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Effectiveness, safety, and cost-effectiveness of norvancomycin in the management of acute hematogenous osteomyelitis in pediatric patients

A retrospective case study

Xueqin Zhang, MS[a], Nan Zhang, MS[a], Yuntao Pei, BS[a], Ningning Hu, MS[a], Xiaohui Chen, MS[a], Liming Zhang, MS[a], Yile Zhao, PhD[a,*]

Abstract

This study was designed to investigate the effectiveness, safety, and cost-effectiveness of norvancomycin in the management of acute hematogenous osteomyelitis in pediatric patients. We conducted a retrospective study on cases of osteomyelitis in pediatric patients treated with norvancomycin or vancomycin at Hebei Children's Hospital from January 2015 to February 2023. The patients were categorized into the norvancomycin group and the vancomycin group. Clinical data regarding efficacy, safety, and cost-effectiveness before and after drug treatment were collected for comparative analysis. Each group contained 104 children. After 14 days of treatment, there were no statistically significant differences in the incidence of adverse events and efficacy indexes between the 2 groups. However, the total hospitalization cost of the norvancomycin group (¥28765.35 ± ¥11835.98) was significantly lower than that of the vancomycin group (¥43776.06 ± ¥33365.30) (P = .000). Additionally, compared to the vancomycin group, both the clinical efficacy cost ratio (290.44 vs 437.76) and bacteriological clearance cost ratio (356.14 vs 576.30) were lower in the norvancomycin group. Norvancomycin demonstrates comparable efficacy to the first-line drug vancomycin in treating acute hematogenous osteomyelitis in pediatric patients. Moreover, norvancomycin can significantly mitigate treatment expenses and exhibit favorable cost-effectiveness.

Abbreviations: AHO = acute hematogenous osteomyelitis, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, MRSA = methicillin-resistant *Staphylococcus aureus*, NEUT = neutrophil, PASS = provenance aware storage system, WBC = white blood cell.

Keywords: acute hematogenous osteomyelitis, cost-effectiveness, effectiveness, norvancomycin, safety

1. Introduction

Acute hematogenous osteomyelitis (AHO) occurs when bacteria invade bone cells and the extracellular matrix, leading to their proliferation. It is typically accompanied by a host inflammatory response, characterized by the onset of symptoms such as fever, local erythema, swelling, and tenderness in the affected bones within 2 weeks.[1] The disease exhibits an acute onset and rapid progression. Failure to administer timely treatment may result in bone destruction, epiphyseal irritation, adjacent joint infection, and other complications. In severe cases, it can progress into chronic osteomyelitis, leading to bone defects, limb deformities, and sensory disturbances.[2] Studies have shown that the prevalence of AHO in children has exhibited a significant increase in recent years, particularly in developing countries where the incidence surpasses that observed in developed nations. Moreover, there is a higher prevalence among boys and younger age groups.[3,4]

The most prevalent etiology of AHO in pediatric patients is *Staphylococcus aureus*, a common gram-positive bacterium that serves as a significant pathogen in both human and animal populations.[5,6] In recent years, the incidence of methicillin-resistant *S aureus* (MRSA) infection has gradually increased due to the growing issue of drug resistance. The proportion

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This retrospective study did not involve additional procedures for standardized clinical protocols, and all data were treated anonymously, thus patient consent was verbally waived by the Ethics Committee of Hebei Children's Hospital.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of Hebei Children's Hospital.

[a] *Department of Pharmacy, Children's Hospital of Hebei, Shijiazhuang City, Hebei Province, China.*

* *Correspondence: Yile Zhao, Department of Pharmacy, Children's Hospital of Hebei, Yuhua District, Shijiazhuang City, Hebei Province 050031, China (e-mail: zyl086559@163.com).*

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of AHO among children infected with MRSA in China ranges from 30% to 40%.[7,8] The bacterium *S aureus* produces a toxin known as panton-Valentine leukocidin, which poses harm to pediatric patients. MRSA exhibits higher virulence and is associated with an increased prevalence of AHO in children, presenting challenges for treatment using conventional antibiotics.[9]

To date, no vancomycin-resistant MRSA strains have been identified, and according to expert consensus, vancomycin is the preferred treatment for AHO in children infected with MRSA or those with an unknown pathogen but complicated by sepsis and a local community MRSA isolation rate of ≥10%.[10] However, the high cost of vancomycin poses a significant economic burden for families, especially considering that AHO is a severe condition requiring prolonged treatment. According to the American Pediatric Infectious Diseases Society guidelines, children with presumed or proven *S aureus*-related AHO should receive 3 to 4 weeks of antibiotic therapy if their disease course is uncomplicated and they respond well to initial treatment.[11]

