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# A Randomized, Controlled Trial of Catheter-Related Infectious Event Rates Using Antibiotic-Impregnated Catheters Versus Conventional Catheters in Pediatric Cardiovascular Surgery Patients

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# A Randomized, Controlled Trial of Catheter-Related Infectious Event Rates Using Antibiotic-Impregnated Catheters Versus Conventional Catheters in Pediatric Cardiovascular Surgery Patients

Elaine G. Cox, Chad A. Knoderer, Aimee Jennings, John W. Brown, Mark D. Rodefeld, Scott G. Walker, and Mark W. Turrentine

We conducted a randomized, controlled clinical trial to determine whether a difference in catheter-associated blood stream infection (CABSI) incidence existed between children who underwent cardiac surgery and had a central venous catheter impregnated with minocycline and rifampin versus those who had a conventional, nonimpregnated catheter after cardiac surgery. Due to a lower number of infections than expected, the study was terminated early. Among 288 evaluable patients, the rates of CABSI and line-related complications were similar between the 2 groups.

## BACKGROUND

Central venous catheter (CVC) use is associated with high risk of catheter-associated blood stream infection (CABSI), increases in morbidity and mortality, and is a significant cost driver. These issues tend to be more complicated in children in whom dependence on central catheters has increased because of limitations on access options. With technical issues compounding placement in ill children, rate of catheter colonization is high and approximately 8% result in infection [1]. Pediatric cardiac intensive care unit (PICU) patients are at higher risk for CABSI because of the presence of multiple catheters, long hospitalization, increased transfusions, and prolonged high levels of support, including extracorporeal membrane oxygenation (ECMO) [2].

Efforts to decrease hospital-associated infections intensified after CABSI was declared a “never event” by the Centers for Medicare and Medicaid, and the effectiveness of antibiotic-impregnated catheters in further reducing infections has gained much interest [3]. Because of the paucity of controlled trials of antibiotic-impregnated catheters in children, efficacy and safety questions remain. Our objective was to determine whether a difference in CABSI incidence existed between CVCs impregnated with minocycline and rifampin (M/R) versus conventional, nonimpregnated (C/S) catheters used in children after cardiac surgery.

## METHODS

Patients were eligible for the study if they were <18 years of age, underwent cardiovascular surgery from October 2006 to March 2010 at Riley Hospital for Children, and had a case complexity that warranted a CVC placement for longer than 3 days. Exclusion criteria were as follows: (1) drug allergy to minocycline, other tetracyclines, or rifampin; (2) ventricular assist device therapy; (3) ECMO therapy; (4) cardiac transplant; (5) active infection; and (6) delayed closure of sternum. The study was approved by the Institutional Review Board at Indiana University.

The study was a prospective, randomized controlled trial. Patients undergoing cardiac surgery who required placement of a double lumen central venous catheters (4 Fr, 8 cm, 5 Fr, 8 cm or 12 cm long; Cook Critical Care, Bloomington, IN) were randomized with 1:1 allocation to receive either the M/R or the C/S catheter. Study catheters were assigned a random identification number

(by Cook Critical Care) and packed in identical catheter trays. The randomization scheme consisted of blocks of six identical catheter trays stocked with the above catheters in a randomized sequence. Although the color of the SPECTRUM catheter was unique and visible to the inserting physician at the time of implantation, it was not documented and was not visible after its placement. Thus, the clinical and infection control teams were in effect blinded to study arm into which each patient had been assigned. Catheters were inserted into the subclavian, femoral, or jugular vein under full sterile conditions in 1 of 2 designated operating rooms by cardiovascular surgeons and anesthesiologists only. Skin preparation was in compliance with guidelines with betadine for those patients younger than 2 months of age, and ChloroPrep was used for older patients. Full patient draping was used on every case. Surgery-related data included placement location, inserting physician, cardiac defect, cardiac repair, cardiopulmonary bypass time, ischemic time, cut time, and intraoperative antibiotic administration. Cefuroxime was the standard postoperative antibiotic, which is routinely given at our hospital for cardiovascular surgery prophylaxis and administered for 24 hours. Patients with an allergy received either vancomycin or clindamycin prophylaxis. Postoperative care was done in the PICU and the Heart Center step down unit managed by the pediatric cardiovascular team.

