

Original Article

Prevalence and antimicrobial resistance of bacterial meningitis in China from 2017 to 2021: a multicenter retrospective study

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Abstract

Introduction: This study aims to investigate the changing epidemiology and antimicrobial susceptibility of bacteria isolated from cerebrospinal fluid (CSF) in the Shandong region.

Methodology: We conducted a retrospective analysis of bacterial distribution and resistance patterns in CSF samples, utilizing data from the SPARSS network and analyzed with WHONET 5.6 software.

Results: A total of 3968 pathogenic bacterial strains were isolated, consisting of 70.6% Gram-positive bacteria, 27.2% Gram-negative bacteria, and 0.2% fungi. The six most commonly detected bacteria were coagulase-negative staphylococcus, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Escherichia coli*, and *staphylococcus aureus*. Analysis revealed gender and seasonal variations in the distribution of CSF pathogens, with a higher incidence observed in males and during autumn compared to other seasons. The susceptibility profiles of these bacterial species varied significantly, with many exhibiting multidrug resistances. *A. baumannii* showed a high resistance rate to cephalosporins and carbapenems but was sensitive to tigecycline and polymyxins. For treating multidrug-resistant *A. baumannii* infections, polymyxin-based combinations with tigecycline or sulbactam are recommended for adults, while tigecycline combined with meropenem is suggested for children. *Enterobacteriaceae* species were generally sensitive to carbapenems, such as meropenem and other carbapenems that can penetrate the blood-brain barrier can be recommended. Linezolid and vancomycin are the first choice for treating common gram-positive bacterial infections.

Conclusions: The high resistance rates observed among common CSF isolates and their varied distributions across different demographics highlight the necessity for customized treatment strategies.

Key words: bacterial meningitis; children; adults; season; cerebrospinal fluid; pathogenic spectrum.

J Infect Dev Ctries 2024; 18(8):1233-1240. doi:10.3855/jidc.19352

(Received 07 October 2023 – Accepted 21 December 2023)

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Introduction

Meningitis is a prevalent infectious disease with a high mortality and disability rate [1-3], and its incidence has been increasing annually [4,5]. Rapid initiation of antimicrobial therapy is crucial for achieving favorable outcomes in the early stage of the disease [6]. However, clinicians often must rely on empirical antibiotic treatment until the specific pathogen is identified. Currently, there are limited multicenter reports, both domestic and international, focusing on the pathogen composition and susceptibility patterns of bacterial meningitis over extended periods. Understanding the distribution and antibiotic resistance of pathogenic bacteria in cerebrospinal fluid (CSF) is clinically significant for selecting appropriate empirical antimicrobial therapy. Therefore, we conducted a retrospective analysis of the species composition and antibiotic sensitivity of

isolates from CSF from the Shandong Province Pediatric Antimicrobial Resistance Surveillance System (SPARSS) network from 2017 to 2021.

Methodology

Study Area, Design, and Period

Isolates recovered from CSF in Shandong province from January 2017 to December 2021 were collected from 58 member units of the SPARSS network. Repeated isolates from the same patient were excluded.

Study Population

Participants were categorized into the following age groups: Newborns (≤ 28 days), children (> 29 days to 14 years), and adults (> 14 years). Due to the limited number of neonatal isolates, they were combined with the > 29 days to 14 years age group for the drug sensitivity analysis.

Table 1. Strains and constituent ratios of bacteria isolated from CSF, SPARSS, 2017-2021.

Year	Numbers of hospital	Total	Strains Number	%
2017	40	113911	725	0.6
2018	44	144528	761	0.5
2019	50	184669	877	0.5
2020	55	166906	734	0.4
2021	58	217140	871	0.4

Laboratory Method

Pathogens were identified at the species level using an automatic identification system, mass spectrometry, the API system, and manual methods. For drug sensitivity testing, we employed the minimum inhibitory concentration (MIC) method, disk diffusion method and E-test method. The drug sensitivity results were interpreted according to the breakpoint of Clinical & Laboratory Standards Institute (CLSI) M100 33rd edition guidelines. Quality control strains included *Staphylococcus aureus* ATCC (American Type Culture Collection) 25913, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 to ensure the accuracy and reproducibility of the antibiotic susceptibility testing procedure.

