



Antibiotic-Impregnated Catheters for Ventriculoperitoneal Shunt in Neonates and Infants: A Systematic Review and Meta-Analysis

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Key words

- Antibiotic-impregnated catheters
- Hydrocephalus
- Infection
- Meta-analysis
- Ventriculoperitoneal shunt

Abbreviations and Acronyms

AIC: Antibiotic-impregnated catheter

CI: Confidence interval

CSF: Cerebrospinal fluid

OR: Odds ratio

RCT: Randomized controlled trial

VP: Ventriculoperitoneal

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Citation: *World Neurosurg.* (2025) 201:124195.

<https://doi.org/10.1016/j.wneu.2025.124195>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

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INTRODUCTION

Hydrocephalus is an abnormal accumulation of cerebrospinal fluid (CSF) within the ventricles, resulting in increased intracranial pressure and potentially leading to brain damage. It occurs when there is an imbalance between the amount of

BACKGROUND: Ventriculoperitoneal shunt (VPS) is the standard treatment for hydrocephalus in neonates and infants, but is commonly complicated by shunt infections. Antibiotic-impregnated catheters (AICs) have been introduced to mitigate infection risk; however, their effectiveness remains uncertain.

METHODS: We conducted a systematic review and meta-analysis comparing outcomes in neonates and infants who underwent VPS with and without AICs. Primary outcomes included shunt infection risk, time to first infection, and infections caused by gram-positive cocci and gram-negative rods. Pooled odds ratios (ORs), mean differences, and 95% confidence intervals (CIs) were calculated using random-effects models.

RESULTS: Seven studies encompassing 1,009 patients were included. The use of AICs was associated with a significant three-fold reduction in overall shunt infection risk compared to standard catheters (OR 0.27; 95% CI 0.15–1.03; $P < 0.01$; $I^2 = 0\%$). Subgroup analysis showed significant infection risk reduction in infants (OR 0.29; 95% CI 0.12–0.67; $P = 0.004$) and neonates (OR 0.26; 95% CI 0.11–0.62; $P < 0.01$). AICs led to a significant decrease in gram-positive cocci infections (OR 0.20; 95% CI 0.06–0.69; $P = 0.01$) but not gram-negative rod infections. The time to first infection was significantly prolonged in the AIC group (mean difference 4.6 months; 95% CI 2.2–6.9; $P < 0.01$). Lower infection risk persisted at 6 months and beyond.

CONCLUSIONS: AICs substantially reduce infection risk and delay infection onset in neonates and infants undergoing VPS, particularly for gram-positive bacteria. Routine use is recommended.

CSF produced and the rate at which it is absorbed. This condition is particularly prevalent among neonates and infants, with 88 cases in every 100,000 births worldwide.^{1,2}

Ventriculoperitoneal (VP) shunting is a common neurological procedure, and it is estimated that approximately 30,000 VP shunts are placed in the United States each year.² It remains the primary and most frequent intervention for managing hydrocephalus, effectively diverting excess CSF to the peritoneal cavity.^{3,4} Despite its effectiveness, revision rates can reach up to 50% yearly for each complication, such as infections, which may lead to shunt malfunction, repeated surgical

interventions, and increased morbidity and mortality up to 1%–2.7% in this vulnerable population.^{2,5,6} These infections compromise the shunt procedure and impose significant clinical and economic burdens due to extended hospital stays and long-term antibiotic therapy.⁷ Shunt infection is considered one of the most costly implant-related infections, with a cost of more than 50,000 USD per infection in the United States.⁸

Antibiotic-impregnated catheters (AICs), available for more than 2 decades, incorporate 0.054% rifampin and 0.15% clindamycin, which have been shown to effectively inhibit colonization.^{9,10} Given that the majority of shunt infections

result from device colonization by nonpathogenic gram-positive cocci, primarily *Staphylococcus epidermidis* and *Staphylococcus aureus*, typically introduced during surgery, AICs have been used to reduce the risk of infection in VP shunts for hydrocephalus.^{2,4} However, their routine use in daily neurosurgical practice remains limited due to their high costs.^{3,4,6}

This meta-analysis aims to evaluate the efficacy of AICs in preventing infections for VP shunts in infants and neonates with hydrocephalus.

METHODS

This systematic review and meta-analysis adhered to the established guidelines of the Cochrane Collaboration and the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement.¹¹ To ensure methodological rigor, this systematic review was prospectively registered in the Prospective Register of Systematic Reviews database (CRD42024536438).

Search Strategy

We systematically searched PubMed, Cochrane, and Embase from inception to April 2024. To enhance the retrieval of pertinent studies, we used a Boolean search strategy that combined Medical Subject Headings terms with keywords. The used search strategy included the following search terms and their variations: “Hydrocephalus,” “shunt infection,” “device-related infections,” “antibiotic-impregnated,” “cerebrospinal fluid shunt,” “congenital,” “infantile,” “neonate,” “children,” “pediatric,” “less than 1 year,” and “newborn”.

Inclusion Criteria

This meta-analysis set stringent inclusion criteria, requiring studies to meet specific eligibility standards. First, studies had to focus on neonates and infants diagnosed with various forms of hydrocephalus. Second, eligible studies included case-control studies, cohort analyses, and randomized controlled trials (RCTs) comparing AICs versus non-AICs. Studies without a control group or those involving adult populations were systematically excluded to maintain the methodological

integrity and consistency of the synthesized data.

