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Zhou, Wen Xiu; Hou, Wen Bo; Zhou, Chao; Yin, Yu Xia; Lu, Shou Tao; Liu, Guang; Fang, Yi; Li, Jian Wen; Wang, Yan; Liu, Ai Hua; Zhang, Hai Jun

Published in:
Journal of Korean Neurosurgical Society

DOI (link to publication from Publisher):
[10.3340/jkns.2019.0219](https://doi.org/10.3340/jkns.2019.0219)

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Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Zhou, W. X., Hou, W. B., Zhou, C., Yin, Y. X., Lu, S. T., Liu, G., Fang, Y., Li, J. W., Wang, Y., Liu, A. H., & Zhang, H. J. (2021). Systematic review and meta-analysis of antibiotic-impregnated shunt catheters on anti-infective effect of hydrocephalus shunt. *Journal of Korean Neurosurgical Society*, 64(2), 297-308.
<https://doi.org/10.3340/jkns.2019.0219>

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Systematic Review and Meta-Analysis of Antibiotic-Impregnated Shunt Catheters on Anti-Infective Effect of Hydrocephalus Shunt

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Objective : Shunt infection is a common complication while treating hydrocephalus. The antibiotic-impregnated shunt catheter (AISC) was designed to reduce shunt infection rate. A meta-analysis was conducted to study the effectiveness of AISCs in reduction of shunt infection in terms of age, follow-up time and high-risk patient population.

Methods : This study reviewed literature from three databases including PubMed, EMBASE, and Cochrane Library (from 2000 to March 2019). Clinical studies from controlled trials for shunt operation were included in this analysis. A subgroup analysis was performed based on the patient's age, follow-up time and high-risk population. The fixed effect in RevMan 5.3 software (Cochrane Collaboration) was used for this meta-analysis.

Results : This study included 19 controlled clinical trials including 10105 operations. The analysis demonstrated that AISC could reduce the infection rate in shunt surgery compared to standard shunt catheter (non-AISC) from 8.13% to 4.09% (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.40–0.58; $p=0.01$; $I^2=46\%$). Subgroup analysis of different age groups showed that AISC had significant antimicrobial effects in all three groups (adult, infant, and adolescent). Follow-up time analysis showed that AISC was effective in preventing early shunt infections (within 6 months after implant). AISC is more effective in high-risk population (OR, 0.24; 95% CI, 0.14–0.40; $p=0.60$; $I^2=0\%$) than in general patient population.

Conclusion : The results of meta-analysis indicated that AISC is an effective method for reducing shunt infection. We recommend that AISC should be considered for use in infants and high-risk groups. For adult patients, the choice for AISC could be determined based on the treatment cost.

Key Words : Antibiotic-impregnated shunt catheters · Cerebrospinal fluid · Hydrocephalus · Infections.

• Received : October 31, 2019 • Revised : December 31, 2019 • Accepted : February 4, 2020

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INTRODUCTION

Despite advances in catheter technology, shunt infection remains an issue of great concern for patients and surgeons. Patients who develop infection have a two-fold risk of mortality and a three-fold the time of shunt-related operations than those without infection. The reported prevalence of shunt infection varies from 1.5% to 69%^(7,24). In a recent multicenter study of 41 pediatric hospitals in the United States, the rate of cerebrospinal fluid shunt infection ranged from 4.1% to 20.5%⁽¹⁾. Interestingly, Choux et al.⁽⁹⁾ indicated that a 0% infection rate is not an impossible goal. Although the incidence of shunt infection has decreased in developed countries in recent years^(8,15), infection remains a major cause of neurosurgical morbidity and mortality in developing countries.

Shunt infection is associated with lower IQ, poorer grades, increased seizure incidences, psychomotor retardation and decreased quality of life in children^(19,39). This also increases cost-related burden on the healthcare system and families. Coagulase-negative *Staphylococcus* is the main bacterial flora causing shunt infection because of its ability to form a biofilm on implanted materials. *Staphylococcus aureus* and Gram-negative bacilli are also common bacteria that cause shunt infection^(38,40).

The control catheter in this study was made from silicone with no antimicrobial coating (non-antibiotic-impregnated shunt catheter, non-AISC). Recently, neurosurgeons have started using AISC in order to reduce the risk of shunt infection. The commonly used antimicrobial coating for shunt catheters contains 0.15% clindamycin and 0.054% rifampin⁽¹²⁾. The AISC system releases antibiotics to the catheter lumen and surrounding tissue at least 50 days after implantation^(5,34). A recent non-systematic review suggested that AISC reduces the risk of ventriculo-peritoneal shunt infections⁽¹⁷⁾. Konstantelis et al.⁽²⁸⁾ analyzed the effectiveness of antibiotic-impregnated coatings, silver-ion coatings and hydrogel coatings against infection. Thomas et al.⁽⁴⁸⁾ analyzed the effectiveness of AISCs in neonatal and adult patients. In conclusion, despite reports of effectiveness of these catheters, the published data for infection is not consistent. The meta-analysis of AISC infection with respect to follow-up time and high-risk patient population has not been systematically studied previously. Therefore, we report a comprehensive analysis of AISC effectiveness in this study.