Results

Composition of strains isolated from CSF (2017-2021)

The geographical distribution of SPARSS member units included in this study is depicted in Figure 1. The number of hospitals, the count of bacteria isolated from CSF, and the proportion of CSF isolates to total isolates for the same year are shown in Table 1. From 2017 to 2021, the proportion of pathogens isolated from CSF ranged from 0.4% to 0.6%.

Strain distribution

From 2017 to 2021, 3968 pathogenic bacteria strains were isolated from the CSF of these 70.6% (2800/3968) were Gram-positive bacteria, 27.2% (1079/3968) were Gram-negative bacteria, and 2.2% (89/3968) were fungi. The most frequently detected

bacteria were coagulase-negative staphylococci (CoNS) (50.7%), *Acinetobacter baumannii* (7.6%), *Klebsiella pneumoniae* (4.3%), *Streptococcus pneumoniae* (4.3%), *E. coli* (3.8%), and *S. aureus* (3.5%) (Table 2). The comparative analysis of the species composition isolated from male and female samples was presented in Table 3. The proportion of isolates was higher in males than that in females, particularly during childhood and adulthood.

Distribution of bacteria isolated from CSF in different age groups

In neonatal patients, the top five isolated pathogens were CoNS, *E. coli*, *E. faecium*, *S. agalactiae* and *S. aureus*. In children, the most frequently isolated pathogens were CoNS, *S. pneumoniae*, *E. coli*, *S. aureus* and *A. baumannii*. Among adult patients overall, the leading pathogens were CoNS, *A. baumannii*, *K.*

Figure 1. The member units’ geographical distribution of SPARSS network.

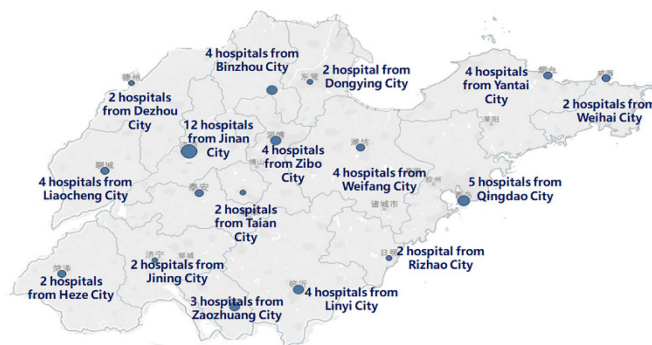


Table 2. Distribution of bacterial species isolated from CSF, SPARSS, 2017-2021.

Organism	2017		2018		2019		2020		2021		Total	
	strains	%	strains	%	strains	%	strains	%	strains	%	strains	%
<i>CNS</i>	349	48.1	370	48.6	453	51.7	394	53.6	445	51.1	2011	50.7
<i>A. baumannii</i>	66	9.1	56	7.3	74	8.4	52	7.1	54	6.2	302	7.6
<i>K. pneumoniae</i>	35	4.8	35	4.6	36	4.1	33	4.5	32	3.7	171	4.3
<i>S. pneumoniae</i>	40	5.5	40	5.3	38	4.3	24	3.3	28	3.2	170	4.3
<i>E. coli</i>	34	4.7	27	3.5	33	3.8	31	4.2	26	3	151	3.8
<i>S. aureus</i>	25	3.5	34	4.5	24	2.7	18	2.4	36	4.1	137	3.5
<i>E. faecium</i>	22	3	31	4.1	27	3.1	16	2.2	30	3.5	126	3.2
<i>E. cloacae</i>	13	1.8	15	2	13	1.5	8	1.1	16	1.8	65	1.6
<i>E. faecalis</i>	10	1.4	8	1.1	15	1.7	13	1.8	13	1.5	59	1.5
<i>P. aeruginosa</i>	13	1.8	13	1.7	13	1.5	8	1.1	10	1.1	57	1.4
Others	118	16.3	132	17.3	151	17.2	137	18.7	181	20.8	719	18.1
Total	725	100	761	100	877	100	734	100	871	100	3968	100

Table 3. Distribution of strains in different populations.