Norvancomycin, a glycopeptide antibiotic manufactured by the North China Pharmaceutical Company, exhibits a comparable antimicrobial spectrum to vancomycin and shares similar adverse reactions.[12] However, there are some distinctions between norvancomycin and vancomycin, such as lower drug cost and a variation in molecular structure due to the removal of a methyl group. Additionally, norvancomycin may possess more potent antimicrobial activity while potentially causing less severe side effects.[13] Despite reports suggesting its efficacy in treating other MRSA-related conditions such as respiratory tract and bloodstream infections,[14–16] as well as its use in children with infectious diseases like hematologic malignancies and traumatic endophthalmitis,[15,17] limited research has been conducted on the effectiveness of norvancomycin in managing AHO. However, there is currently no domestic or international study evaluating the clinical efficacy, adverse reactions, and economic aspects of norvancomycin for treating AHO in children infected with MRSA.

2. Materials and methods

2.1. Study patients

The study retrospectively collected data from January 2015 to February 2023 at Children's Hospital of Hebei Province, focusing on the administration of norvancomycin or vancomycin treatment in children with osteomyelitis. Cases were extracted from the provenance aware storage system database. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the research protocol (No. 20231173) received approval from the Ethics Committee of Hebei Children's Hospital on January 20, 2023. In addition, the retrospective study did not involve additional procedures for standardized clinical protocols, and all data were treated anonymously, thus patient consent was verbally waived by the Ethics Committee of Hebei Children's Hospital. The database was queried using the keywords "norvancomycin" and "osteomyelitis" or "vancomycin" and "osteomyelitis." Inclusion criteria for the study were patients aged between 1 month and 18 years, who had received intravenous norvancomycin or vancomycin for a duration of 14 days or more. Exclusion criteria included non-AHO cases, concurrent use of both drugs, and incomplete data.

2.2. Data collection

We utilized standardized data collection forms to gather medical records. The cases were categorized into 2 groups based on the type of drug administered: norvancomycin group and vancomycin group. The following information was obtained: demographic details, total hospitalization costs, occurrence of drug-related adverse reactions during treatment, measurements of white blood cell (WBC), neutrophil (NEUT), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels before treatment, at 7 days, and at 14 days after treatment. Additionally, we assessed disease improvement posttreatment and pathogenic bacteria clearance.

2.3. Security analysis

Norvancomycin and vancomycin can potentially induce a range of adverse reactions in pediatric patients, including rash, diarrhea, renal damage, thrombophlebitis, thrombocytopenia, and granulocytopenia.[18–21] In this study, the adverse reactions between the 2 groups were subjected to statistical analysis to evaluate the safety profile of norvancomycin in children with AHO.

2.4. Efficiency analysis

WBC is commonly used as a standard for diagnosing bacterial infections, an increase in NEUT may indicate an acute infection, and elevated ESR typically indicates the formation of an abscess. The CRP level is particularly elevated in septic arthritis (>100 mg/L), making it the most reliable indicator of a complex disease course and the necessity for prolonged intravenous antibiotic therapy. Additionally, CRP has a short half-life (19 hours), which allows for monitoring of disease response to drug therapy.[22–24] The recent literature has reported a sensitivity of 95% for CRP and 94% for ESR in detecting bone or joint infection, with a combined sensitivity of these 2 indicators reaching 98%.[25] Therefore, the evaluation of AHO diagnosis and drug treatment efficacy can be facilitated by utilizing WBC, NEUT, CRP, and ESR. In this study, the statistical analysis of WBC, NEUT, CRP, and ESR levels in both groups of children on the 7th and 14th day of drug treatment was conducted to assess the effectiveness of norvancomycin in pediatric patients with AHO.

2.5. Economic analysis

The costs associated with pharmacoeconomic studies encompass direct costs, indirect costs, and hidden costs. Direct costs comprise drug expenses, inspection fees, hospitalization charges, comprehensive medical service charges, treatment fees, and consumables expenses. Indirect costs include productivity loss due to absence from work, etc. Hidden costs encompass the emotional distress and physical pain caused by the disease, etc. Due to the presence of numerous uncertain factors in the latter 2 categories, only direct costs were considered in this study.[26] The clinical efficacy cost ratio and bacteriological efficacy cost ratio can be utilized to investigate the economic aspects of norvancomycin treatment compared to vancomycin in managing MRSA infection.[27] The direct cost was assessed and the cost ratios (clinical efficacy cost ratio = total cost/clinical efficacy rate, bacteriological efficacy cost ratio = total cost/bacterial clearance rate) were calculated to evaluate the economic aspects of norvancomycin in treating children with AHO.