MATERIALS AND METHODS

All randomized controlled trials were ethically approved. Based on the inclusion and exclusion criteria in this study, any research that conforms to the following criteria was included in the high-risk subgroup. 1) A priori as prematurity (<37 weeks gestational age), 2) shunts placed immediately post-meningitis, 3) conversion of external ventricular drains to shunt, 4) children with previous external ventricular drainage, and 5) frequent nosocomial infections. Shunting refers to ventriculoperitoneal, ventriculoatrial, ventriculopleural, lumbo-peritoneal, cystoperitoneal and subdural shunting. The antibiotics mainly used refer to 0.054% rifampicin and 0.15% clindamycin. The meta-analysis was performed and reported in accordance with Meta-analysis of Observational Studies in Epidemiology guidelines⁽⁴⁷⁾, the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement⁽³¹⁾, and the guidelines of Cochrane Collaboration.

Search methods

PubMed (from 2000 to March 2019), EMBASE (from 2000 to March 2019), and the Cochrane Library (from 2000 to March 2019) were reviewed independently by two authors (W.X.Z. and Y.F.). PubMed was searched using the following terms—‘ventriculo-peritoneal shunt’ or ‘cerebrospinal fluid

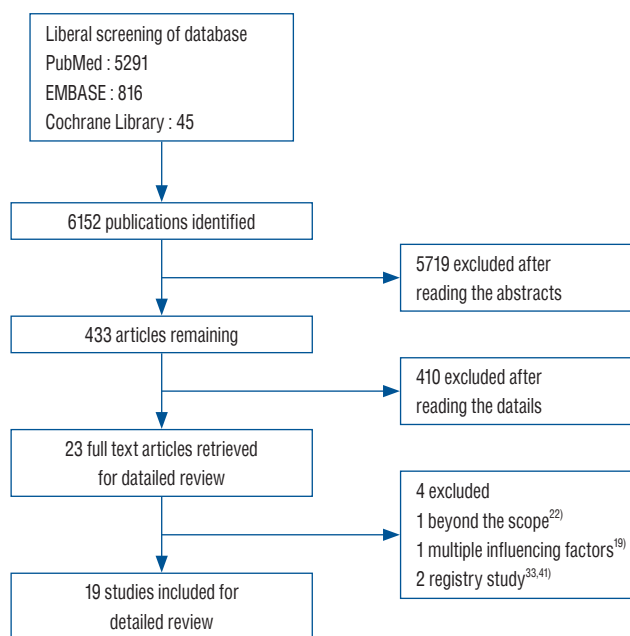


Fig. 1. Selection of studies based on inclusion criteria.

Table 1. Characteristics of included studies comparing AISC and non-AISC shunt

Study	Study design	Region, study period or duration	Population, age, mean/range	No of procedures, AISC/non-AISC	No of infections, AISC/non-AISC	Definitions of infection		Primary outcome	Follow-up duration
						Symptoms, signs, or other laboratory exams	Culture		
Albanese et al. ⁽²⁾ (2009)	Single center/retrospective	Europe, Oct. 2005 to Oct. 2007	Adults, 61.8 years/40–79 years	Total : 18 (6/12)	Total : 0/6 vs. 7/12	N	Y	Infection	≥12 months
Aryan et al. ⁽³⁾ (2005)	Single center/retrospective	USA, Apr. 2001 to Apr. 2003	Underage, 4.5 years/6 months–17 years	Total : 78 (32/46)	Total : 1/32 vs. 7/46	Y	Y	Infection	14–37 months
Yang et al. ⁽⁵⁰⁾ (2016)	Single center/retrospective	China, Jan. 2001 and Feb. 2013	Underage, 1 month–4 years	Total : 807 (504/303)	Total : 10/504 vs. 18/303 ≤1 year : 7/470 vs. 10/266	Y	N	Infection	≥6 months
Eymann et al. ⁽¹¹⁾ (2008)	Single center/retrospective	Europe, Jan. 1998 to Dec. 2006	Adults, 18–86 years Underage, 2 days–12 years	Total : 317 (197/120) Adults : 269 (171/98) Underage : 48 (26/22)	Total : 2/197 vs. 7/120 Adults : 1/191 vs. 4/98 Underage : 1/26 vs. 3/22	N	Y	Infection	≥6 months
Eymann et al. ⁽¹²⁾ (2009)	Single center/retrospective	Europe, Jan. 2002 to Dec. 2007	Underage, 1 day–100 months	Total : 56 (34/22)	Total : 1/34 vs. 3/22	N	Y	Infection	6–75 months
Farber et al. ⁽¹³⁾ (2011)	Single center/retrospective	USA, 2004 to 2009	Adults, 60 years/21–93 years	Total : 500 (250/250)	Total : 3/250 vs. 10/250	N	Y	Infection	12 months
Govender et al. ⁽¹⁶⁾ (2003)	Single center/RCT	Africa, NR	1 month–72 years	Total : 110 (50/60)	Total : 3/50 vs. 10/60	Y	Y	Infection	9–28 months
Gutiérrez-González et al. ⁽¹⁸⁾ (2010)	Single center/retrospective	Europe, Jan. 2004 to Oct. 2008	All	Total : 119 (72/47)	Total : 2/72 vs. 8/47	N	Y	Infection	≥90 days
Hayhurst et al. ⁽²⁰⁾ (2008)	Multicenter/retrospective	Europe, Dec. 2002 to Dec. 2006	Underage, 2 days–16 years	Total : 291 (214/77)	Total : 21/214 vs. 8/77 ≤1 year : 4/47 vs. 5/30	N	Y	Infection	8–42 months
James et al. ⁽²³⁾ (2014)	Single center/retrospective	Europe, 1993 to 2003 and 2005 to 2009	Underage, 0–17 years	Total : 2092 (500/1592)	Total : 25/500 vs. 135/1592	Y	Y	Infection	≥24 months

