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Original article

Impact of *Quick*FISH in addition to antimicrobial stewardship on vancomycin use and resource utilization in cancer patients with coagulase-negative staphylococcal blood cultures

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ABSTRACT

Objective: To evaluate the impact of rapidly identifying coagulase-negative staphylococci (CoNS) from positive blood cultures combined with an established antimicrobial stewardship (AS) programme at a tertiary cancer centre.

Methods: We compared cancer patients ≥18 years old who between 01/1/13 and 12/31/13 had one or more positive CoNS blood culture(s) identified by *Staphylococcus Quick*FISH® (a peptide nucleic acid fluorescence *in situ* hybridization assay) with cancer patients ≥18 years old who had CoNS identified by standard microbiological techniques between 01/01/11 and 12/31/11 (baseline). Positive blood culture results were reported to the clinician by microbiology staff; restricted antibiotics (e.g., vancomycin) required approval by the AS team.

Results: There were 196 baseline and 103 *Quick*FISH patients. Faster median time to organism identification (33 (IQR 27–46) versus 49 (IQR 39–63) hours, $p < 0.001$), more vancomycin avoidance (51/103 (50%) versus 60/196 (31%), p 0.002), shorter median antibiotic duration (1 (IQR 0–3) versus 2 (IQR 0–6) days, p 0.019), fewer central venous catheter (CVC) removals (14/78 (18%) versus 57/160 (36%), p 0.004), and reduced vancomycin level monitoring (16/52 (31%) versus 71/136 (52%), p 0.009) were observed in the *Quick*FISH group. *Quick*FISH implementation was predictive of a lower likelihood of antibiotic therapy prescription (OR 0.35, 95%CI 0.20–0.62, $p < 0.001$). Prior transplant (RR 1.47, 95%CI 1.13–1.92, p 0.004), neutropenia (RR 1.47, 95%CI 1.09–1.99, p 0.012), multiple positive blood cultures (RR 4.23, 95%CI 3.23–5.54, $p < 0.001$), and CVC (RR 1.60, 95%CI 1.02–2.53, p 0.043) were independent factors for antibiotic duration.

Conclusions: *Quick*FISH implementation plus AS support leads to greater avoidance of vancomycin therapy and improved resource utilization in cancer patients with CoNS blood cultures. **S.K. Seo, Clin Microbiol Infect 2018;24:1339.e7–1339.e12**

Introduction

Coagulase-negative staphylococci (CoNS) are the organisms most frequently isolated from blood in both neutropenic and non-neutropenic cancer patients [1]. The presence of a central venous catheter (CVC) is an important risk factor [1,2]. Because CoNS form part of normal skin flora, these organisms are also common

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contaminants in clinical specimens. In studies assessing the significance of CoNS recovered from blood cultures in the general patient population, the majority are deemed to be contaminants, with only 12–25% constituting true bacteraemia [3,4].

Despite established criteria for bloodstream infection by skin commensals [5], prescribers may overtreat because bloodstream infection remains a significant cause of morbidity and mortality in immunocompromised patients. At our oncology centre we found that 14% of these patients received unnecessary vancomycin courses, and that unneeded treatment of CoNS blood culture contaminants led to an excess expenditure of US$5246 per episode [6].

Standard microbiological techniques for identification of organisms implicated in bloodstream infection are based on phenotypic methods that require 48–72 hours to yield final results, although some rapid phenotypic methods (e.g., tube coagulase test) may provide information within a few hours from the time that a blood culture turns positive [7]. Commercially available peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) assays can quickly identify select pathogens directly from positive blood culture bottles [8]. A quicker and less labour-intensive test, *Staphylococcus Quick*FISH® (AdvanDx, Woburn, MA, USA), has been on hand since 2013 to differentiate between *Staphylococcus aureus* and CoNS; it has a turnaround time of <30 minutes and excellent sensitivity and specificity results that are commensurate with those seen with the original PNA FISH kits [9].

Rapid detection of bloodstream infection combined with delivery of that information to healthcare providers can lead to optimization of antimicrobial therapy in general patient populations [10–12]. In one retrospective study, use of PNA FISH to distinguish between *S. aureus* and CoNS combined with an antimicrobial stewardship programme (ASP) led to a significant reduction in median length of hospital stay by 2 days and a trend towards less intravenous vancomycin usage [10]. The exclusion of patients with cancer from this study, however, makes it difficult to draw meaningful conclusions about the utility of PNA FISH in special patient populations. Similarly, there are no data on the role of the second-generation PNA FISH assay in oncology patients.

