<0.001

* Adjusted for age, sex, fever >38.3°C and number of SIRS criteria met. Sputum odds ratio is also adjusted for presence of infiltrate on chest imaging.