2.6. Statistical methods

The clinical data of children with AHO were described by calculating the mean and standard deviation (mean ± SD) or the percentage (%). Data analysis was conducted using IBM SPSS Statistics 28. Descriptive statistics were applied to the data. Categorical variables such as age, sex, disease cure status, bacterial clearance status, and adverse reactions were analyzed using Chi-square analysis. Continuous parameter variables including body weight, length of stay, medication duration, WBC count,

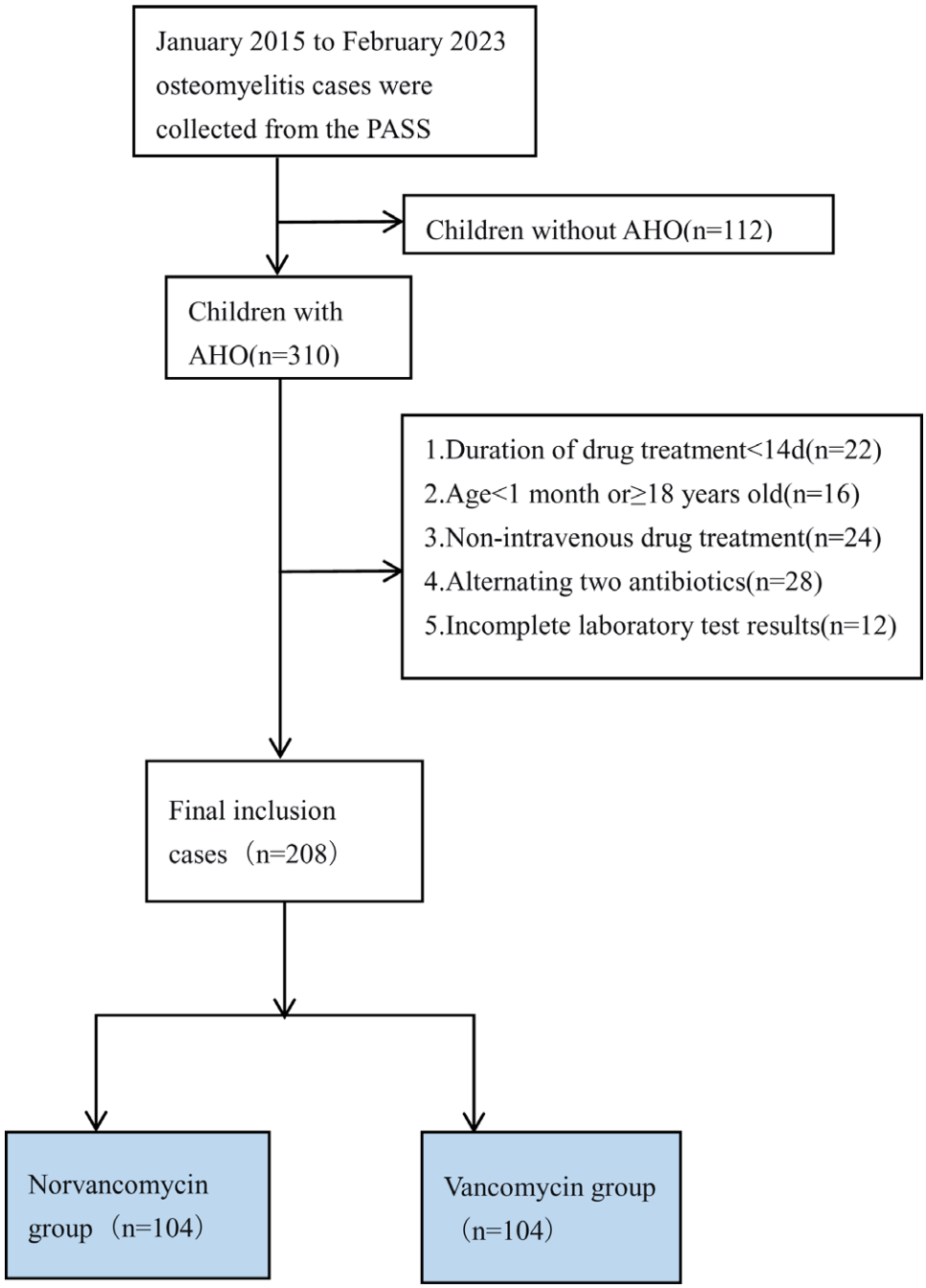

Figure 1. Cases flow diagram of inclusion and exclusion. AHO = acute hematogenous osteomyelitis, PASS = provenance aware storage system.