At our institution there has been a longstanding system of prompt reporting of blood culture results to clinicians who then page the ASP for guidance and antibiotic approval. Our clinical microbiology laboratory adopted *Quick*FISH in January 2013. We aimed to see whether quicker identification of CoNS in adult cancer patients could further influence the initiation and duration of vancomycin therapy.

Methods

Study setting and patients

This historical cohort study was reviewed and approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC), a 471-bed tertiary care cancer centre in New York, NY, USA. All patients 18 years and older who had one or more blood cultures positive for gram-positive cocci in clusters (GPCCs) and CoNS identified by routine microbiological methods between January 1, 2011 and December 31, 2011 made up the baseline group. The post-implementation group (the *Quick*FISH group) consisted of patients 18 years and older with one or more blood cultures positive for CoNS identified by *Staphylococcus Quick*FISH® between January 1, 2013 and December 31, 2013. Patients were excluded when vancomycin was started prior to the identification of GPCCs from blood cultures, or the *Quick*FISH assay was not performed, or the records were incomplete. Medical records were abstracted for demographics, cancer diagnosis, symptoms and signs temporal to blood culture collection, complete blood counts, blood culture specifications (e.g., collection date and time, date and time of GPCC positivity, date and time of GPCC identification), number of blood cultures positive for CoNS, presence of CVC and its management, other utilized resources relevant to CoNS management (vancomycin levels, echocardiogram), antimicrobial use, length of hospital stay, and in-hospital mortality.

Laboratory methods

During baseline, all positive blood cultures with Gram stain showing GPCCs were immediately called and verbally reported as a critical value to the ordering clinician. The positive blood culture was subcultured following standard protocols, and once enough growth was detected (24–48 h) identification was made on the basis of biochemical (catalase and coagulase) reactions. Following the identification of CoNS and *S. aureus*, antimicrobial susceptibility testing was performed by microbroth dilutions using an automated platform (dried Gram-positive panels, Microscan Walkaway *plus* System, Beckman Coulter, Jersey City, NJ, USA); results were available after 24 hours.

With *Quick*FISH implementation, the identification of CoNS and *S. aureus* was performed immediately on all positive blood cultures with a Gram stain showing GPCCs. For patients with multiple positive blood cultures for GPCCs in a 24-hour period, *Quick*FISH was performed only on the first positive culture. Only results of CoNS and/or *S. aureus* (not GPCCs) were verbally reported to the ordering clinician. Susceptibility testing was performed as described in the baseline period.

Result management

MSKCC utilizes a system of prior approval for initiation of vancomycin and other restricted anti-infectives 7 days a week between the hours of 9 a.m. and 10 p.m. After 10 p.m., therapy can be initiated pending review and approval the following morning by antimicrobial stewardship (AS) personnel. When primary teams are notified by clinical microbiology of positive blood culture results, they contact the hospital's ASP for antibiotic approval. The ASP verifies microbiological results by accessing the patient's electronic medical record or by calling microbiology directly. The ASP also flags patients who are initiated on therapy for prospective audit and feedback, unless the patient is followed by the infectious disease consultation team.

Definitions

Laboratory-confirmed bloodstream infection due to CoNS was defined according to established criteria by the Centers for Disease Control & Prevention (CDC) [5]. A contaminant was considered if one of at least two sets of blood cultures was positive for CoNS and/or there was an absence of supporting symptoms (e.g., fever, chills, hypotension). Time to organism identification was defined as time from blood culture collection to organism identification.

Outcomes

Primary outcomes were initiation of therapy—in which only antibiotics with coverage against resistant GPCCs (e.g., vancomycin) were considered as therapy for CoNS—and duration of therapy. A day of therapy was counted when a patient received at least one dose of an antibiotic directed against GPCCs on that day [13]. Secondary outcomes included time to organism identification, CVC removal, echocardiogram performance, vancomycin levels, median length of hospital stay, and in-hospital mortality.