Table 1. Continued

Study	Study design	Region, study period or duration	Population, age, mean/range	No of procedures, AISC/non-AISC	No of infections, AISC/non-AISC	Definitions of infection		Primary outcome	Follow-up duration
						Symptoms, signs, or other laboratory exams	Culture		
Mbabazi-Kabachelor et al. ³⁰⁾ (2019)	Single center/ single-blind RCT	Africa, Apr. 2013 to Sep. 2016	Underage, 0–16 years	Total : 248 (124/124)	Total : 6/124 vs. 8/124	Y	Y	Infection	6 months
Kan and Kestle ²³⁾ (2007)	Single center/ retrospective	USA, Jun. 2003 to Oct. 2005	Underage, a mean age of 7.9 years	Total : 160 (80/80)	Total : 4/80 vs. 7/80	N	Y	Infection	≥9 months
Kandasamy et al. ²⁶⁾ (2011)	Multicenter/ prospective cohort	Europe, Jan. 1993 to Jun. 2007	Underage, 0–16 years	Total : 2544 (581/1963)	Total : 40/581 vs. 155/1963 ≤1 year : 9/153 vs. 52/465	Y	Y	Infection	5–47 months
Lane et al. ²⁹⁾ (2014)	Single center/ retrospective	Africa, NR	Underage, the average age is 11.3 years	Total : 160 (80/80)	Total : 4/80 vs. 11/80	Y	Y	Shunt failure (shunt infection, and death)	Mean 7.6 months
Parker et al. ³²⁾ (2009)	Single center/ retrospective	USA, Jan. 1997 to Dec. 2007	Underage & adults, 6.5 years/ 1 day–20 years	Total : 1072 (502/570)	Total : 16/502 vs. 64/570	N	Y	Infection	AISC : 74.3 months Non-AISC : 34.6 months
Pattavilakom et al. ³⁵⁾ (2007)	Single center/ prospective cohort	Australia, Jul. 1995 to Jun. 2005	All	Total : 794 (243/551)	Total : 3/243 vs. 36/551	Y	Y	Infection	6–42 months
Raffa et al. ³⁹⁾ (2015)	Single center/ retrospective	Italy, 2002 to 2012	Underage, 1 day–1 year	Total : 48 (22/26)	Total : 2/22 vs. 9/26	N	Y	Infection	≥1 year, mean 8±3 years
Ritz et al. ⁴²⁾ (2007)	Single center/ retrospective	Europe, 2 years	All	Total : 598 (190/408)	Total : 5/86 vs. 10/172	Y	N	Infection	Not report
Steinbok et al. ⁴⁵⁾ (2010)	Multicenter/ prospective cohort	International, Jan. 2006 to Jan. 2008	0–84 years	Total : 433 (46/387)	Total : 0/46 vs. 14/387	Y	Y	Infection	≤90 days

AISC : antibiotic-impregnated shunt catheter, N : no; Y : yes, RCT : randomized controlled trial, NR : no reference

shunts' and 'infection'. EMBASE and Cochrane Library were searched using the following terms—'cerebrospinal fluid shunting and infection'.

Study selection

The study had to meet the following inclusion criteria, 1) retrospective or prospective randomized controlled trials of AISC versus non-AISC in antimicrobial effects of hydrocephalus shunt, 2) language used is English, and was excluded if, 1) less than 10 cases, 2) no control group, 3) repetitive published study.

Data extraction

The extracted data included study design, geographic area, follow-up time, population characteristics and outcomes (infection, mortality). Information obtained from the studies

was recorded in standard data collection form by author (W.X.Z.), and two other authors (Y.F. and Y.W.), who independently examined these articles. Differences of opinion were resolved through discussion.

Quality assessment

The quality of randomized and nonrandomized studies was independently determined using the Cochrane Handbook^{21,46} by authors (W.X.Z. and Y.F.). Differences of opinion were resolved through discussions and consultation with two other authors (Y.W. and J.W.L.).