NEUT count, ESR level, CRP level, and total hospital expenses were analyzed using the Student *t* test. Statistical significance was considered at a *P* value <.05.

3. Results

A total of 422 cases were collected from the provenance aware storage system database during the study period. Out of these cases, 112 cases of chronic osteomyelitis were excluded, leaving a remaining 310 cases comprising children with AHO. Children with AHO who did not meet the inclusion criteria were further excluded: 22 cases had a duration of drug treatment <14 days, 16 cases were either younger than 1 month or older than 18 years, 24 cases received nonintravenous drug treatment, 28 cases were treated with alternating 2 antibiotics, and finally, 12 cases had incomplete laboratory test results. Consequently, a total of 208 children with AHO met the inclusion criteria for this study. Based on the type of drug used, these children were divided into 2 groups: norvancomycin group and vancomycin group, each group consisting of 104 children (Fig. 1).

The baseline data, including age, sex, weight, duration of medication, length of hospital stay, WBC, NEUT, ESR, and CRP before medication as presented in Table 1, did not exhibit any significant differences between the 2 groups.

The incidence of adverse reactions, such as rash, diarrhea, renal damage, thrombophlebitis, thrombocytopenia, and granulocytopenia during the treatment period did not differ significantly between the 2 groups, as indicated in Table 2.

After 7 days of treatment, there were no significant differences in WBC, ESR, and CRP levels between the 2 groups. NEUT in the norvancomycin group (38.41% ± 24.88%) was significantly

Table 1

Baseline characteristics in the vancomycin group and norvancomycin group.

Characteristics	Vancomycin group (n = 104)	Norvancomycin group (n = 104)	T/Chi-square-value	*P* value
Age (yr)	4.82 ± 4.15	4.69 ± 4.13	−0.222	.825
Male/female	55 (52.9)/49 (47.1)	57 (54.8)/47 (45.2)	0.077	.781
Weight (kg)	20.29 ± 14.16	19.58 ± 13.18	−0.373	.710
Duration of medication (d)	16.18 ± 6.55	15.99 ± 5.69	0.226	.821
Length of hospital stay (d)	29.86 ± 11.43	27.57 ± 10.89	−1.479	.141
WBC before medication ($\times 10^9$/L)	16.98 ± 7.13	15.64 ± 7.80	−1.29	.198
NEUT before medication (%)	65.60 ± 22.61	62.20 ± 20.62	−1.135	.258
ESR before medication (mm/h)	42.69 ± 38.27	45.49 ± 39.80	0.515	.607
CRP before medication (mg/L)	81.26 ± 68.70	80.37 ± 65.76	−0.96	.924

Data are presented as mean ± standard deviation or number (%)/number (%).

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NEUT = neutrophil, WBC = white blood cell.

Table 2

Comparison of adverse reactions between the vancomycin group and norvancomycin group.

Adverse reactions	Vancomycin group (n = 104)	Norvancomycin group (n = 104)	Chi-square -value	*P* value
Rash	5	4	0.116	.733
Diarrhea	8	7	0.072	.789
Renal damage	2	2	0.000	1.000
Thrombophlebitis	1	1	0.000	1.000
Thrombocytopenia	0	0	0.000	1.000
Granulocytopenia	2	5	1.330	.249
Total number	18 (17.31)	19 (18.27)	0.033	.856

Data are presented as number or number (%).

lower than that in the vancomycin group (45.21% ± 24.26%) (P = .047). There were no significant differences in WBC, NEUT, ESR, and CRP levels between the 2 groups after 14 days of treatment (Table 3).

The total cost during hospitalization in the norvancomycin group (¥28,765.35 ± ¥11,835.98) was significantly lower than that in the vancomycin group (¥43,776.06 ± ¥33,365.30), as depicted in Figure 2 (P = .000). Compared to the vancomycin group, both the clinical efficacy cost ratio (290.44 vs 437.76) and bacteriological clearance cost ratio (356.14 vs 576.30) were lower in the norvancomycin group, specific data can be found in Table 4.

