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Original Article

Prolonged antimicrobial prophylaxis following cardiac device procedures increases preventable harm: insights from the VA CART program

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Abstract

Background: The rate of cardiovascular implantable electronic device (CIED) infection is increasing coincident with an increase in the number of device procedures. Preprocedural antimicrobial prophylaxis reduces CIED infections; however, there is no evidence that prolonged postprocedural antimicrobials additionally reduce risk. Thus, we sought to quantify the harms associated with this approach.
Objective: To measure the association between *Clostridium difficile* infection (CDI), acute kidney injury (AKI) and receipt of prolonged postprocedural antimicrobials.
Methods: CIED procedures entered into the VA Clinical Assessment Reporting and Tracking Electrophysiology (CART-EP) database during fiscal years 2008–2016 were included. The primary outcome was 90-day incidence of CDI and the secondary outcome was the 7-day incidence of AKI. The primary exposure measure was duration of postprocedural antimicrobial therapy. Associations were measured using Cox-proportional hazards and binomial regression.
Results: Prolonged postprocedural antimicrobial therapy was identified following 3,331 of 6,497 CIED procedures (51.3%), and the median duration of prophylaxis was 5 days. Prolonged postprocedural antimicrobial use was associated with increased risk of CDI (hazard ratio [HR], 2.90; 95% confidence interval [CI], 1.54–5.46). Of the 27 patients who developed CDI, 11 subsequently died. Postprocedural antimicrobial use with ≥2 antimicrobials was associated with an increased risk of AKI (OR, 4.16; 95% CI, 2.50–6.90). The impact was particularly significant when one of the dual agents prescribed was vancomycin (adjusted OR, 8.41; 95% CI, 5.53–12.79).
Conclusions: Prolonged antimicrobial prophylaxis following CIED procedures increases preventable harm; this practice should be discouraged in procedural settings such as the cardiac electrophysiology laboratory.

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Placement of cardiovascular implantable electronic devices (CIEDs), such as pacemakers and implantable cardioverter-defibrillators (ICDs) is rising as the population ages.[1] Devices are increasingly implanted into patients older than 75 years of age and with multiple comorbidities, who have a higher risk of procedure and medication-related adverse events.[2] Infections complicate an estimated 1%–2% of CIED procedures, and incidence rates have nearly doubled over the past decade.[3,4] Procedure-related CIED infections cause considerable harm; the absolute 6-month mortality following a deep cardiac device infection is 18%.[5] Thus, preventing these infections is a major clinical priority.

The American Heart Association (AHA) and the Infectious Diseases Society of America (IDSA) endorse preincisional antimicrobial prophylaxis and recommend single-dose cefazolin or cefuroxime for cardiac device procedures[6–9]; continuing prophylaxis beyond 24 hours following skin closure is not recommended. The Centers for Disease Control guidelines for the prevention of surgical site infections (SSIs) recommend against post-closure antibiotics for clean and clean-contaminated procedures, including cardiac procedures.[10,11] The Surgical Care Improvement Project (SCIP) limited periprocedural antibiotic use to 24 hours

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(48 hours for cardiac surgery) as part of a larger surveillance and reporting program.[12] The implementation of these measures are complimentary to recent studies that demonstrate expanded and prolonged antimicrobial prophylaxis following invasive surgical procedures is associated with increases in acute kidney injury (AKI) and *Clostridium difficile* infection (CDI).[13,14]

The SCIP measures for outpatient procedures, including CIED procedures, did not include an assessment of postprocedural antibiotic use. Also, 2 recent studies have demonstrated that prolonged duration of antimicrobial prophylaxis is common following cardiac device implantation procedures; however, data are limited regarding the potential harms of this approach.[15,16] Thus, we sought to measure the association between prolonged postprocedural antimicrobial prophylaxis and incidence of adverse events in a large, multicenter cohort of Veterans Affairs (VA) patients.

Methods

Databases

The VA Clinical Assessment Reporting and Tracking (CART) program is a national quality initiative integrated into the VA electronic medical record; CART reporting is mandatory for all cardiac catheterization procedures and optional for electrophysiology procedures, including device implantations and revisions.[15,17] Data collected prospectively as part of the CART program include procedure type, date of procedure, patient demographics (age, sex), vital status and comorbidities (eg, diabetes, renal disease, and heart disease). The CART data have been combined with other data from the VA Corporate Data Warehouse (CDW), including pharmacy and administrative data, to create a single national data repository.