Data synthesis and statistical analysis

The RevMan 5.3 software of the Cochrane Collaboration was used for data analysis, using fixed effects model. The odds ratio (OR) and 95% confidence intervals (CIs) were calculated

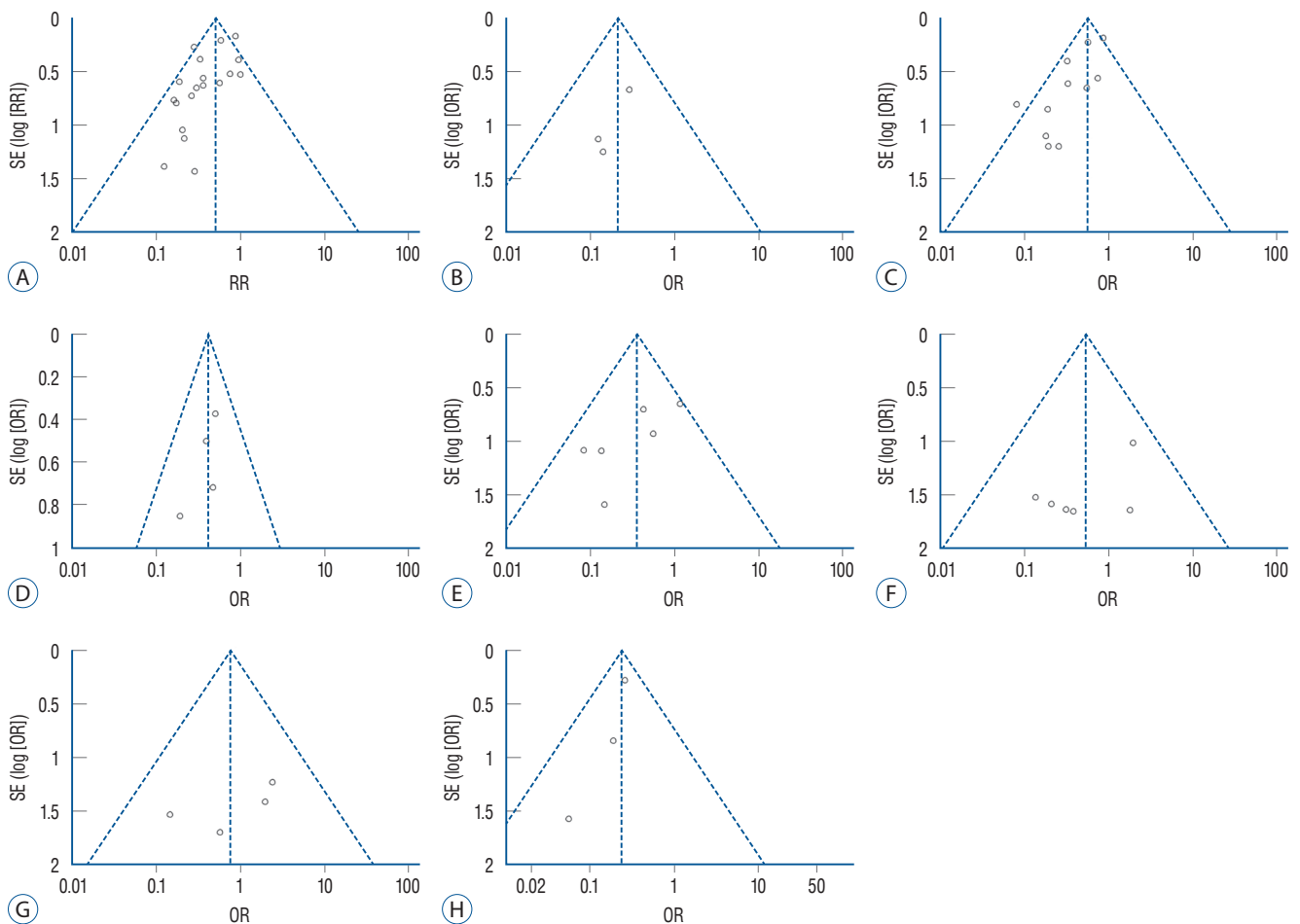


Fig. 2. Funnel plot to assess publication bias. A : A total of 19 studies, B : adult group, C : underage group, D : infant group, E : 0–3 months group, F : 4–6 months group, G : >6 months group, H : high-risk group. SE : standard error, RR : risk ratio, OR : odds ratio.

for all outcomes. Heterogeneity across studies was assessed based on a standard chi-squared test with significance being set at $p < 0.05$ or $I^2 > 50\%$. The extent of publication bias was estimated through visual inspection of funnel plot asymmetry.

RESULTS

Description of studies

It was initially determined to include 23 articles^{2,3,11-13,16,18-20,22,23,25,26,29,30,32,33,35,39,41,42,45,50}, and finally confirmed to 19 articles^{2,3,11-13,16,18,20,23,25,26,29,30,32,35,39,42,45,50}, four of which were excluded (Fig. 1)^{19,22,33,41}. Details of the 19 studies included are in Table 1. The quality of the literatures were assessed in the Supplementary Tables 1 and 2.