Data Extraction

A rigorous 2-reviewer standardized data collection system was implemented to ensure data accuracy and minimize bias. Two authors (E.S. and A.A.) independently and meticulously extracted data following predefined search criteria and quality assessment standards. This collaborative approach was crucial in affirming the credibility and consistency of the data collected for this meta-analysis.

Outcome Measures

The efficacy outcomes included the risk of shunt infection as the primary outcome and the time to first infection. Three subgroup analyses were conducted: one for the risk of infection by gram-positive cocci, another for the risk of infection by gram-negative rod bacteria, and a third for the risk of infection during the first 6 months and beyond 6 months postsurgery.

Quality Assessment and Risk of Bias

The Risk Of Bias In Nonrandomized Studies of Interventions tool was applied

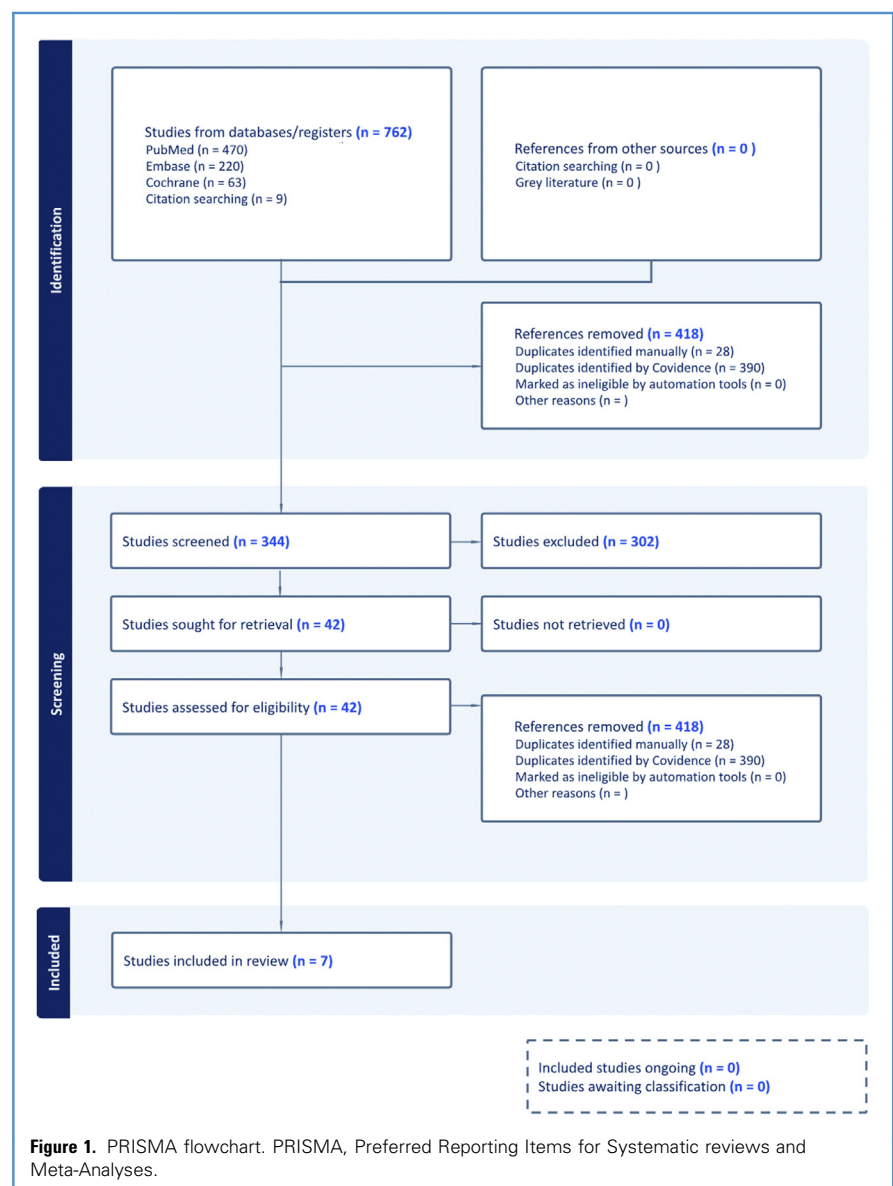


Table 1. Baseline Characteristics of Included Studies

Study, Year	Study Design	Country	Cohort Size (Total)	VP Shunt with AIC, N (%)	VP Shunt without AIC, N (%)	Preterm VP Shunt with AIC/without AIC	Female, N (%)	Age (Mean or Median)	Follow-Up (Mean or Range)	Outcomes Reported
Jager, 2017 ⁷	ROCS	Australia	47	23 (48.9%)	24 (51.1%)	N/R	17 (36.2%)	N/R	12 months	TTFI, risk of shunt infections
Yang, 2016 ¹¹	ROCS	China	736	470 (63.9%)	266 (36.1%)	N/R	N/R	With AIC: 17.1 months Without AIC: 13.7 months	6 months	Risk of shunt infections
Raffa, 2015 ⁸	ROCS	Italy	48	22 (45.8%)	26 (54.2%)	10/10	22 (45.8%)	66 days	> 1 year	TTFI, risk of shunt infections, gram-positive cocci, and gram-negative rod infections
Saleh, 2023 ⁹	ROCS	Saudi Arabia	100	50 (50%)	50 (50%)	22/23	N/R	N/R	Mean: 28.3 ± 10, range: 9–48 months	TTFI, risk of shunt infections, gram-positive cocci, and gram-negative rod infections
Elfadle, 2022 ¹²	ROCS	Egypt	25	12 (48%)	13 (52%)	3/2	14 (56%)	N/R	6 months	Risk of shunt infections
Moussa, 2016 ¹⁰	RCT	Egypt	40	20 (50%)	20 (50%)	2/3	17 (42.5%)	A: 37.8 days B: 34.9 days C: 39.1 days	Mean of 8.9 months, range: 2–12	TTFI risk of shunt infections, gram-positive cocci, and gram-negative rod infections