4. Discussion

The data from the China Antimicrobial Resistance Surveillance Network revealed that the prevalence of MRSA among children in China ranged from 29.3% to 30.9%.[8,28] According to the expert consensus on the treatment of AHO in children, vancomycin is recommended as the initial choice for treating AHO in children who have been diagnosed with MRSA infection or have an unclear etiology, are complicated with sepsis, and reside in a local community where the MRSA isolation rate is ≥10%.[10]

The cost of vancomycin is higher, whereas norvancomycin exhibits a comparable antibacterial spectrum at a lower expense. The objective of this study is to investigate the safety, efficacy, and cost-effectiveness of norvancomycin in the treatment of AHO in pediatric patients. Retrospective collection and statistical analysis were conducted on clinical data from children with MRSA infection or AHO complicated by sepsis of unknown etiology at Hebei Children's Hospital over the past 8 years. The findings revealed that norvancomycin can achieve comparable therapeutic outcomes to vancomycin, the preferred drug, while avoiding additional adverse reactions associated with vancomycin. Furthermore, norvancomycin has demonstrated potential for reducing treatment costs and alleviating economic burdens on families managing AHO in children.

The susceptibility of glycopeptide antibiotics to allergic reactions has been reported, and this finding is supported by the higher occurrence of rash and diarrhea in children treated with norvancomycin and vancomycin.[18,29] According to the drug package insert, vancomycin or norvancomycin may induce pseudomembranous enteritis, characterized by symptoms such as nausea, vomiting, abdominal pain, and diarrhea. Considering the young age of the patients enrolled in this study (with a mean age of 4.82 years for children in the vancomycin group and 4.69 years for children in the norvancomycin group) and their vulnerable gastrointestinal function, it is plausible that bacterial or viral infections could easily disrupt normal gut function leading to infectious diarrhea. Therefore, it can be inferred that the observed diarrhea in this study might be attributed to infectious causes rather than antibiotic-associated diarrhea. In addition, the NEUT count of children receiving drug treatment for 7 days in the norvancomycin group was significantly lower than that in the vancomycin group (P = .047). Furthermore, after a 14-day drug treatment, the NEUT count as well as WBC and CRP levels were slightly lower in the norvancomycin group compared to the vancomycin group. Therefore, it can be inferred that norvancomycin may exhibit greater efficacy than vancomycin in treating children with AHO. However, these findings should be validated through large-scale prospective clinical trials.

Currently, the Hebei Children's Hospital procures norvancomycin from North China Pharmaceutical at a unit price of 53.96 yuan, while vancomycin is sourced from Eli Lilly at a higher unit price of 103.99 yuan, approximately twice that of norvancomycin. Variations in economic development levels, medical resource distribution, regional policies, and drug procurement costs may result in slight differences in the unit prices of drugs purchased by different healthcare institutions. Consequently, disparities in total hospitalization costs for these 2 drugs among patients residing in different regions can be expected. Therefore, it should be noted that the conclusion drawn from this study regarding the cost-effectiveness of norvancomycin compared to vancomycin for children with AHO may not be universally applicable to other medical institutions; thus necessitating large-scale multicenter clinical trials for verification.

There were several advantages of our study. First, this is the first study to investigate the safety and efficacy of norvancomycin in pediatric patients with AHO. Second, this is the first economic study to investigate the utilization of norvancomycin in pediatric patients with AHO, thereby providing a theoretical foundation for clinicians to identify more cost-effective drugs and develop economically viable and safe medication regimens. Third, the sample size of this study is substantial, thereby enabling a more accurate reflection of the data's precision.

Table 3

Comparison of effectiveness between the vancomycin group and norvancomycin group.

Effectiveness index	Vancomycin group (n = 104)	Norvancomycin group (n = 104)	T/Chi-square-value	*P* value
WBC after 7 d of medication ($\times 10^9$/L)	9.22 ± 5.61	7.87 ± 5.27	–1.794	.074
WBC after 14 d of medication ($\times 10^9$/L)	7.09 ± 4.32	6.59 ± 4.44	–0.823	.412
NEUT after 7 d of medication (%)	45.21 ± 24.26	38.41 ± 24.88	–1.997	.047*
NEUT after 14 d of medication (%)	37.70 ± 23.01	34.75 ± 22.19	–0.938	.349
ESR after 7 d of medication (mm/h)	32.39 ± 32.15	31.00 ± 31.50	–0.314	.754
ESR after 14 d of medication (mm/h)	25.54 ± 25.98	26.80 ± 25.35	0.347	.729
CRP after 7 d of medication (mg/L)	14.57 ± 26.65	9.79 ± 17.93	–1.502	.135
CRP after 14 d of medication (mg/L)	8.66 ± 15.25	5.65 ± 10.30	–1.650	.101
Cases of effective treatment	104 (100)	103 (99.04)	1.005	.316
Cases of bacterial clearance	79 (75.96)	84 (80.77)	0.709	.400

Data are presented as mean ± standard deviation or number (%).