The 19 studies included two randomized controlled trials, and there was certain heterogeneity in the findings ($p = 0.02$; $I^2 = 44\%$). Publication bias was detected (Fig. 2), which may be due to the tendency of researchers to publish superior results. However, we have not attempted to assess in detail since it was difficult to determine study quality in this area. No heterogeneity was found in the subgroup analysis.

Research data

A total of 19 studies were included in this meta-analysis. Data analysis showed that AISC had obvious advantages in terms of antimicrobial properties (OR, 0.48; 95% CI, 0.40–0.58; $p < 0.05$; $I^2 = 46\%$; Fig. 3), however, the data was heterogeneous.

Age-based subgroup

This study divided patients into three groups based on patient age (Fig. 4), i.e., adult group (≥ 18 years), underage group (< 18 years) and infant group (≤ 1 year). Eleven studies of underage patients showed significantly better results with AISC (OR, 0.57; 95% CI, 0.45–0.72; $p = 0.05$; $I^2 = 45\%$), and the analysis was considerably significant ($p < 0.01$). Overall, four of the 11 studies were investigated in both the underage and the infant group. This analysis showed that the use of AISC in infant group (OR, 0.42; 95% CI, 0.25–0.70; $p = 0.77$; $I^2 = 0\%$; $p < 0.01$) was better than that in the underage group. There were only three studies in the adult group, and the results clearly showed that the use of AISCs in adult patients was significantly better (OR, 0.21; 95% CI, 0.08–0.59; $p = 0.76$; $I^2 = 0\%$; $p < 0.01$) than that of the entire patient population. Results indicated that the antimicrobial effects of using AISC in adult group is superior

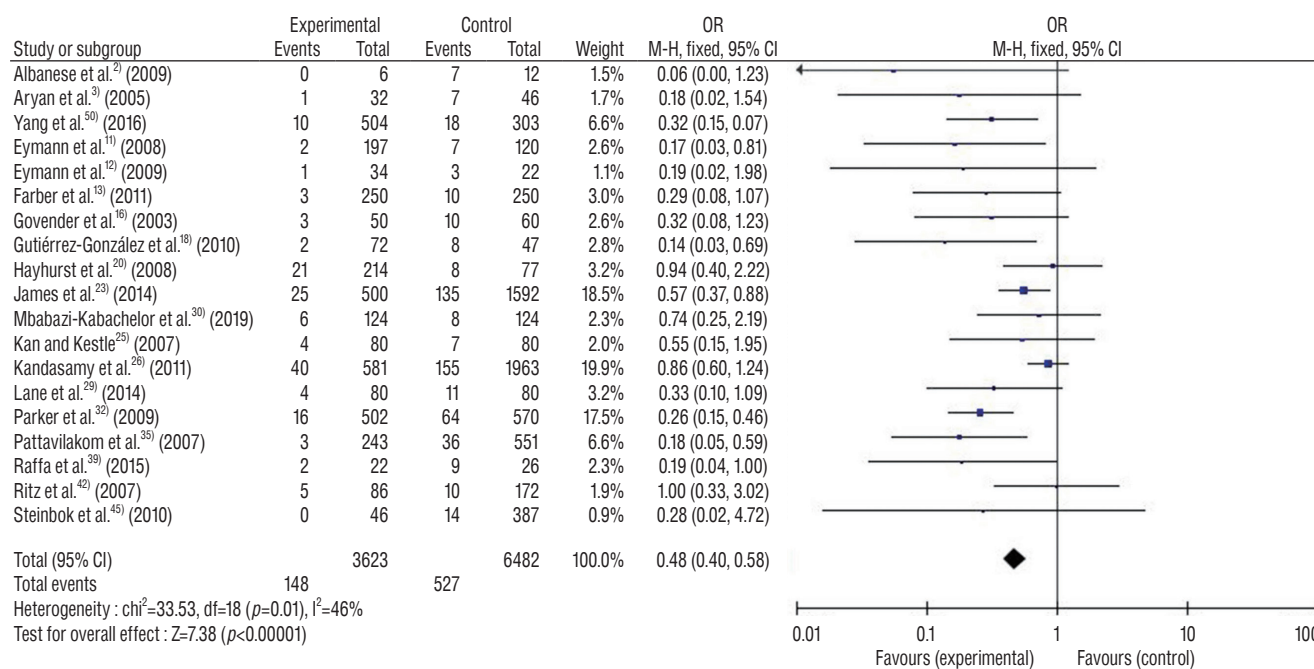


Fig. 3. Comprehensive analysis of anti-infection effect of AISC. OR : odds ratio, M-H : mantel-haenszel, CI : confidence interval, AISC : antibiotic-impregnated shunt catheter.

to that in underage group, and the antimicrobial effect of using AISC in infant group was better than that in the underage group.