P, ventriculoperitoneal; AIC, antibiotic-impregnated catheter; ROCS, retrospective observational cohort study; N/R, not reported; TTFI, time to first infection; RCT, randomized controlled trial.

to assess the risk of bias among the included nonrandomized studies.¹² The assessed domains included confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Randomized control trials were assessed based on the risk of bias by using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (Risk of Bias 2), in which studies are scored as high, low, or unclear risk of bias in 5 domains.¹³ The quality was assessed by 2 authors (O.K. and E.S.). The layout of the figures was produced using robvis.¹⁴

Statistical Analysis

To assess each different outcome, odds ratios (ORs) and mean differences with accompanying 95% confidence intervals (CIs) were used. Heterogeneity across studies was evaluated using the I^2 statistic. A significance level of $P < 0.05$ and I^2 value exceeding 50% were considered indicative of substantial heterogeneity. A random-effect model was used for all outcomes. Additionally, a random-effects meta-regression analysis was conducted. All statistical analyses were performed using Stata 14 software (StataCorp, College Station, Texas).

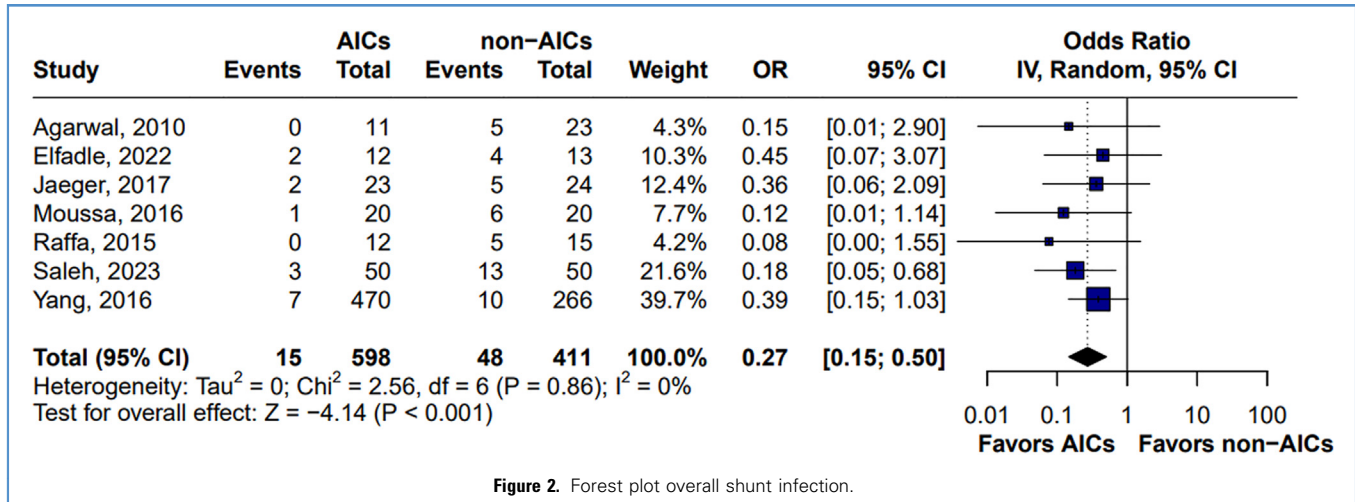
RESULTS

The initial search produced 762 relevant studies (Figure 1). After removing duplicate records and ineligible studies, 42 remained and were fully reviewed based on the inclusion criteria. Finally, 7 studies were included (1 RCT¹⁵ and 6 observational studies^{16–21}) comprising 1009 patients. 589 (58%) infants received AICs for VP shunt and 411 (42%) received non-AICs. The follow-up period ranged from 6 to 48 months. Study characteristics are presented in Table 1.

We observed a notable variability among studies concerning the duration of therapy, the type of AICs employed, and follow-up periods.

Shunt Infections

The pooled analysis of 7 studies^{15–21} demonstrated that the risk of shunt infections was 2.5% (15 of 598) in AICs and 11.6% (48 of 411) in non-AICs. AICs were



significantly associated with an approximately 3-fold reduction in the risk of shunt infection (OR: 0.27; 95% CI: 0.15–1.03; $P < 0.01$; $I^2 = 0\%$) compared to non-AICs. There was no heterogeneity across the studies (Figure 2).