Data analysis

Descriptive comparisons between years were analysed with Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. Logistic regression was used to determine which factors were associated with a patient being put on anti-infective therapy for CoNS. Poisson models were used to determine which factors were associated with the number of days a patient was on anti-infective therapy for CoNS. Factors that were significant in the univariate analysis were tested in the multivariate analysis and backward selection was used to determine the final logistic and Poisson models. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed in SAS 9.4 (SAS Institute, Inc, Cary, NC, USA).

Results

Overall, a total of 684 patients had one or more positive blood cultures for CoNS, of which 385 patients were excluded (Fig. 1). Of 299 evaluable patients, 223 (75%) were assessed to have contaminant blood cultures.

Comparison across groups

Demographic and other patient characteristics are shown in Table 1. There were 196 baseline patients and 103 patients in the *Quick*FISH group. Compared with the baseline patients, the *Quick*FISH group contained significantly more male patients, patients with a haematological malignancy, and neutropenic patients (Table 1). The time to organism identification was significantly shortened to a median of 33 hours (interquartile range (IQR) 27–46) in the *Quick*FISH group compared to a median of 49 hours (IQR 39–63) in the baseline group ($p < 0.001$) (Table 1). While not statistically significant, median length of hospital stay was 3 days shorter in the *Quick*FISH group: 12 days (IQR 5–27) versus 15 days (IQR 7–29) (p 0.19).

Management of positive blood cultures

Although the proportion of patients who had a CVC was similar between the two groups, there were significantly fewer CVC removals in the *Quick*FISH group (14/78, 18%) compared to baseline (57/160, 36%) (p 0.004). There were no differences in the proportion of patients who underwent echocardiogram to rule out valvular involvement (baseline 7/196, 4% versus *Quick*FISH 3/103, 3%, p 0.99). No doses of vancomycin were given in 51 of 103 patients (50%) in the *Quick*FISH group compared to 60 of 196 baseline patients (31%) (p 0.002). Antibiotic duration was shortened to a median of 1 day (IQR 0–3) in the *Quick*FISH group versus a median of 2 days (IQR 0–6) in the baseline group (p 0.019). There was also less monitoring of vancomycin levels in the *Quick*FISH group (16/52, 31% versus 71/136, 52%, p 0.009).

We then analysed factors to examine their association with antibiotic administration via logistic regression. *Quick*FISH implementation and increasing age were predictive of a lower likelihood of being prescribed antibiotic therapy, whereas male sex, prior haematopoietic stem cell transplantation (HSCT), neutropenia, multiple positive blood cultures, and presence of CVC were predictive of a