Cohort development

Cardiac device procedures, including implantations and revisions of permanent pacemakers, ICDs, biventricular pacemaker ICDs, and biventricular pacemakers entered into the CART-EP program during the period from October 2008 to September 2016 were included. For patients with multiple procedures entered in CART, only the first was included. Cases that could not be matched to administrative data in the CDW were excluded. To ensure that postprocedural antimicrobials were administered for prevention and not for other clinical indications, a sample of cases from all participating facilities underwent manual review to delineate the reason for the antimicrobial order.

Outcomes and exposures

The primary outcome measure was incidence of laboratory-defined CDI during the 90-day period following the procedure (any positive *C. difficile* toxin assay, PCR or culture), based on established windows of *C. difficile* risk following antimicrobial exposure.[18] All case patients with a CDI diagnosis underwent planned manual review by a trained clinician, including review of scanned-in paper records from outside facilities to identify all antimicrobial orders in the 6-month period prior to the procedure, the reason for the order, and confounding factors (e., recent hospitalization, comorbidities, proton pump inhibitor use, and previous CDI diagnosis[19]) that may have impacted the relationship between prolonged prophylaxis and CDI diagnosis.

The secondary outcome was the 7-day incidence of postprocedural AKI, as defined by the Acute Kidney Injury Network (AKIN) recommendations; AKIN definitions are calculated based on a change from baseline renal function.[20]

The primary exposure was postprocedural antimicrobial administration. Prolonged exposure was defined as inpatient or outpatient antimicrobial therapy lasting for >24 hours after the device implantation or revision procedure.[15,21,22] Antimicrobial prescriptions filled within 7 days prior to the procedure were included if they continued for at least 24 hours after the procedure. Duration was determined based on the start date of the earliest antimicrobial prescription and calculated based on the number of doses dispensed. The impact of duration of antimicrobials was also evaluated for both outcomes. The risk of combination regimens was estimated for the AKI outcome. Combination regimens included multiple antibiotics prescribed at the same time or prescribed sequentially for the purposes of postprocedural prophylaxis.

Statistical analysis

Demographic and clinical characteristics of CIED patients by use of prolonged postprocedural antibiotics were compared. We used χ^2 tests to compare categorical variables and Mann-Whitney tests for continuous variables. Epidemic curves of the outcomes of CDI and AKI were constructed using the R package epitools.[23]

The association between prolonged prophylaxis and the 90-day CDI outcome was estimated and tested using Cox proportional hazards models. To account for clustering by facility, a robust estimator of the covariance matrix was used. Due to the low number of CDI events, only 1 confounding variable was included in the regression models. Based on previous reports of CDI risk factors,[19] days of hospitalization prior to procedure (ie, 0 days, 1–6 days, and ≥7 days) were chosen. To ensure results were robust, sensitivity analyses were completed using other known risk factors (ie, age, diabetes, sex, nursing home admittance within 60 days prior to the procedure, proton pump inhibitor use, and year of procedure). Similar models were used to evaluate the effect of the duration in days of postprocedural antimicrobial use.

Generalized estimating equations were used to evaluate AKI, controlling for age, diabetes, sex, nursing home admittance within 60 days prior to the procedure, and year of procedure. AKI was evaluated as a binary outcome with an assumed binomial distribution, logit link function, and an exchangeable structure, to allow for clustering by facility. Similar models were used to evaluate the effects of (1) duration of postprocedural antimicrobial use; (2) combination antimicrobial therapies (2 or more, 1 only, and none); and (3) combination therapy involving vancomycin and another antimicrobial (yes vs no). Combination regimens may have been coadministered (eg, cefazolin plus vancomycin) or serial (eg, cefazolin followed by trimethoprim and sulfamethoxazole).