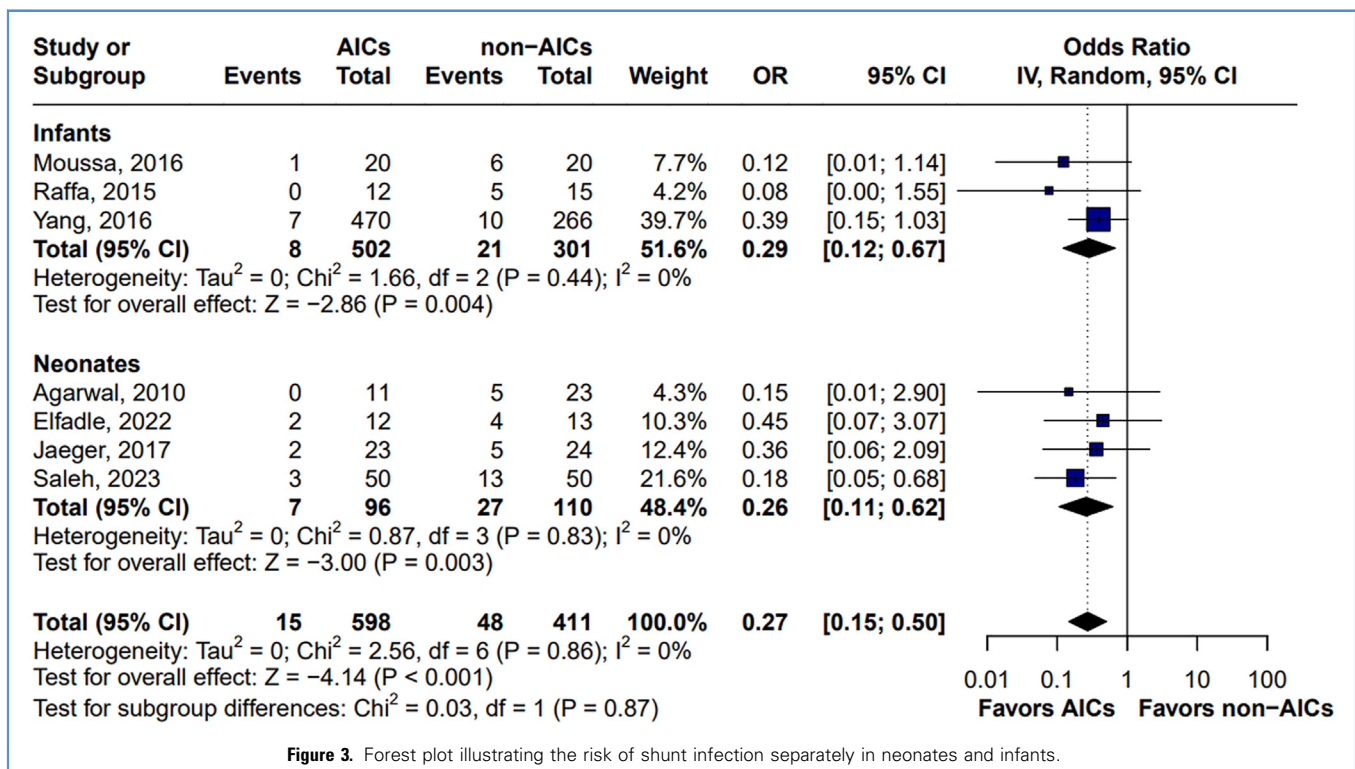
Subgroup analysis of 3 studies^{15,16,18} revealed that the risk of shunt infection is significantly lower in infants (OR: 0.29; 95% CI: 0.12–0.67; $P < 0.01$; $I^2 =$

0%) in the AIC group. Another subgroup analysis of 4 studies^{17,19–21} showed that the risk of shunt infection is significantly lower in neonates (OR: 0.26; 95% CI: 0.11–0.62; $P < 0.01$; $I^2 = 0$) in the AIC group compared to the non-AIC group (Figure 3).

Subanalysis of 3 studies^{18–20} revealed a lower risk of infection before 6 months of follow-up (OR: 0.37; 95% CI: 0.16–0.85; P

< 0.01 ; $I^2 = 0$) and after 6 months of follow-up (OR: 0.19; 95% CI: 0.08–0.47; $P = 0.02$; $I^2 = 0$) in the AIC group versus in the non-AIC group based on the analysis of 4 studies^{10–12,16} (Figure 4). Specifically, the risk is reduced by 63% within 6 months and by 81% more than 6 months after surgery.

