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# Assessment of Impact of Peptide Nucleic Acid Fluorescence *In Situ* Hybridization for Rapid Identification of Coagulase-Negative Staphylococci in the Absence of Antimicrobial Stewardship Intervention▽

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**Peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) was instituted at Boston Medical Center for the rapid identification of coagulase-negative staphylococci (CoNS). Without active notification or antimicrobial stewardship intervention, a pre- and postimpact analysis showed no benefit of this assay with respect to the length of hospital stay or vancomycin use.**

Peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) technology allows for the rapid identification (as quickly as 2.5 h) of *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) directly from blood cultures signal-positive for Gram-positive cocci in clusters (GPCCL). Commercially available PNA FISH assays include a single-probe assay, *S. aureus* PNA FISH (AdvanDx, Woburn, MA), and more recently, a dual-probe *S. aureus*/CoNS PNA FISH kit (AdvanDx). In a study conducted by Forrest et al., laboratory use of the single-probe *S. aureus* PNA FISH assay to rule out *S. aureus* and rapidly identify presumptive CoNS-positive blood cultures contributed to decreased hospital length of stay (LOS) and decreased hospital costs and was associated with a trend toward lower vancomycin usage (2). In that study, PNA FISH results were reported in real time to an antimicrobial stewardship team (AST) who assessed the need for vancomycin and controlled its release. There are limited data to support that this test requires some form of active reporting and/or physician assistance to be of clinical benefit. In November 2006, the single-probe *S. aureus* PNA FISH assay was introduced at Boston Medical Center (BMC) without administrative support for active reporting or AST input. We conducted a retrospective, pre/post-PNA FISH study at BMC to determine whether there would be a similar impact of the PNA FISH assay on LOS and vancomycin usage for patients with pseudobacteremia (i.e., a positive blood culture of no clinical significance likely representing a contaminant) due to CoNS in the absence of active AST intervention.

By using a random-number generator, patients with blood cultures positive for CoNS between May 2005 and October 2006 (before PNA FISH was introduced) and between December 2006 and May 2008 (after PNA FISH was introduced) were randomly selected and evaluated for inclusion in the study. The electronic medical record was used to collect all information. Patients with CoNS bacteremia that was likely to be clinically significant were excluded. The primary outcome of the study was hospital LOS in days before and after the introduction of the PNA FISH assay. The secondary outcome was the number of days of vancomycin treatment as a response to a positive Gram stain from a signal-positive blood culture; the positive Gram stain was reported as the critical action value (CAV). Vancomycin initiation was considered to be a response if it was started within 24 h of the CAV. Per protocol, CAVs were verbally communicated (within 60 min) to a relevant licensed care provider, as well as being documented in the electronic medical record during both time periods. After implementation of the PNA FISH assay, signal-positive blood cultures showing GPCCL were batched once daily and the assay was performed on the overnight shift. Blood culture reports were updated with PNA FISH results in the electronic medical record by 5 a.m. the following morning, but verbal notification was not repeated. This study had 80% power to detect a difference in LOS of 1.5 days with a sample size of 100 patients per group. Differences in vancomycin treatment duration were analyzed using Student's *t* test. In analyzing hospital LOS data, multivariable gamma regression with a log link function was used, with the gamma regression treatment effect expressed as a ratio of means. Data analysis was performed using SAS version 9.13.

A total of 199 patients (100 in the pre-PNA FISH group and 99 in the post-PNA FISH group) were included in the study (1 patient from the post-PNA FISH group was excluded from the analysis due to a prolonged hospital LOS of 228 days). Results demonstrated that the PNA FISH test accurately identified all 199 CoNS isolates as "not *S. aureus*," and there were no dual infections. There were no statistically significant differences between the two groups in age, gender, hospital location (intensive care unit [ICU] versus non-ICU ward), and reason for admission. There were no statistically significant differences in overall hospital LOS between the two groups (Table 1). The mean LOS ratio—the ratio of the mean LOS for the pre-PNA

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TABLE 1. LOS and duration of vancomycin use for pre- and post-PNA FISH groups

| Group (*n*) | Mean hospital LOS (days) ± SD (median; range) | Mean duration (days) of vancomycin treatment ± SD (median; range) |
|---|---|---|
| Pre-PNA FISH patients (100) | 18.7 ± 16.5 (13.0; 2.0–83.3) | 4.15 ± 4.03 (2.9; 0.3–19.2) |
| Post-PNA FISH patients (99) | 20.9 ± 21.0 (13.7; 1.8–113.5) | 3.51 ± 3.43 (1.8; 0.3–10.8) |
| *P* value | 0.35 | 0.49 |

FISH group to the mean LOS for the post-PNA FISH group—was 0.89 (95% confidence interval [CI], 0.70 to 1.13). Matching by month of positive blood culture to control for potential seasonal confounders did not alter the results. There was no statistically significant difference in mean days of vancomycin treatment duration (4.15 days for the pre-PNA FISH group versus 3.51 days for the post-PNA FISH group) (Table 1). Among those for which vancomycin treatment was initiated, there was a higher proportion of patients in the post-PNA FISH group than in the pre-PNA FISH group who were treated with vancomycin for ≤1 day, but the results were not statistically significant (29.4% versus 13.6%; $P = 0.17$). The mean time to identification of CoNS after the CAV for the pre-PNA FISH group was 0.94 days (22.6 h; range, 0 to 3.2 days), compared to 0.63 days (15.1 h; range, 0.12 to 2.3 days) for presumptive identification of CoNS using the PNA FISH assay, a difference of 7.5 h ($P < 0.0001$).

Our study demonstrated that the *S. aureus* PNA FISH assay for the rapid detection of presumptive CoNS pseudobacteremia, when implemented without active reporting of results or additional support from an AST, did not reduce LOS or vancomycin use. In published studies, utilization of the PNA FISH test has been shown to decrease hospital LOS, antimicrobial usage, hospital costs, and mortality at other tertiary-care teaching hospitals (1, 2, 3). However, in those studies, the PNA FISH test was supported by an AST who was notified of all PNA FISH results. Even without AST intervention, prompt and direct notification of PNA FISH results detecting both CoNS and *S. aureus* was associated with reduced mortality, less antibiotic use, and a trend toward reduced hospital stay and charges in a prospective, randomized, controlled trial conducted by Ly et al. (4). It is recognized that batch testing of any rapid assay diminishes the intended advantages of such technology. This study did not specifically examine the effect of daily batching of PNA FISH results on clinical utilization of the test. Nevertheless, positive impacts of the PNA FISH test with AST intervention, despite once-daily batch testing, were demonstrated in other studies (2). New technologies for the rapid diagnosis of infection are advocated as a way to reduce inappropriate antimicrobial use, LOS, and health care costs. However, without real-time notification and/or administrative support and intervention, those benefits may not be realized.

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