All analyses were completed using SAS version 9.4 software (SAS Institute, Cary, NC) and R version 3.4.0 software.[24]

Results

In total, 6,832 CIED procedures in 6,801 unique patients at 42 different VA medical centers were entered into the CART-EP database during the study period, and 329 follow-up device

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procedures after initial CART entry in 305 subjects were excluded. An additional 6 patients were excluded due to lack of administrative data. Thus, the final cohort included 6,497 procedures in unique patients. Based on previous analysis, this cohort represents ~30% of CIED procedures within the national VA healthcare system.[15]

Participants were predominantly male (98.1%) and the median age was 71.4 years (interquartile range [IQR], 64.8–80.8) (Table 1). Most procedures performed were permanent pacemaker implantations (56.4%) and ICD implantations (28.4%). Prolonged antimicrobial prophylaxis was administered following 3,331 CIED procedures (51.2%). In these cases, the median duration of postprocedural therapy was 5 days (IQR, 5–7 days). A small minority of these were from prescriptions initiated prior to the procedure and continued >24 hours postprocedure (N = 67, 2%). Approximately 25% of the cohort underwent manual review to determine reason for the postprocedural antimicrobial; manual review validated that the vast majority of prescriptions were for prophylactic purposes. Characteristics of patients who did and did not receive prolonged postprocedural prophylaxis are presented in Table 1.

Clostridium difficile infection

Prolonged prophylaxis was associated with a higher incidence of CDI when compared to patients who received SSI guideline-concordant prophylaxis (Table 2; unadjusted hazard ratio [HR], 2.72; 95% CI, 1.46–5.07). The association between prolonged prophylaxis and CDI outcome persisted after controlling for preprocedural hospitalization (HR, 2.90; 95% CI, 1.54–5.46). Sensitivity analyses of models including other potential confounding variables had similar results.

Among the 27 patients who developed CDI, one case was misclassified as a permanent device procedure (patient received a temporary pacing wire rather than a permanent device intervention). After excluding this case, the remaining 26 cases were incident cases in unique patients. N = 11 CDI patients (42%) died within a 6-month follow-up period after CIED implantation; 8 of 11 patients who died had received prolonged antimicrobial prophylaxis, including 4 in whom the prophylactic antibiotic was the only antibiotic exposure in the 6 months prior to CDI diagnosis (Appendix 1). In addition to the 11 deaths, 1 patient who received prolonged prophylaxis developed toxic megacolon requiring colectomy.

Overall, 19 of 27 (69%) CDI patients received prolonged postprocedural antibiotics. Among the CDI patients, antimicrobials used for prophylactic purposes included cephalexin (n = 9), clindamycin (n = 4), and doxycycline (n = 3), among others (n = 3). Of the CDI patients, 17 patients, including 10 patients who received prolonged post-CIED antibiotics, had received other antibiotic therapy in the 6 months prior to CDI diagnosis for a variety of indications. In 9 of 26 patients, the prophylaxis was their only antibiotic exposure (Appendix 1). The use of clindamycin for prolonged prophylaxis appeared to be a particularly large driver of prophylaxis-related CDI; in patients receiving clindamycin, the prolonged prophylaxis was their only antimicrobial exposure during the 6-month period prior to the CDI diagnosis.

Acute kidney injury (AKI)

Among the 6,497 unique patients who had a CIED procedure, 2,797 (43%) patients had pre- and postprocedural creatinine measurements available for analysis. In this group, prolonged prophylaxis with a single agent was not associated with increased odds of AKI (OR, 1.26; 95% CI, 0.84–1.91). However, prolonged postprocedural prophylaxis with regimens containing multiple antimicrobials (≥2) was associated with increased AKI odds (OR, 4.16; 95% CI, 2.50–6.90). The association was particularly strong among patients who received combinations containing vancomycin (OR, 8.41; 95% CI, 5.53–12.79).

Sensitivity analyses

We repeated the statistical models after excluding the observation that was misclassified as a device procedure. The results did not change substantially for any outcome.