Leave-one-out analysis indicated that excluding individual studies did not affect



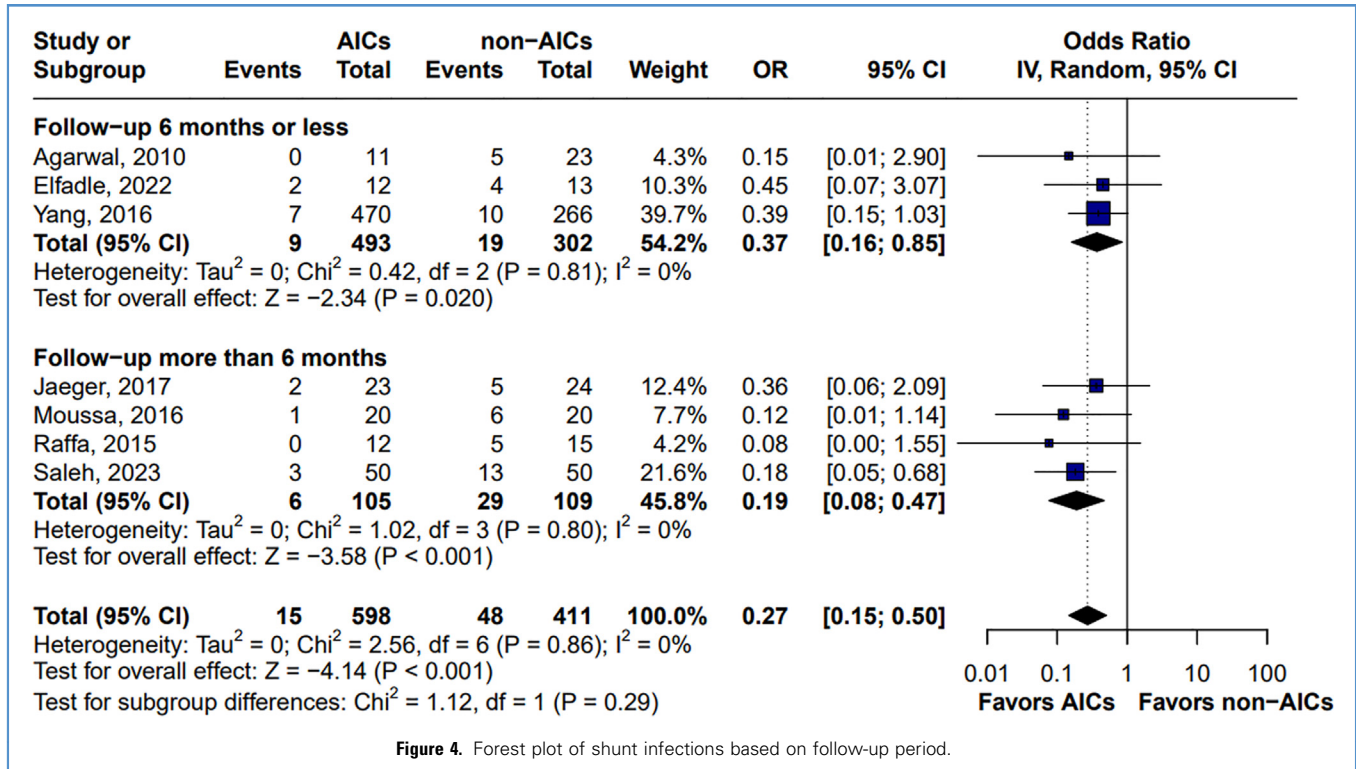


Figure 4. Forest plot of shunt infections based on follow-up period.

the findings regarding shunt infections (Figure 5). The funnel plot's shape and symmetry revealed no evidence of publication bias.

Time to Develop the First Shunt Infection

Analysis of 3 studies^{16,17,21} comprising 195 patients revealed that the AIC group took significantly longer time to develop the first infection (mean difference: 4.5

months; 95% CI: 2.2 to 6.9 months; P < 0.01; I² = 69%) (Figure 6).

Gram-Positive Cocci and Gram-Negative Rod Infections

Analysis of 3 studies¹¹⁻¹³ comprising 113 patients revealed a significantly lower occurrence of gram-positive cocci infections (OR: 0.20; 95% CI: 0.06-0.69; P = 0.01; I² = 0%) in the AIC group

(Figure 7). However, the occurrence of gram-negative bacilli infection was statistically not significant (OR: 0.23; 95% CI: 0.01-7.27; P = 0.40; I² = 77%) (Figure 8).

Quality Assessment

The quality of the included non-randomized studies was evaluated using the Risk Of Bias In Nonrandomized Studies of Interventions tool; 4 studies were rated as having a moderate overall risk of bias, while 1 study (Yang 2016) was rated as having a serious overall risk. Moderate risk due to confounding and participant selection was observed across all studies. Yang 2016 demonstrated serious bias in intervention classification. All studies had low risk in other domains, including missing data and outcome measurement. These findings underscore the importance of carefully interpreting the pooled results.

Additionally, regarding the assignment of participants to intervention and assessment of outcome biases within a single RCT, the risk was deemed high. Individual appraisals of studies are reported in Figure 9 and Table 2 for 6 nonrandomized studies.

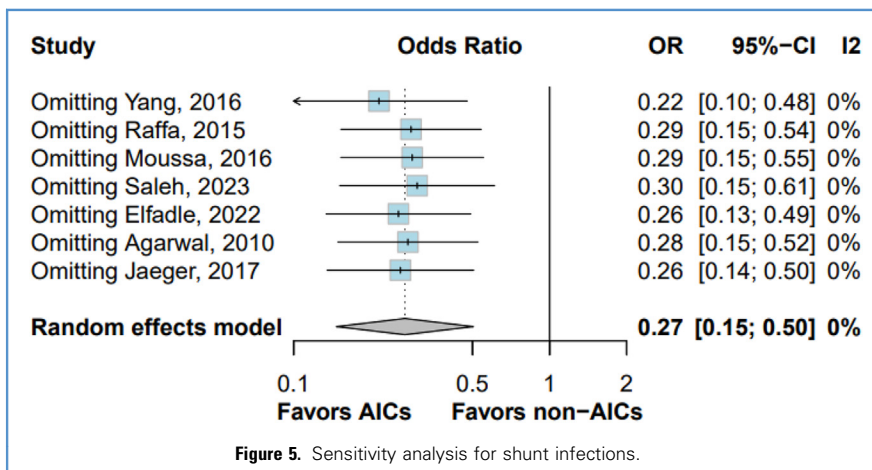


Figure 5. Sensitivity analysis for shunt infections.