Follow-up schedule

The incidence of infection during different follow-up period was also analyzed (Fig. 5). We divided the follow-up time into three stages : 0–3 months, 4–6 months, and longer than 6 months. The infection was defined as early infection (0–6 months) and late infection (longer than 6 months) according to Sciubba et al.⁴⁴⁾. Our results showed that AISC has good antimicrobial effect (OR, 0.36; 95% CI, 0.19–0.73; $p=0.25$;

$I^2=25\%$; $p<0.01$) in the 0–3 months follow-up period, the antimicrobial effects decreased with increase in follow-up time. We found that the antimicrobial effect was still strong at 3–6 months (OR, 0.55; 95% CI, 0.20–1.52; $p=0.62$; $I^2=0\%$; $p=0.25$). The antimicrobial effect of AISC was basically non-existent (OR, 0.80; 95% CI, 0.23–2.77; $p=0.48$; $I^2=0\%$; $p=0.75$) at the end of 6 months after implantation. We did not observe any late shunt infection increase in AISC after 6 months of implantation (in the case of AISC group, 0–3 months infection rate : 4.27%, 3–6 months infection rate : 1.22%, longer than 6 months : 1.83%). This was consistent with other studies having a follow-up period longer than 6 months^{2,16,39,42)}.

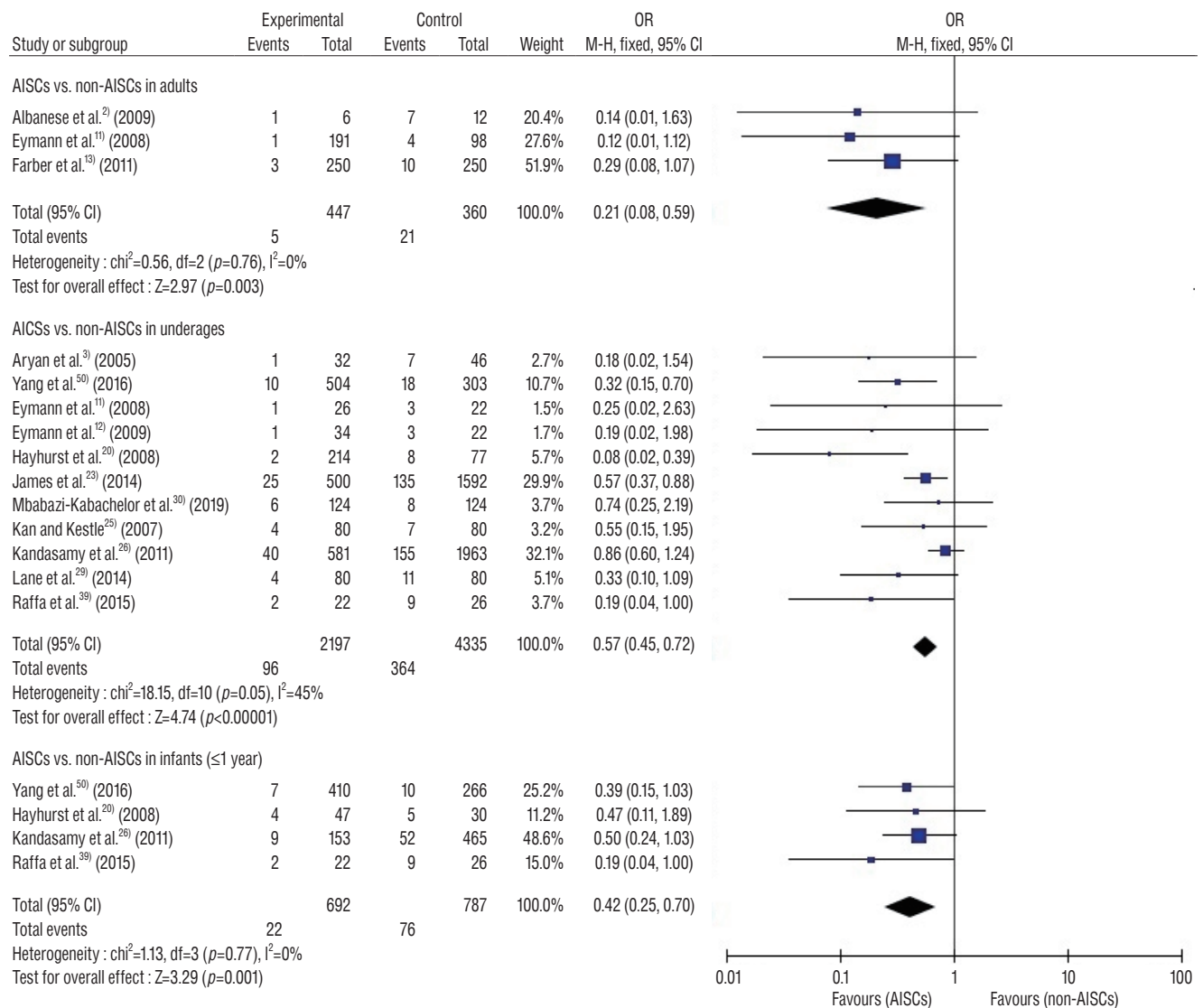


Fig. 4. Age-based subgroup analysis of the anti-infective effect of AISC. OR : odds ratio, M-H : mantel-haenszel, CI : confidence interval, AISC : antibiotic-impregnated shunt catheter.