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NEUT = neutrophil, WBC = white blood cell.

*Indicates $P < .05$.

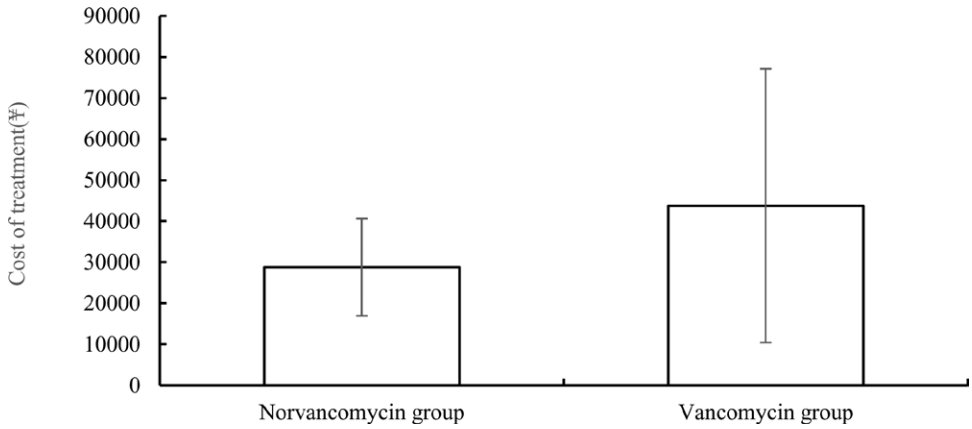

Figure 2. Total cost of treatment for both groups. Data are presented as mean ± standard deviation.

Table 4

Cost-effectiveness ratio between the vancomycin group and norvancomycin group.

		Clinical		Microbiology	
	Cost (¥)	Clinical efficacy (%)	Clinical efficacy cost ratio	Bacteriological clearance (%)	Bacteriological clearance cost ratio
Vancomycin group (n = 104)	43776.06	100	437.76	75.96	576.30
Norvancomycin group (n = 104)	28765.35	99.04	290.44	80.77	356.14

Data are presented as mean.

There were some limitations of our study. First, the present study is a retrospective analysis conducted at a single center, which may introduce certain inherent biases into the obtained results. Second, the lack of data on hearing monitoring in children precluded the study of norvancomycin ototoxicity in pediatric patients with AHO. Third, the imaging examinations, such as magnetic resonance imaging and B-ultrasound, were not obtained in this study, therefore, only laboratory tests were utilized to determine the treatment of the disease. Fourth, the study did not include long-term follow-up data to evaluate the extended efficacy and adverse effects of norvancomycin in pediatric patients with AHO.

5. Conclusion

The glycopeptide antibiotic norvancomycin can achieve the same therapeutic efficacy as the first-line drug vancomycin without increasing the risk of additional adverse reactions. In terms of the economy, norvancomycin has demonstrated a significant potential for reducing treatment costs associated with AHO in children, thereby alleviating the financial burden on their families. However, it is important to acknowledge certain limitations of this study, including its retrospective analysis at a single center and the absence of audiometry and imaging data as well as long-term follow-up. Therefore, future multicenter prospective randomized controlled trials that provide comprehensive information on drug safety, efficacy, and cost-effectiveness are necessary to validate the findings of this study.

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Author contributions

Conceptualization: Xueqin Zhang, Yile Zhao.
Funding acquisition: Xueqin Zhang.
Project administration: Xueqin Zhang, Yile Zhao.
Writing—original draft: Xueqin Zhang.

Writing—review & editing: Xueqin Zhang, Nan Zhang, Yile Zhao.
Data curation: Nan Zhang, Xiaohui Chen.
Formal analysis: Yuntao Pei, Xiaohui Chen, Ningning Hu.
Investigation: Yuntao Pei.
Software: Yuntao Pei, Ningning Hu.
Methodology: Liming Zhang.
Validation: Liming Zhang.
Supervision: Yile Zhao.

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