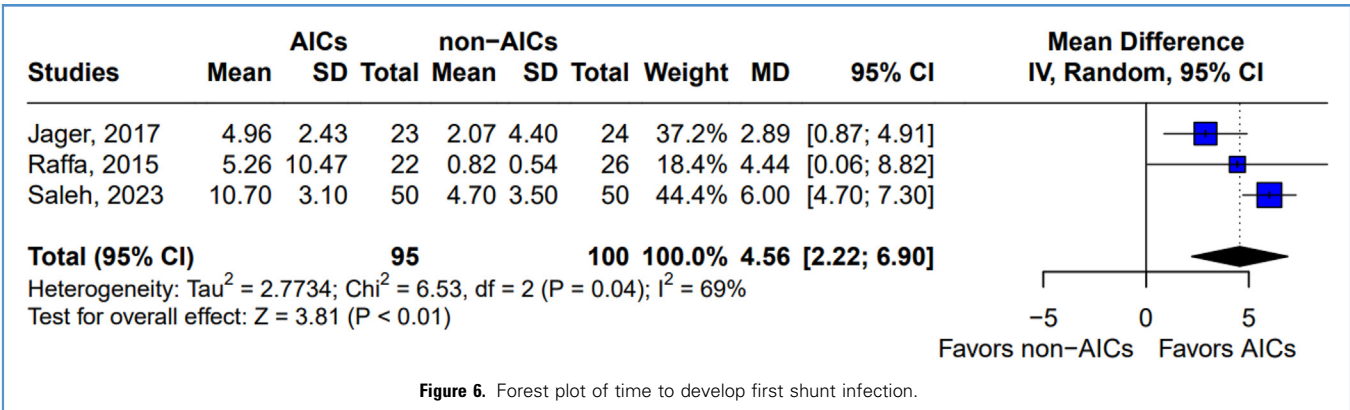


Figure 6. Forest plot of time to develop first shunt infection.

DISCUSSION

In this meta-analysis, we found that the use of AICs in infants and neonates was associated with a decreased risk of CSF infection following VP shunt placement.

Several risk factors for infections have been identified, like the age at shunt insertion, prematurity, myelomeningocele, and posthemorrhagic hydrocephalus, which continues to contribute to significant morbidity within the pediatric hydrocephalus population, especially in very young patients.²²⁻²⁴ Parker et al. emphasized the results of a subgroup of premature neonates following acute bacterial meningitis.²⁵

Previous studies have demonstrated a reduced risk of shunt infections with AICs in pediatric and adult patients.²⁴⁻³⁷ In our meta-analysis study, we have confirmed those findings in infants and neonates

that were previously unexplored populations.

AICs have proven to be significantly cost-effective compared to non-AICs in the United States, primarily due to the reduced shunt-related infections. In a study by Edwards et al. (2015)³⁰ involving 100 patients undergoing shunt placement, AICs were associated with 0.5 less deaths, 71 less hospital days, 11 less surgical procedures, and net cost savings of \$128,228. A subanalysis revealed even greater benefits: 1.9 less deaths, 611 less hospital days, 25 less surgeries, and a cost reduction of \$346,616, all of which were linked to a lower infection rate. Similarly, Farber et al. (2010)³⁶ analyzed 500 shunt procedures—250 with AICs and 250 without AICs—encompassing adults and children. They noted that the

infection rate in the AIC group was significantly lower (1.2%) than in the non-AIC group (4.0%), resulting in direct cost savings of approximately \$472 per shunt procedure. Additionally, Parker et al. (2015)³⁷ evaluated data from 1770 pediatric shunt cases (AIC: 229; standard: 1541). Infection rates were noticeably lower in the AIC group (2.6% vs. 7.1%). For each de novo shunt, the infection-related cost was \$1650 for AIC compared to \$3954 for pediatric patients. Despite these advantages, Parker et al.³⁷ noted that the broader adoption of AICs remains limited, primarily due to the higher initial cost, which is approximately \$400 more per catheter. While this upfront expense poses a barrier, particularly in high-volume centers, the substantial downstream savings associated with reduced infection rates