Discussion

Although there is no evidential basis to support that prolonged prophylaxis reduces CIED infections, this practice is common across many clinical settings, including VA hospitals, the private sector, and academic medical centers.[15,16] In this national, multicenter cohort of VA patients undergoing CIED procedures, prolonged prophylaxis was associated with increases in preventable patient harm, including CDI. Prolonged prophylaxis with combination regimens, particularly those containing vancomycin, were also associated with increases in AKI. Similar results have been found following traditional surgical procedures.[13,14,25–27]

Studies examining the impact of prolonged duration of prophylaxis following traditional surgeries demonstrate no reduction in the incidence of SSI.[11,28] This lack of efficacy resulted in the integration of a set measure for discontinuing postsurgical prophylactic antibiotics into SCIP. The goal of this measure was to promote discontinuation of prophylactic antibiotics within 24 hours of surgery end time (48 hours for cardiac surgery).[22] This measure was highly effective and was discontinued at the end of 2016 after compliance reached >98% among procedures included under its umbrella. Notably, outpatient SCIP measures did not include an assessment of the duration of antibiotic prophylaxis, and prolonged duration continues to be common in this setting.[29]

Increasing the duration of antimicrobial exposure is strongly associated with CDI across many studies, including in surgical settings.[26,30] Older age and medical comorbidities also increase the risk of CDI. The population of patients undergoing CIED placement is enriched among older patients; increasing age was also associated with increased propensity to receive prolonged antimicrobial courses.[15] In our study, prolonged postprocedural antimicrobial use was associated with a 3-fold increase in the odds of developing CDI compared to patients who received guideline-concordant regimens. Given the frequency with which VA patients use providers outside of the VA system, our estimates of harm from prolonged prophylaxis likely underestimate the true burden of these adverse events. The association between prophylaxis and postprocedural CDI was particularly striking among patients who received clindamycin as their prolonged prophylactic agent, and these findings are consistent with other studies demonstrating that clindamycin is a strong driver of CDI.[31,32]

Although some patients who developed CDI had additional antimicrobial exposures, prolonged prophylaxis adds to unnecessary cumulative exposure. The substantial morbidity associated

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Table 1. Patient and Procedural Characteristics for Index Device Procedure

Variable	Total (N = 6,497), No. (%)[a]	Postprocedure Antibiotics (<24 h) (N = 3,166), No. (%)[a]	Prolonged Postprocedure Antibiotics (>24 h)(N = 3,331), No. (%)[a]	*P* Value
Demographics				
Age, median (IQR)	71.4 (64.8–80.8)	70.4 (64.0–79.8)	72.4 (65.5–81.6)	< .0001
Male sex	6,373 (98.1)	3,107 (98.1)	3,266 (98.0)	.80
Race				
White	5,615 (86.4)	2,770 (87.5)	2,845 (85.4)	.012
Black	770 (11.9)	354 (11.2)	416 (12.5)	
Other	112 (1.7)	42 (1.3)	70 (2.1)	
Comorbidities				
BMI, median (IQR)	28.5 (25.2–32.5)	28.7 (25.5–33.0)	28.2 (24.8–32.2)	< .0001
Diabetes	3,004 (46.2)	1,475 (46.6)	1,529 (45.9)	.58
Chronic kidney disease	1,987 (30.6)	953 (30.1)	1,034 (31.0)	.41
Dialysis	180 (2.8)	77 (2.4)	103 (3.1)	.11
INR, median (IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.2)	1.1 (1.0–1.3)	< .0001
GFR, median (IQR)	68.0 (51.5–82.0)	68.6 (52.0–81.0)	67.5 (51.0–82.8)	.49
CLC stay within 60 d	37 (0.6)	18 (0.6)	19 (0.6)	.99
PPI	1,796 (27.6)	893 (28.2)	903 (27.1)	.32
Prior events				
Days of hospitalization prior to surgery				
0	4,488 (69.1)	2,137 (67.5)	2,351 (70.6)	.025
1–6	1,613 (24.8)	823 (26.0)	790 (23.7)	
≥7	396 (6.1)	206 (6.5)	190 (5.7)	
C. difficile within 1 year of procedure	24 (0.4)	11 (0.3)	13 (0.4)	.78
Procedural details				
Biventricular pacemaker	150 (2.3)	67 (2.1)	83 (2.5)	.31
Biventricular pacemaker/ICD	869 (13.4)	442 (14.0)	427 (12.8)	.18
Permanent pacemaker	3,664 (56.4)	1,657 (52.3)	2,007 (60.3)	< .0001
ICD	1,844 (28.4)	1,011 (31.9)	833 (25.0)	< .0001
Antibiotic exposures				
Total days on postprocedural antibiotics, median (IQR)	3.0 (0.0–5.0)	0.0 (0.0–0.0)	5.0 (5.0–7.0)	< .0001
Periprocedural antibiotic	3,433 (52.8)	1,773 (56.0)	1,660 (49.8)	< .0001
Periprocedural topical antibiotic	53 (0.8)	23 (0.7)	30 (0.9)	.44
Postprocedural topical antibiotic	155 (2.4)	102 (3.2)	53 (1.6)	< .0001