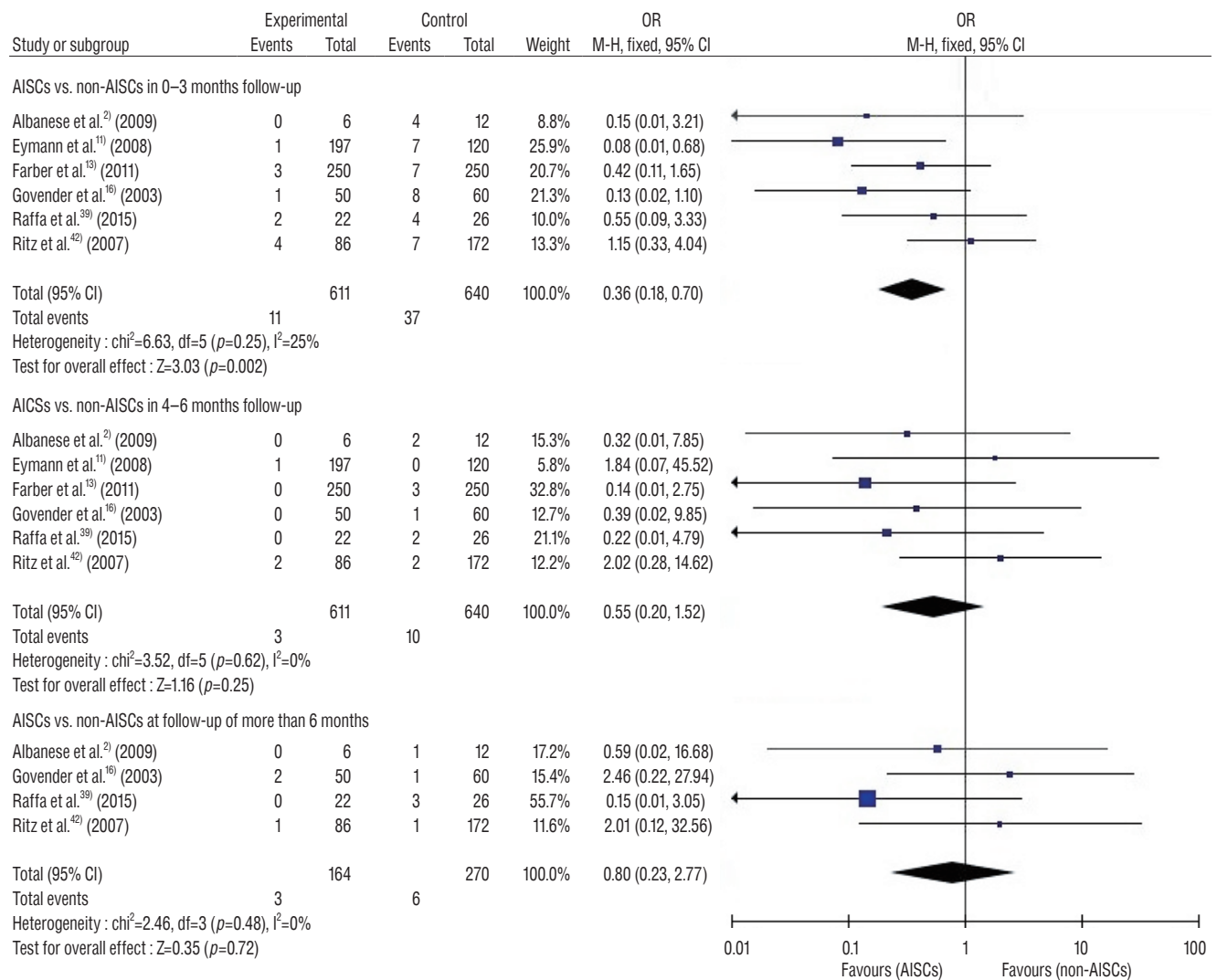


Fig. 5. Anti-infective effect of AISC in subgroups with different follow-up time. OR : odds ratio, M-H : mantel-haenszel, CI : confidence interval, AISC : antibiotic-impregnated shunt catheter.

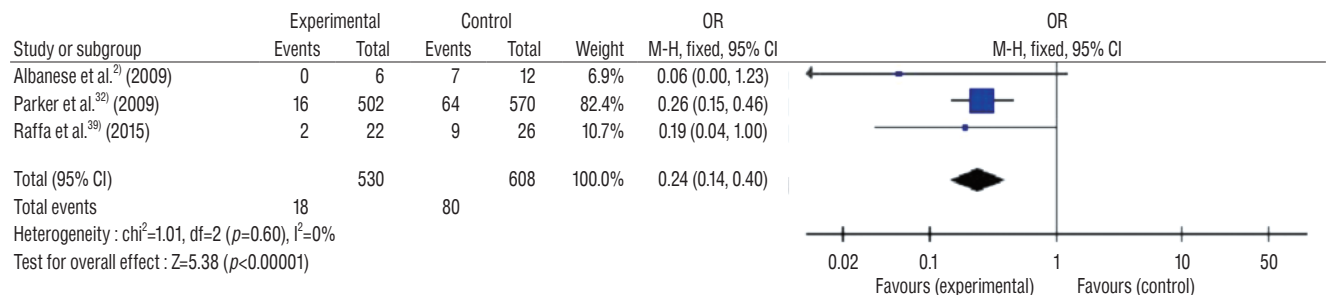


Fig. 6. Analysis of anti-infection effect of AISCs in high-risk subgroup. OR : odds ratio, M-H : mantel-haenszel, CI : confidence interval, AISC : antibiotic-impregnated shunt catheter.