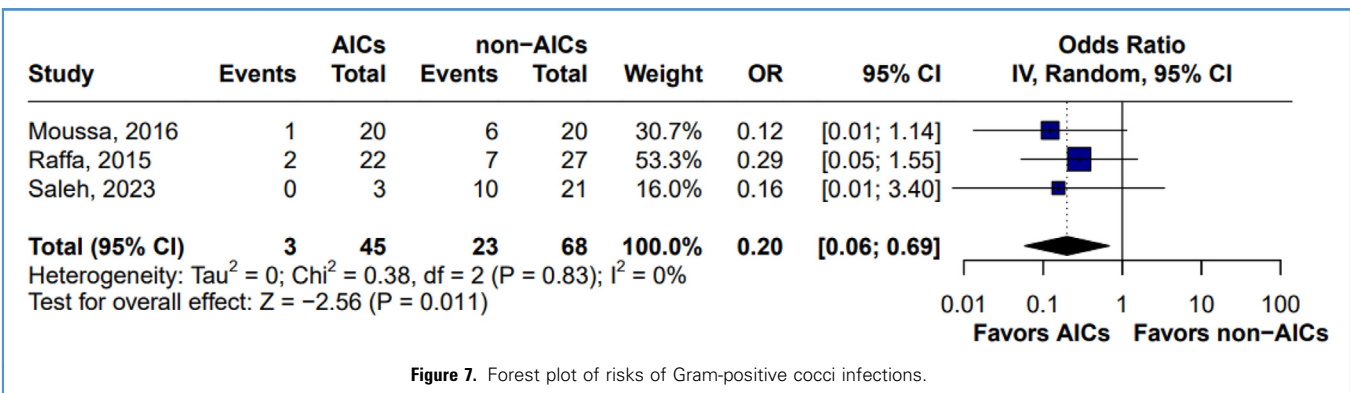


Figure 7. Forest plot of risks of Gram-positive cocci infections.

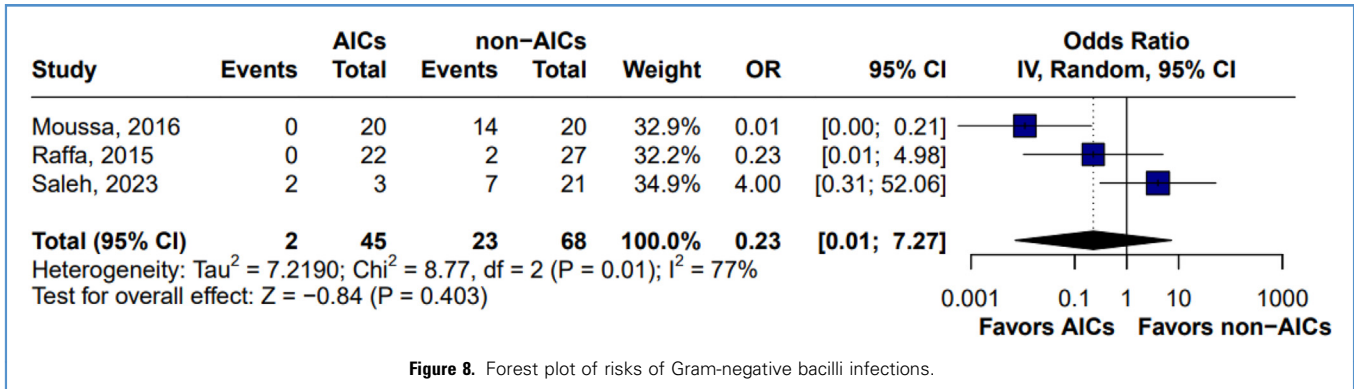


Figure 8. Forest plot of risks of Gram-negative bacilli infections.

make AICs a cost-effective strategy in shunt management.³⁷

Ragel et al. observed that the use of intraventricular gentamicin and

vancomycin injections, in combination with systemic antibiotics, significantly reduced the incidence of perioperative shunt infections. They suggested that this

approach could extend prophylactic coverage into the CSF, thereby preventing bacterial seeding.³¹

Our results regarding the risk of gram-positive cocci infections and gram-negative rod infections differ from those reported by Konstantelias et al., who observed no notable distinction in the risk of gram-positive cocci infections but noted an increased risk of gram-negative rod infections in AICs.^{32,33} Additionally, an 8-year retrospective cohort study showed that intravenous combined with intraventricular/intrathecal polymyxin B, with non-AIC, increased CSF microbiological eradication (P < 0.001), lower 30-day mortality (P = 0.032), and improved clinical outcomes compared to intravenous administration alone in postneurosurgical intracranial infections caused by carbapenem-resistant gram-negative bacteria.³⁴

Our observation that the time to first infection is longer with AICs compared to non-AICs contrasts with the findings of Kan et al., who reported no difference in the time to infection between the 2 groups.³⁵ Although studying adults, Farber et al. observed that catheter-related infections occurred earlier, with an average onset of 2 months postoperatively in the non-AIC group and later in the AIC group.³⁶ This aligns with our observations in infants and neonates. Additionally, Raffa et al. showed that patients treated with non-AICs had a 4-fold increased risk of shunt infection during the first year after surgery compared to those treated with AICs.¹⁶

A key strength of this meta-analysis lies in its inclusion of a relatively large and diverse sample size, encompassing studies across a broad time frame.