The standard of care for incisions included a semipermeable membrane dressing that was changed every 96 hours. When present, gauze dressings were changed every 48 hours. Catheter site assessment was made with each dressing change, and the surrounding area was disinfected with a chlorhexidine solution. Administration sets and all add-on devices were changed routinely every 96 hours and every 24 hours when blood or lipids were infused, per hospital policy.

The primary outcome measure was incidence of CABSIs per 1000 catheter days per standard terminology. All CABSIs were determined by hospital infection control specialists according to accepted National Healthcare Safety Network criteria at the time of study. Quantitative cultures and differential time to positivity were not available at the microbiology laboratory of the study institution. A secondary outcome measure was episodes of clinical sepsis and/or infection with identified source other than the CVC.

Daily evaluation through hospital discharge included fever, blood pressure, white blood cell count, platelet count, glucose, arrhythmia, urine output, or additional antibiotic administration. Any catheter related complication, including pneumothorax, thrombosis, occlusion, displacement, leakage, fracture, or fragmentation, was recorded.

Categorical measures were tabulated, and treatment differences were assessed with a  $\chi^2$  or Fisher's exact test. Continuous measures were summarized using means and standard deviations. Analysis was performed on an intention-to-treat basis. According to protocol, a blinded interim analysis was performed by an independent data safety monitoring board upon 50% (290 patients) of study enrollment.

## RESULTS

The total number of enrolled patients was 326 with 288 deemed evaluable. Reasons for exclusion included: open chest (10), ECMO (5), inability to place catheter (16), catheter inadvertently inserted in wrong vessel (3), preexisting infection (1), no assent obtained (1), biopatch instead of

standard dressing (1), and study catheter placed and removed in the operating room (1). Groups were evenly split between the 2 catheters (M/R = 146, C/S = 142). Demographics, RACHS-1 scores, and procedural information did not vary significantly between groups (Table 1). The number of catheter days were similar (M/R = 866 and C/S = 828).

The number of infections was exactly the same with 3 in each group. Rates of CABSI in both groups were quite small (M/R = 3.46/1000 catheter days and C/S = 3.62/1000 catheter days), and there was no statistically significant difference between the 2 groups (95% confidence interval, -3.4%–3.2%;  $P > .99$ ). All 6 CABSIs were noted to occur in children <2 years of age. Three infections occurred in the internal jugular location (M/R = 2 and C/S = 1), 2 in the femoral location (C/S = 2), and 1 in the subclavian vein (M/R = 1). Organism and line day of infection also were not significantly different between groups with *Escherichia coli* and *Streptococcus mitis* in the M/R group on days 3 to 17; and coagulase-negative staphylococcus, methicillin-susceptible *Staphylococcus aureus*, and *Candida albicans* being recovered on days 5–11 in the C/S catheters.

**Table 1 Primary Results**

	M/R(n= 146)	C/S (n= 142)	P Value
<b>Demographics</b>			
Age (month) <sup>a</sup>	12 (6.6–29.3)	12.9 (5.9–42.3)	.88
Weight (kg) <sup>a</sup>	8.8 (6.5–13)	8.9 (5.8–13.7)	.68
Gender (male)	51.4%	53.5%	.72
Cardiopulmonary bypass time (minutes) <sup>b</sup>	97.6 ± 48.9	103.9 ± 55.7	.31
Anesthesia time (minutes) <sup>b</sup>	371.1 ± 77.2	375.4 ± 82.8	.64
Ischemic time (minutes) <sup>b</sup>	43.3 ± 31.8	43.9 ± 30.6	.88
Surgery duration (minutes) <sup>b</sup>	212.5 ± 72.4	214.5 ± 87.5	.84
OR time (minutes) <sup>b</sup>	371.8 ± 72.4	376.3 ± 87.5	.63
<b>Outcomes</b>			
ICU days <sup>a</sup>	3(2–4)	2 (1–4)	.71
Total hospital duration (days) <sup>a</sup>	6(5–10)	6 (4–9)	.74
Antibiotic days <sup>a</sup>	6(3–11.5)	3.5 (2–7)	.19
All complications	10.3%	12%	.7
Hemothorax	0.7%	0%	>.99
Bleeding at catheter insertion site	1.4%	0%	.49
Venous thrombosis (in cannulated blood vessel)	0%	0.7%	.49
Catheter leak (requiring repair or removal)	2.1%	2.1%	>.99
Catheter displacement (requiring replacement)	0%	0.7%	.49
Catheter occlusion (requiring removal or thrombectomy)	2.7%	3.5%	.74