Note. IQR, interquartile range; BMI, body mass index; INR, international normalized ratio; GFR, glomerular filtration rate; CLC, community living center; PPI, proton pump inhibitor; ICD, implantable cardioverter-defibrillator.
[a]Unless otherwise specified.

with CDI underscores the importance of stewardship efforts for improving clinical outcomes.[33]

In addition to CDI, this study also measured antimicrobial-associated risk of AKI. We found combination prophylaxis regimens—particularly those containing vancomycin—to be strong drivers of post-CIED AKIs. [14] Given the retrospective nature of the study, we were not able to ascertain whether this was due to the nephrotoxicity of the agent, the patient population who

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Table 2. Results of *C. difficile* and Acute Kidney Injury Outcomes in Patients Receiving Prolonged Postprocedural Antibiotics Following Cardiovascular Implantable Electronic Device Procedures

A. Relationship Between Postprocedure Antimicrobial Exposure and *C. difficile* Infection (Cox Proportional Hazards Model)						
			Unadjusted		Adjusted[a]	
Total Cases	No. of Events	Exposure	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
6,497	27	Prolonged antibiotics (>24 h)	2.72 (1.46–5.07)	.002	2.90 (1.54–5.46)	.001
		Total days of antibiotics[b]	1.04 (1.02–1.05)	<.001	1.03 (1.02–1.05)	<.001
B. Relationship Between Postprocedure Antimicrobial Exposure and Acute Kidney Injury (GEE Model)						
			Unadjusted		Adjusted[c]	
Total Cases	No. of Events	Exposure	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
2,797	222	Prolonged antibiotics (>24 h)	1.24 (0.80–1.90)	0.336	1.26 (0.84–1.91)	.267
		Total days of antibiotics	1.01 (0.98–1.04)	0.475	1.01 (0.98–1.04)	.50
		No. of antibiotics - 1 (vs none)	0.92 (0.61–1.38)	0.683	0.93 (0.63–1.38)	.718
		No. of antibiotics - 2 or more (vs none)	4.01 (2.48–6.47)	<.001	4.16 (2.50–6.90)	<.001
		Vancomycin+other antibiotic	7.87 (5.37–11.54)	<.001	8.41 (5.53–12.79)	<.001

Note. HR, hazard ratio; CI, confidence interval.
Note. OR, odds ratio; CI, confidence interval.
[a]Controlling for days of hospitalization prior to procedure (0, 1–6, ≥7).
[b]Interval value: Each additional day of antibiotics.
[c]Controlling for year of procedure, age, sex, diabetes, hospitalization/healthcare exposure (CLC) in the previous 60 days.

received the vancomycin, or some combination of these factors. However, despite these limitations, these findings suggest that shortening the duration of periprocedural antibiotic prophylaxis—particularly when prescribing vancomycin—to preoperative and intraoperative doses may improve clinical outcomes by reducing AKIs without increasing CIED infections.[25] Additional consideration might also be given to limiting vancomycin use specifically to patients with known MRSA colonization or severe β-lactam allergy. This approach follows the evidence regarding the beneficial effect of preoperative antibiotic prophylaxis and would reduce the harms caused by longer antimicrobial exposure.

