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Comparison of pediatric ventriculo-peritoneal shunt infections arising in antibiotic-impregnated and standard catheters: a multicenter observational study

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Antibiotic-impregnated ventricular shunt catheters (AIVSCs) with 0.15% clindamycin and 0.054% rifampin are commonly used to prevent ventriculo-peritoneal (VP) shunt infections. Initially approved by the United States Food and Drug Administration in 2003 (https://www.integralife.com/file/general/1561404015.pdf), they have antimicrobial activity documented for minimum 31 days (https://www.accessdata.fda.gov/cdrh_docs/pdf11/K110560.pdf). These antibiotics were chosen as they cover the majority of *Staphylococcus aureus* and may provide some activity against coagulase negative staphylococci.[1] These normal skin flora account for the majority of VP shunt infections. In the largest randomized controlled trial (RCT) to date, AIVSCs significantly reduced the risk of infection compared with standard shunts (cause-specific hazard ratio (HR) 0.38).[2] This effect was mainly due to a reduction in staphylococcal infections; the number of gram-negative infections was similar in both groups. Observational studies[3–5] and a meta-analysis[6] in children support the findings of this RCT. The objective of this study was to examine the spectrum of pathogens, time to infection, and outcomes with AIVSCs vs standard shunts.

This study was conducted by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) at pediatric tertiary care hospitals in Canada (n=5) and the United States (n=3). Ethics approval was obtained from the Health Research Ethics Board at the University of Alberta (Pro00092852) and then from each site. This is a secondary analysis of a previously reported multicenter cohort study[7] where children under 18 years of age with culture positive VP shunt infections occurring between July 2013 and June 2019 were included if the type of shunt (standard vs AIVSC) could be ascertained.

For descriptive statistics, we used counts (percentages) for binary and categorical variables, and median (interquartile range, IQR) for continuous variables. For comparative statistics, we used Pearson's Chi-Square or Fisher's exact test for binary or categorical variables, as appropriate. We used the nonparametric Mann-Whitney U test for continuous variables. Data analyses were performed in the R statistical environment (version 3.6.2)[8] and figures were created using GraphPad Prism version 6 (GraphPad Software Inc., La Jolla, CA, USA, 2012).

Fifty-nine children met the eligibility criteria (table 1). Clinical characteristics, cerebrospinal fluid (CSF) parameters, and outcomes were similar among patients with standard and AIVSCs (table 1). The proportion of AIVSC infections increased over calendar time (p=0.0025) (figure 1A) presumably because most shunts placed from 2018 onward were AIVSCs (figure 1A). The ratio of staphylococci to other microorganisms did not change significantly over time (p=0.20, figure 1B).

Eight of 14 (57%) standard shunt infections and 22 of 45 (49%) AIVSC infections were caused by staphylococci (odds ratio (OR)=0.72, 95% confidence interval (CI)=0.21 to 2.4, p=0.76). The distribution of pathogens was

Table 1 Characteristics of 59 children with cerebrospinal fluid shunt infections

Characteristics	Standard shunt (n=14)	Antibiotic shunt (n=45)	P value
Female, n (%)	5 (36)	18 (40)	>0.99
Preterm birth, n (%)	5 (36)	27 (60)	0.20
Age at shunt placement (years), median (IQR)	1.0 (0.29–11)	0.38 (0.13–2.3)	0.11
Age at shunt infection (years), median (IQR)	3.1 (0.72–13)	0.58 (0.38–5.5)	0.11
Interval from shunt placement to infection (days), median (IQR)	60 (20–380)	40 (24–77)	0.70
Infections in first 31 days after shunt placement, n (%)	6 (43)	13 (29)	0.52
Signs and symptoms, n (%)			
Fever (≥38.2°C) in hospital	10 (71)	23 (51)	0.23
History of fever at home	3 (21)	7 (16)	0.69
Nausea	1 (7.1)	3 (6.7)	>0.99
Vomiting	4 (29)	16 (36)	0.75
Seizures	1 (7.1)	2 (4.4)	0.56
Other neurological symptoms	2 (14)	6 (13)	>0.99
Irritability	3 (21)	16 (36)	0.51
Lethargy	4 (29)	10 (22)	0.72
Poor feeding	2 (14)	10 (22)	0.71
Abdominal pain	4 (29)	4 (8.9)	0.081
Pathogen, n (%)			0.47
Coagulase negative staphylococci	6 (43)	13 (29)	
Staphylococcus aureus (methicillin susceptible)	1 (7)	7 (16)	
Staphylococcus aureus (methicillin resistant)	1 (7)	2 (4)	
Cutibacterium acnes	2 (14)	1 (2)	
Enterococcus faecalis	0 (0)	2 (4)	
Other Gram positive*	1 (7)	4 (9)	
Pseudomonas aeruginosa	0 (0)	3 (7)	
Other Gram negative†	0 (0)	6 (13)	
Candida spp‡	1 (7)	1 (2)	
Polymicrobial	2 (14)	6 (13)	
CSF parameters			
CSF WBC count (cells/µL), median (IQR)	69 (31–250)	54 (9–420)	>0.99
Proportion neutrophils (%), median (IQR)	45 (4.5–63)	42 (12–79)	0.58
Shunt procedures, n (%)			0.61
Shunt removed, EVD placed, and shunt later replaced	10 (71)	30 (67)	
Shunt removed, EVD placed, and shunt never replaced	1 (7)	6 (13)	
Shunt externalized and externalized part eventually replaced	1 (7)	2 (4)	
Shunt removed and not replaced	0	4 (9)	
Infected shunt retained	0	1 (2)	
Other§	2 (14)	2 (4)	
Outcomes, n (%)			
Complication	7 (50)	18 (40)	0.73
ICU admission	5 (36)	20 (44)	0.79
Duration of hospitalization (days), median (IQR)¶	34 (20–51)	26 (14–47)	0.35
Fatal outcome	1 (7.1)	2 (4.4)	0.56