Abbreviations: C/S, nonimpregnated catheters; ICU, intensive care unit; OR, operating room; M/R, minocycline and rifampin-coated catheters.

<sup>a</sup>Data reported as median (interquartile range).

<sup>b</sup>Data reported as mean (+/- standard deviation).

There were no statistically significant differences in catheter complications between groups as shown in Table 1, and, overall, complications were rare in either group in every category. Noncatheter-related infections did not differ between groups. There were 8 of 146 (rate = 9.24) in the M/R group and 4 of 141 (rate = 8.48) in the C/S group ( $P = .38$ ).

Results of the interim analysis demonstrated that the expected infection rate was substantially less than postulated and resulted in no overall statistical difference with regard to infectious outcomes between catheters. It was expected that the study would be highly unlikely to show a statistical difference, even with the substantial additional enrollment, and was therefore stopped.

## DISCUSSION

With an increasing focus on infection risk, central catheter bundles have been used in efforts to prevent CABSIs. Implementation has been effective in adults but there is limited evidence in children. Berneholtz et al [4] demonstrated a reduction in CABSIs rate from 7.7 to 1.4 after implementation of such techniques, and others have shown benefits as well [5].

Utilization of chlorhexidine-silver-coated catheters led to a minimal decrease in CABSIs that is beyond that seen based on education alone [6]. Early studies demonstrated decreased catheter colonization and were suggestive of decreased infection with a possible associated cost savings, although [7, 8] the decreased microbe colonization could not be directly translated to decreased infection [9, 10]. One observational trial in critically ill children demonstrated longer onset to infection compared with conventional catheters [11].

Our study demonstrates no statistical differences in CABSIs in children after cardiac surgery in M/R compared with C/S catheters. CABSIs secondary to a staphylococcal organism was not observed in the M/R catheters. No infections occurred in patients older than 2 years of age and none in the M/R catheters placed in the femoral location, often the easiest access in small children. Further studies may be warranted to assess the impact that M/R catheters may have in these populations. Our study raises the question that perhaps antibiotic-impregnated catheters cannot lower CABSIs rates further when they are already extremely low; however, in areas that have applied measures without reaching the desired goals, there could be some benefit in adding these catheters.

Anecdotally, practitioners have commented that the antibiotic-impregnated catheters are more difficult to insert and have increased complications. Our data dispute this assertion because there were no statistically significant differences in any of the complications when comparing M/R versus C/S catheters. However, the study lacked sufficient power to make definitive statements regarding complications.

During study enrollment, infection control led efforts to reduce the PICU CABSIs rate and resulted in a decrease in overall line infection rate from a monthly peak of 14.5 to a low of 0.0 and an average of less than 4 per 1000 catheter days during our study period. This reduction in baseline CABSIs resulted in the study being underpowered to detect a significant difference between catheters and is a significant limitation, making it difficult to pinpoint the independent impact of the catheters. Because of low rates of infection, only a large multicenter study is likely to generate the numbers required for statistical power.

## CONCLUSIONS

Our results indicate that the M/R catheter can be safely used in children, including those who weigh less than 10 kg, despite no current US Food and Drug Administration guidelines for that age group. No difference was observed in infectious outcomes between M/R and C/S central venous line catheters, possibly due to the extremely low baseline infection rate. There is no evidence that complications are increased with their use. Further studies with larger subject enrollment may be necessary to definitively answer such questions.

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