A common argument for continuing to administer prolonged prophylaxis is that lack of evidence of benefit does not equate to evidence that the practice is not effective. However, a simple decision analysis based on known adverse events demonstrates that no plausible effect estimate for CIED infection reduction due to prolonged prophylaxis would make the intervention attractive. Based on the attributable harm of prolonged prophylaxis (CDI risk difference, 0.29%), the number needed to harm (NNH) to cause 1 additional CDI case following receipt of prolonged postprocedural antibiotics is 335. Given an estimated incidence of CIED infection of 1%,[3,4] prolonged postprocedural antimicrobials would have to reduce the absolute incidence of CIED infections by >30% to outweigh the preventable harm from additional CDI cases. An effect estimate of this size is highly unlikely given the existing data.[11] Furthermore, these effect estimates do not weigh the mortality rate among the patients who developed CDI (42%) versus patients who developed CIED infections (4.6%–11.3%).[34] Accounting for this difference would drive the necessary effect estimate for CIED risk reduction even higher for the intervention to yield a clinical benefit. In addition, these effect estimates did not consider other adverse events, such as AKI and antimicrobial resistance, which further bias the decision against prolonged prophylaxis.

A major barrier to improving antimicrobial use in the electrophysiology laboratory may be a systematic bias in how feedback about adverse events is delivered to providers. Because the management of CIED infections requires repeat procedures and interventions, electrophysiologists are aware of the severity and harms of this outcome. However, electrophysiologists are often not informed about other types of adverse events, such as severe CDI, which can result from other aspects of the intervention, including the type and duration of antimicrobial prophylaxis. Thus, the clinical decision to prescribe postprocedure antimicrobials is based on high-quality feedback regarding one of the adverse outcomes (eg, CIED infections) but on low-quality information about others (eg *C. difficile* infections). Thus, one strategy to improve care might be to improve the surveillance feedback loop regarding the prevention of antimicrobial-associated patient harms, particularly in cases where no clinical benefit is expected.

This study has several limitations. First, CART-EP does not capture all electrophysiology laboratory procedures, but rather a subset based on voluntary entry. Thus, it is possible that this sample is not representative of all CIED procedures. Procedures and adverse events that occurred outside of the VA would not be captured in the VA CDW and therefore would not have been identified. However, this is unlikely to have significantly changed our findings. Recent studies suggest that in outpatient surgeries among dually eligible VA-Medicare patients, very few return to non-VA emergency departments or hospitals.[35,36]

In addition, VA pharmacy databases were used to identify antimicrobial prescriptions. Because of our reliance on VA data, it is possible that not all antimicrobial prescriptions may have been captured, particularly those that may have been written by non-VA providers. Thus, it is possible that not all antimicrobial orders were identified and that some of the observed cases of CDI were attributable to unidentified antimicrobial exposures. However, recent studies suggest that the vast majority of systemic antimicrobial orders in the postprocedural period are captured in the VA EMR.[37] Our findings are also strengthened by the manual reviews—including scanned-in paper records from outside hospitals—of the records for all laboratory-confirmed CDI patients.

Our power to adjust for multiple cofounding variables was limited by the small absolute number of CDI cases. However, we attempted to address this limitation with detailed manual review of all CDI cases to improve transparency. A major limitation of our AKI analysis was that pre- and postprocedural creatinine measurements were not available for all patients. This limitation may have introduced selection bias into this sample; it is possible that the patients who received multiple measurements were at inherently higher risk of both AKI and antimicrobial exposure. However, the association between AKI and vancomycin exposure has been well described, as has been the association between combination antimicrobial regimens and AKI, which puts our findings into a larger context.

In conclusion, prolonged postprocedural prophylaxis—particularly with combination regimens—may be associated with increased odds of preventable harm. These harms should be considered when weighing the risks and benefits of different antimicrobial prophylaxis strategies and durations. Future iterations of quality improvement measures, such as SCIP, should encompass a broader array of clinical settings, including the electrophysiology laboratory. Consideration should be given to improving surveillance and feedback to cardiac electrophysiology providers to include not only procedure-related harms but also harms associated with prevention interventions (eg, the downsides of unnecessary antimicrobial use). Also, these providers should be considered for inclusion in multidisciplinary stewardship initiatives. Expanding the scope of antimicrobial stewardship and infection prevention programs is essential as clinical care is increasingly delivered outside of inpatient settings of care and invasive procedures are performed outside of traditional operating rooms.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.170

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