Numbers represent n (%) unless otherwise indicated.
**Streptococcus mitis* complex (n=2); Group B streptococcus (n=1); *S. dysgalactiae* (n=1); *Bacillus* spp (n=1).
†*Enterobacter cloacae* (n=2); *Klebsiella aerogenes* (n=1); *E. coli* (n=1); *Acinetobacter* spp. (n=1); *Klebsiella oxytoca* (n=1).
‡*C. parapsilosis* (n=1); *C. lusitaniae* (n=1).
§New shunt placed at time of removal of original shunt (n=1); shunt externalized then removed without replacing it (n=1); shunt removed and EVD placed, EVD infected and removed (n=1); shunt removed completely and eventually replaced 19 days later (n=1).
¶Among survivors (n=56).
CSF, cerebrospinal fluid; EVD, external ventricular drain; ICU, intensive care unit; IQR, interquartile range; WBC, white blood cell.

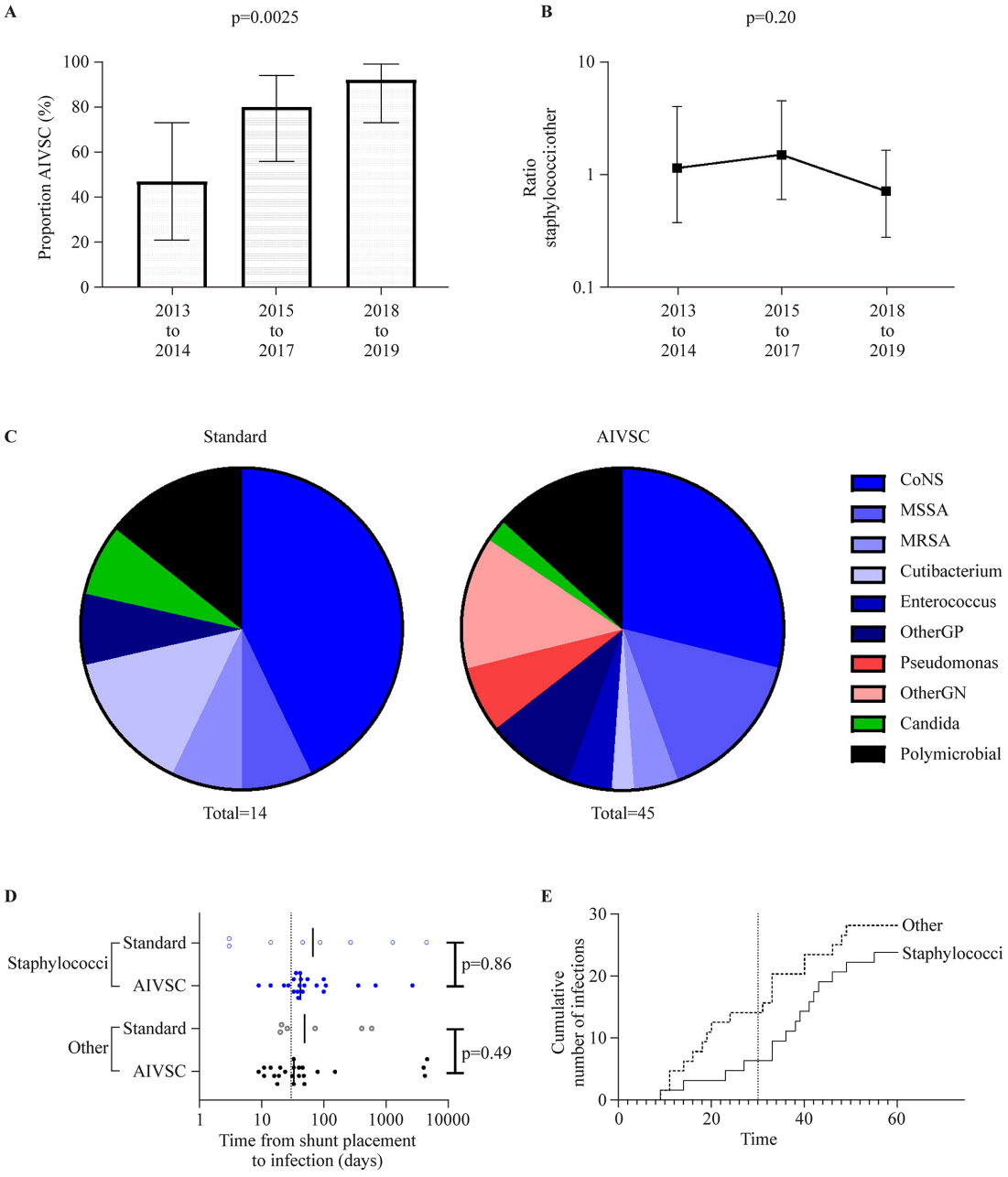

Figure 1 Infections of standard and antibiotic-impregnated ventricular shunt catheters (AIVSCs). (A) The proportion of AIVSC infections increased over calendar time. (B) The ratio of staphylococci to other microorganisms did not change significantly over time. (C) The distribution of pathogens was not statistically significantly different. (D) The time from shunt insertion to infection in AIVSCs vs standard shunts for staphylococci and for other organisms. (E) The ratio of incident staphylococcal to other infections in the first month among patients with AIVSCs and in the second month. AIVSCs, antibiotic-impregnated ventricular shunt catheters; CoNS, coagulase-negative staphylococci; GN, Gram-negative;.GP, Gram-positive; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

not statistically significantly different between standard and AIVSCs (p=0.47). All *Pseudomonas* species (n=3) and other Gram-negative infections (n=6) arose in patients with AIVSCs (figure 1C).

The median time to shunt infection post-operatively was 60 days in the standard group and 40 days in the AIVSC group, respectively (p=0.70) and was not different between standard and AIVSCs, for staphylococci (p=0.86) or other microorganisms (p=0.49) (figure 1D). Among AIVSCs, the ratio of incident staphylococcal to other infections in the first month was 4:9, (0.44, 95% CI=0.077 to 1.4) and appeared higher in the second month, when the ratio was 11:9 (1.2, 95% CI=0.47 to 3.3) (figure 1E).

The impact of widespread use of AIVSCs on the distribution of pathogens implicated in VP shunt infections appears to be modest in a real-world setting. Our results help contextualize findings from the previously mentioned RCT,[2] which showed a cause-specific HR of 0.38 for infection among AIVSCs, driven mainly by a reduction in staphylococci. Clinicians may be tempted to infer that staphylococcal infections