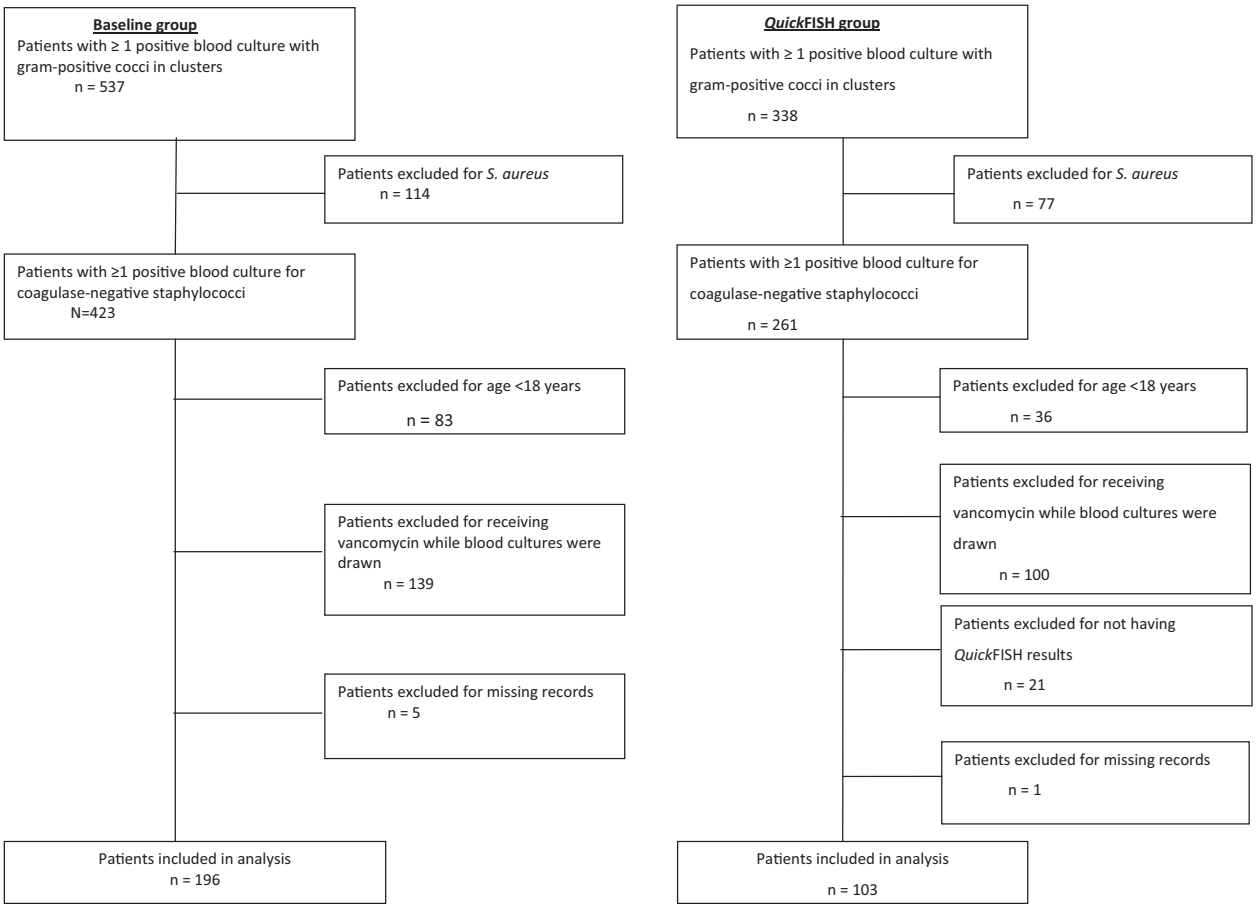

Fig. 1. Patient flow chart.

Table 1
Demographic and other characteristics of patients with one or more blood cultures positive for coagulase-negative staphylococci (CoNS)

	Baseline (n = 196)	*Quick*FISH (n = 103)	Total (n = 299)	p
Patient characteristics:				
Median age (range)	61 (21–93)	62 (22–84)	61 (20–93)	0.88
Male, n (%)	91 (46)	64 (62)	155 (52)	0.011
Cancer diagnosis, n (%)				0.001
• haematological malignancy	63 (32)	55 (53)	118 (40)	
• solid tumour	132 (67)	48 (47)	180 (60)	
• none	1 (1)	0 (0)	1 (0)	
Prior HSCT, n (%)	40 (20)	28 (27)	68 (23)	0.19
Presence of CVC, n (%)	160 (82)	78 (76)	238 (80)	0.23
Neutropenia at blood culture collection, n (%)	18 (9)	20 (19)	38 (13)	0.017
Microbiologic characteristics:				
Single positive blood culture, n (%)	129 (66)	77 (75)	206 (69)	0.12
Median time to organism identification, hours (IQR)	49 (39–63)	33 (27–46)	44.6 (33–61)	<0.001
Management of blood culture results:				
Clinical impression of contaminant result, n (%)	141 (72)	82 (80)	223 (75)	0.16
CVC removal, n (%)[a]	57 (36)	14 (18)	71 (31)	0.004
Echocardiogram, n (%)	7 (4)	3 (3)	10 (3)	0.99
No vancomycin doses given, n (%)	60 (31)	51 (50)	111 (37)	0.002
Median antibiotic duration, days (IQR)	2 (0–6)	1 (0–3)	1 (0–5)	0.019
Vancomycin level monitoring, n[b]	71 (52)	16 (31)	87 (46)	0.009
Clinical outcomes				
Median hospital duration, days (IQR)	15 (7–29)	12 (5–27)	14 (6–29)	0.19
In-hospital mortality, n (%)	22 (11)	15 (15)	14 (6–29)	0.46

CVC, central venous catheter; HSCT, haematopoietic stem cell transplantation; IQR, interquartile range.
[a] The denominator consisted of patients who had a CVC.
[b] The denominator consisted of patients who received vancomycin therapy.