High-risk patients

The antimicrobial effectiveness of AISC in high-risk patients was analyzed (Fig. 6). The results of three studies indicated that the anti-infective effect of AISC in high-risk population (OR, 0.24; 95% CI, 0.14–0.40; $p=0.60$; $I^2=0\%$; $p<0.01$) was higher than that of the entire patient population group.

DISCUSSION

This meta-analysis analyzed the effectiveness of AISC in preventing shunt infection compared with that of non-AISC. In sensitivity analysis, heterogeneity was found to be caused by large samples.

A total of 19 studies were divided into three groups according to patient age. Our results showed that the antimicrobial effect of AISC was related to patient age. The most prominent antimicrobial effect was found in the adult group, and it was superior in the infant group compared to the underage group. This was consistent with the results of Konstantelias et al.²⁸⁾. In the Bayston study, the rate of infection for hydrocephalus shunting was higher in non-AISC subgroup amongst infants. The closer the age of the patient to the adult population, the lower the infection rate⁴⁾. This is also consistent with our statistical results. This could be attributed to issues in the child's immune system development, fragility of the skin and high density of skin bacteria³⁷⁾. Farber showed that AISC usage could reduce infection-related cost per patient¹⁴⁾. However, in adults from lower socio-economic strata, non-AISC is an alternative, especially where there are fewer high-risk factors. Since the results analyzed showed that adult patients have low infection rate (5.8%) compared to those of other two groups (infant 9.66% and underage 8.40%), it is recommended to consider non-AISC implant to reduce the cost of treatment, unless high risk factors prevail.

The infection rate in 19 studies (divided into three groups) was analyzed based on the follow-up period. It can be seen that infection mainly occurred in the early stages of implantation and the late infection rate decreased with increase in follow-up time^{10,27,36)}. The study indicated consistency with previous reported results. Early infection may be caused by perioperative bacterial colonization on the shunt and acute immune reaction to implanted device, although the cause of late infection is clinically unclear^{6,36,43,49)}. The statistical results of non-AISC dem-

onstrated that the infection rate was higher in the early stage of shunting (post implant 0–3 months), proving that antimicrobial effects of AISC was most required during this stage. Once the follow-up period exceeded 6 months, AISC tended to lose its antimicrobial function due to drug dilution, however, it did not lead to an increase in the incidence or toxicity of late period shunt infection. This research further indicated that the antimicrobial effects of AISC within 3–6 months of implantation got weaker compared to the first 0–3 months, and it totally lost antimicrobial function after 6 months.

Three studies were included in the analysis of anti-infective properties of AISCs in high-risk populations. AISC was obviously effective in the high-risk population. In high-risk patients, the use of AISC reduced the incidence of shunt infections from 13.16% for non-AISCs to 3.40%, which was consistent with the infection rate of 4.08% in the general population using AISC; the infection rate using non-AISC for the general population is 8.13%. There are several factors in high-risk groups, like coexisting symptoms, invasive surgeries, prolonged bed rest, inactivity, repeated exposure to bacterial environment in the hospital and other factors that can cause infection. Under these high-risk factors, the infection rate with the use of antimicrobial catheters had the same effect as with the use of antibiotics in the general population, which proved that antimicrobial catheters were most effective in high-risk populations. We recommend using antimicrobial catheters in high-risk populations.

Limitation

Most of the studies included in this meta-analysis are single-center, retrospective data with certain limitations. The present meta-analysis showed that AISC could reduce the incidence of complications associated with infection. However, large multi-center RCTS are still needed to further confirm this result.

CONCLUSION

Subgroup analysis of demonstrated patient age is an important factor associated with shunt infection, especially in infant population, that has a higher predilection for infections. The follow-up time analysis indicated that the antimicrobial effects should remain effective for at least 6 months in order to reduce the infection rate in the 3–6 months post-implantation

period, which could be achieved by improving drug efficacy and coating technology. AISC is recommended for high-risk patients who are susceptible to infection. Non-AISCs may be considered for adult patients without high-risk infection factors, to reduce the cost of treatment. The revision of implanted shunt and hydrocephalus etiology are also significant factors accounting for patient infection, which are not included in this analysis and deserve further investigation in the future in terms of efficiency and safety.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : HJZ, WBH, AHL

Data curation : WXZ, YF, YW, JWL

Formal analysis : CZ, YXY, STL, GL

Funding acquisition : HJZ

Methodology : WBH, WXZ

Project administration : HJZ, WBH

Visualization : WXZ, WBH

Writing - original draft : WXZ, WBH

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• Supplementary materials

The online-only data supplement is available with this article at <https://doi.org/10.3340/jkns.2019.0219>.

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