are uncommon in AIVSCs, whereas they accounted for 31% of all infections arising in AIVSCs in our study. Like the RCT, two observational study also reported an increase in the proportion of Gram-negative infections with the use of AIVSCs.[9 10] The first reported Gram-negative bacilli in 23 of 46 (50%) infections of AIVSCs vs 22 of 68 (32%) standard shunts[9] while the second reported Gram-negative bacteria in 91% of AIVSCs vs 50% of standard shunts (p=0.04).[10] It is of note that if one excludes polymicrobial infections, all nine Gram-negative infections in the current study occurred in the AIVSC group (table 1), suggesting that with a larger sample size one might have been able to demonstrate increased risk of Gram-negative infection with AIVSCs.

AIVSCs may select for bacteria resistant to clindamycin and rifampin. In our series, no rifampin resistance was documented in shunt infection pathogens, but many laboratories only report rifampin susceptibilities on request. A previous study documented four rifampin-resistant coagulase-negative staphylococci (CoNS) shunt infections over a 4year period in 125 adults and children with AIVSCs (incidence 3.2%).[11]

Ideally, AIVSCs would prevent all infections with susceptible pathogens. It is not clear whether failures occur because antibiotics cannot overcome contamination events at shunt placement or whether the concentration of antibiotics in the AIVSC becomes too low over time to remain effective, potentially explaining the trend towards a higher proportion of staphylococcal infections in the second vs the first month after placement in the current study. Perhaps biofilm eventually prevents antibiotics from reaching the bacteria. In our study, AIVSC and standard shunts had similar intervals between shunt placement and infection, in favor of the first of these three theories.

A limitation of this study is that we do not know the number of patients who had AIVSCs vs standard shunts placed during the study period.

In summary, the proportion of staphylococcal infections remained high (31%) among children with AIVSCs in our multicenter pediatric observational study. Clinicians should recognize that staphylococci remain the dominant pathogens when infection arises in an AIVSC.

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