greater likelihood of antibiotic therapy prescription on univariate analysis (Table 2). *Quick*FISH implementation, age, male sex, neutropenia, and multiple positive blood cultures were independently associated with prescription of antibiotic therapy on multivariate analysis (Table 2). We also analysed factors to assess their association with duration of antibiotic therapy via Poisson regression. Age, haematological malignancy, prior HSCT, neutropenia, multiple positive blood cultures, presence of CVC, and echocardiogram were significantly associated with antibiotic duration on univariate analysis (Table 3). HSCT, neutropenia, multiple positive blood cultures, and presence of CVC were independently associated with duration of therapy in multivariate analysis (Table 3).

Discussion

We describe here the impact of *Quick*FISH in the management of adult cancer patients with CoNS recovered from blood. This second-generation assay has demonstrated excellent sensitivity and specificity for the detection of both *S. aureus* and CoNS. The ease and speed of this test has the potential to improve therapeutic interventions [9,14]. Following *Quick*FISH implementation, we found a significantly faster median time to organism identification, a higher proportion of patients avoiding vancomycin therapy, a shorter median antibiotic duration, fewer CVC removals, and less monitoring of vancomycin levels.

Faster organism identification is comparable to the findings of other studies employing PNA FISH technology in the management of enterococcal bacteraemia or candidaemia [15,16]. However, a proactive approach is needed to take advantage of the quick recognition of the organism as has been demonstrated in prior studies on the PNA FISH assay to distinguish between *S. aureus* and CoNS [10–12]. Otherwise no benefit with respect to antibiotic optimization or other resource utilization is seen [17]. Depending on available personnel and resources, implementation strategies

Table 2
Univariate and multivariate logistic regression for predictors of antibiotic administration

Variable	Univariate OR (95%CI)	p	Multivariate OR (95%CI)	p
Period				
Baseline	Ref		Ref	
*Quick*FISH	0.45 (0.28–0.74)	0.001	0.35 (0.20–0.62)	<0.001
Age	0.81[a] (0.96–0.99)	0.015	0.82[a] (0.96–0.99)	0.040
Male	1.84 (1.14–2.96)	0.012	2.26 (1.31–3.87)	0.003
Cancer diagnosis				
Solid tumour	Ref			
Haematological malignancy	1.32 (0.81–2.15)	0.264		
Prior HSCT	2.06 (1.12–3.78)	0.020		
Neutropenia	2.93 (1.25–6.91)	0.014	2.76 (1.06–7.18)	0.037
Number of positive blood cultures				
One	Ref		Ref	
Multiple	5.58 (2.93–10.66)	<0.001	5.58 (2.84–10.94)	<0.001
Presence of CVC	2.42 (1.37–4.28)	0.002		

CI, confidence interval; HSCT, haematopoietic stem cell transplantation; OR, odds ratio; CVC, central venous catheter.
[a] OR is per a 10 unit increase.

Table 3
Univariate and multivariate Poisson regression for predictors of antibiotic duration

Variable	Univariate RR (95%CI)	p	Multivariate RR (95%CI)	p
Period				
Baseline	Ref			
*Quick*FISH	0.82 (0.59–1.15)	0.256		
Age	0.99 (0.98–1.00)	0.040		
Male	1.27 (0.93–1.73)	0.136		
Cancer diagnosis				
Solid tumour	Ref			
Haematological malignancy	1.70 (1.26–2.30)	<0.001		
Prior HSCT	1.70 (1.24–2.35)	0.001	1.47 (1.13–1.92)	0.004
Neutropenia	1.98 (1.38–2.84)	<0.001	1.47 (1.09–1.99)	0.012
Number of positive blood cultures				
One	Ref		Ref	
Multiple	4.71 (3.59–6.19)	<0.001	4.23 (3.23–5.54)	<0.001
Presence of central venous catheter	2.77 (1.62–4.73)	<0.001	1.60 (1.02–2.53)	0.043
Echocardiogram performed	4.55 (2.98–6.96)	<0.001		

CI, confidence interval; HSCT, haematopoietic stem cell transplantation; RR, rate ratio.

should be customized to the institution when considering introduction of rapid diagnostics.