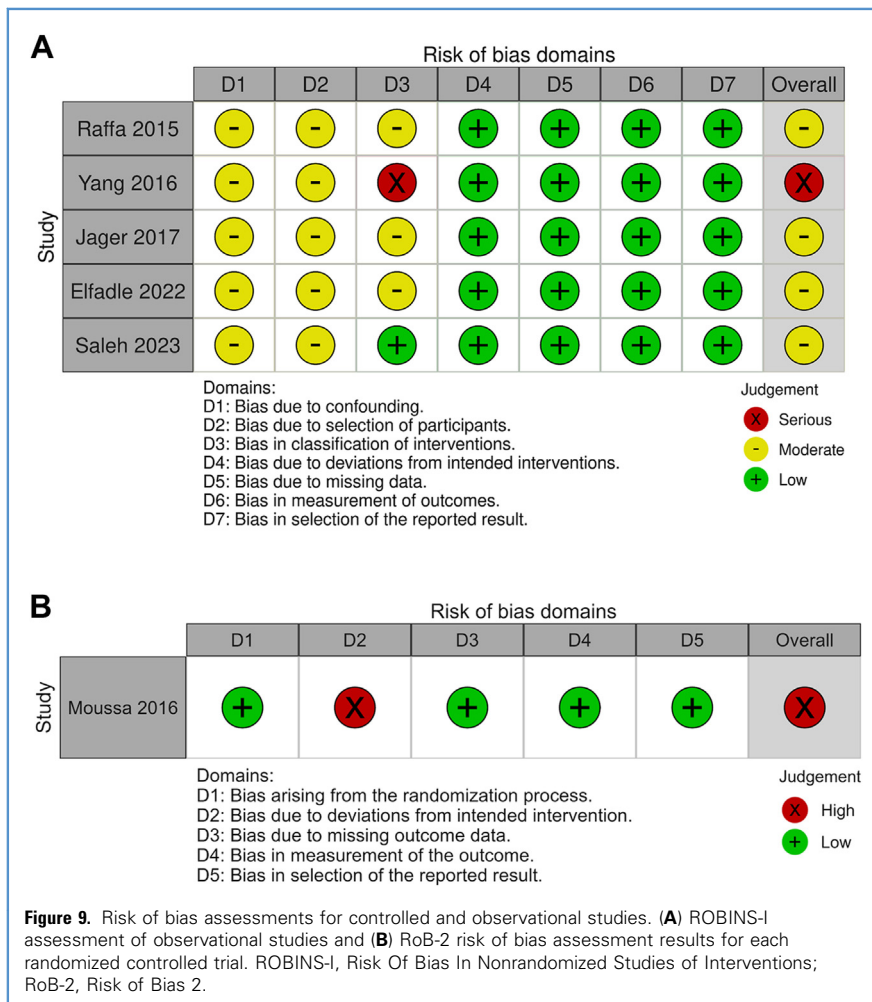


Table 2. Risk of Bias for Nonrandomized Studies

Study (Year)	Selection			Comparability		Outcome			Overall
	Representativeness of Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Outcome not Present at Start	Comparability of Cohorts	Assessment of Outcome	Follow-Up Length	Adequacy of Follow-Up	
Raffa, 2015	*	*	*	*	**	*	*	*	9
Yang, 2016	*	*	*	*	=	*	*	*	7
Jager, 2017	*	*	*	*	=	*	*	*	7
Elfadle, 2022	*	*	*	*	**	*	*	*	9
Sahel, 2023	*	*	*	*	-	*	*	*	7

"=" symbol is used for could not be determined; "*" symbol is used for no stars given.

Additionally, our assessment of potential biases indicated a low risk of bias within the included studies. This strengthens our confidence in the observed effects. However, certain limitations require acknowledgment. First, the predominant portion of the included studies lacked randomization. Second, the absence of patient-level data hindered the assessment of supplementary outcomes, such as mortality, hospitalization rates, operative duration, presence of CSF leaks, cost analysis, occurrence of late complications, and impacts on quality of life. Finally, subgroup analysis was not feasible due to insufficient data on pre-term and post-term neonates and a lack of detailed information on the etiology of hydrocephalus. Future studies should focus on these areas. Additional RCTs should be conducted in the future to investigate these limitations.

CONCLUSION

Our findings demonstrate that the use of AICs in VP shunts for infants and neonates significantly reduces the risk of shunt infections, especially those caused by gram-positive cocci, and delays the onset of the first infection. The routine use of AICs in pediatric neurosurgery is recommended, particularly in this vulnerable population, although it may have an initial higher cost.

CRedit AUTHORSHIP CONTRIBUTION STATEMENT

Walter Fagundes: Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aisha Rizwan Ahmed:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Formal analysis. **Yasmin Picanço Silva:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation. **Oguz Kagan Sahin:** Visualization, Methodology, Investigation, Formal analysis, Data curation. **Rabbia Jabbar:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis. **Iago Nathan Simon Petry:** Methodology, Investigation, Formal analysis, Data curation. **Pawel Łajczak:** Visualization, Validation, Software,

Resources, Methodology, Investigation, Formal analysis, Data curation. **Eshita Sharma:** Visualization, Validation, Software, Resources, Methodology, Investigation. **Fabio Victor Vieira Rocha:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Rohan Sabloak:** Methodology, Investigation, Formal analysis, Data curation. **Mir Wajid Majeed:** Investigation. **Numa Rajab:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Herika Negri Brito:** Writing – review & editing, Visualization, Validation.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any

commercial or financial relationships that could be construed as a potential conflict of interest.

Received 23 April 2025; accepted 12 June 2025

Citation: World Neurosurg. (2025) 201:124195.

<https://doi.org/10.1016/j.wneu.2025.124195>

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

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