One successful strategy has relied on microbiology staff promptly reporting PNA FISH results to providers [11,12,18]. In a prospective randomized controlled trial, Ly and colleagues demonstrated a shortened median antibiotic duration for CoNS from 2.5 to 0 days ($p < 0.01$), suggesting that enhanced communication between the laboratory and clinicians likely facilitates reduction in unnecessary antibiotic use for false-positive blood cultures [11]. Another tactic is to report PNA FISH results directly to the institutional ASP, where the need for vancomycin is then determined. Even though there were only 87 evaluable patients who had CoNS blood cultures, Forrest et al. reported a trend for a greater number of patients in the PNA FISH group who did not receive vancomycin compared to the control group (PNA FISH 17% versus control 9%, p 0.06) and a trend for reduced vancomycin utilization (PNA FISH 2.6 defined daily dose (DDD)/patient versus control 4.8 DDD/patient, p 0.06) [10].

In examining our well-established system of real-time notification of positive blood culture results to primary teams and ASP oversight of restricted antibiotics, approximately one third of patients avoided vancomycin altogether for contaminated blood cultures, and the median antibiotic duration was 2 days in the baseline group. The addition of *Quick*FISH to this system further increased vancomycin avoidance from 31% to 50% and shortened median antibiotic duration from 2 days to 1 day. The reduction in vancomycin level monitoring in the *Quick*FISH group was probably a result of increased vancomycin avoidance. Another finding was the significant reduction in CVC removals in the *Quick*FISH group. Retaining a well-functioning CVC is a boon for the cancer patient because management is contingent on stable venous access for chemotherapy, blood transfusion, drug administration, fluid resuscitation, and clinical monitoring [19]. Cancer patients have many mitigating factors that contribute to duration of hospitalization. Nevertheless, although not significant, median length of hospital stay was shortened by 3 days in the *Quick*FISH group. Prior studies in non-cancer patients have similarly found reductions in median length of hospital stay by 2 days using the PNA FISH assay [10,11].

The value of *Quick*FISH is primarily in the avoidance of vancomycin initiation following CoNS blood cultures that are determined to be clinically insignificant. This factor was found on both univariate and multivariate analysis to be predictive of a patient being less likely to be prescribed antibiotic therapy. Conversely, neutropenia and multiple positive blood cultures were predictors for the prescription of antibiotic therapy. After organism identification, and after the decision to treat or not is made, clinical factors such as prior HSCT, neutropenia, multiple positive blood cultures, and presence of a CVC influence antibiotic duration. Although we use the CDC criteria for bloodstream infection definitions, the unique cancer population in our study might lead to differences in blood culture interpretation for some patients. For example, treatment of a single positive blood culture for CoNS may be appropriate in a febrile, neutropenic patient with a CVC [6].

We did not examine the effect of *Quick*FISH on mortality attributable to inappropriate treatment of true bacteraemia due to CoNS. However, CoNS bacteraemia is known to be associated with lower mortality compared to patients with bloodstream infection involving other pathogens, even in febrile, neutropenic patients [20]. Additionally, inappropriate empirical therapy may not necessarily be associated with CoNS bacteraemia-related mortality [21].

Besides *Quick*FISH, other rapid diagnostic technologies are available—such as matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry and multiplexed nucleic acid amplification tests (NAATs)—that when integrated with AS intervention have also been useful in the management of patients with CoNS blood cultures [22,23]. These options allow laboratories to select the method that works best for their individual workflow and antimicrobial stewardship policies.

There are limited data on the role of rapid diagnostics and antimicrobial stewardship in immunocompromised hosts [24]. Our study is the first to describe the impact of the *Quick*FISH assay in a cancer patient population that included patients with solid tumours or haematological malignancies and HSCT recipients. While the *Quick*FISH group had more patients with haematological malignancies and/or neutropenia, we still found a significant reduction in the utilization of vancomycin and other resources.

In summary, *Quick*FISH implementation combined with active antimicrobial stewardship support led to greater avoidance of vancomycin, shorter antibiotic duration, reduced vancomycin level monitoring, and fewer CVC removals in cancer patients with positive CoNS blood cultures. Additional studies examining the impact of rapid diagnostics in cancer patients should be encouraged.

Transparency declaration

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