No.	Newborn			Pediatric			Adult		
	Organism	strains	%	Organism	strains	%	Organism	strains	%
1	CNS	41	41.8	CNS	206	38.3	CNS	1763	52.9
2	<i>E. coli</i>	17	17.3	<i>S. pneumoniae</i>	78	14.5	<i>A. baumannii</i>	278	8.4
3	<i>E. faecium</i>	8	8.2	<i>E. coli</i>	33	6.1	<i>K. pneumoniae</i>	163	4.9
4	<i>S. agalactiae</i>	6	6.1	<i>S. aureus</i>	25	4.6	<i>S. aureus</i>	106	3.2
5	<i>S. aureus</i>	5	5.1	<i>A. baumannii</i>	23	4.3	<i>E. coli</i>	101	3.0
6	<i>E. cloacae</i>	2	2.1	<i>S. agalactiae</i>	22	4.1	<i>E. faecium</i>	96	2.9
7	<i>E. faecalis</i>	2	2.1	<i>E. faecium</i>	20	3.7	<i>S. pneumoniae</i>	91	2.7
8	<i>K. pneumoniae</i>	2	2.1	<i>A. lwoffii</i>	10	1.9	<i>E. cloacae</i>	61	1.8
9	<i>S. sanguinis</i>	2	2.1	<i>E. faecalis</i>	10	1.9	<i>P. aeruginosa</i>	50	1.5
10	<i>S. mitis</i>	1	1	<i>H. influenzae</i>	10	1.9	<i>E. faecalis</i>	47	1.4
11	Others	12	12.2	Others	101	18.8	Others	576	17.3
12	Total	98	100.0	Total	538	100.0	Total	3332	100.0

pneumoniae, *S. aureus* and *E. coli* (see Table 4). No fungal strains were found in neonates, while eight fungal strains, all belonging to candida were isolated from pediatric patients. A total of 81 fungal strains were isolated from adults, including 54 strains of *Cryptococcus neoformans*, 25 strains of *Candida* and two strains of *Aspergillus*.

Seasonal distribution of strains isolated from CSF

The seasonal distribution of pathogenic bacteria from 2017 to 2021 is illustrated in Figure 2. Notably, 218 strains were isolated in February, and 321 strains in July, based on data from 2021. Across the four seasons, the highest number of isolates was recorded in autumn, with 928 isolates.

Antimicrobial Resistance Trends of Major Strains Isolated from CSF (2017-2021)

Analysis of the antibiotic resistance rates of 137 strains of *S. aureus* (Table 5) (including 30 strains from children and 107 strains from adults) and 2011 strains of CoNS (Table 6) (including 247 strains in children and 1764 strains in adults) from 2017 to 2021 revealed the following: The detection rates of methicillin-resistant *S. aureus* (MRSA) over the past five years were 16.0% (4/25), 32.4% (11/34) and 45.8% (11/24), 33.3% (6/18) and 27.8% (10/36), with an average rate of 30.6%. The MRSA rates in children and adults are 30.0% (9/30) and 30.8% (33/107), respectively. MRSA exhibited higher resistance to most commonly used antibiotics compared to methicillin-sensitive *S. aureus*

(MSSA), except for sulfamethoxazole trimethoprim (SXT) and

Figure 2. Seasonal distribution of strains.

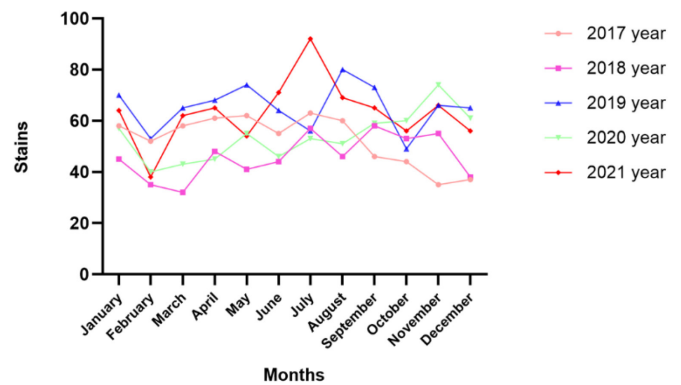


Table 5. Antimicrobial resistance rates of *S. aureus* isolated from CSF, SPARSS.

Antibiotic	MRSA (R%)	MSSA (R%)
Ciprofloxacin	26.7	18.1
Clindamycin	52.9	52.7
Erythromycin	76.4	63.1
Gentamicin	14.3	21.6
Linezolid	0	0
Levofloxacin	18.8	13.8
Moxifloxacin	21.2	14.3
Penicillin G	100	82.8
Q/D	5	16.9
Rifampin	9.1	0
SXT	14.7	24.2
Tetracycline	24	14.9
Tigecycline	0	0
Vancomycin	0	0

Table 4. Stratified distribution of CSF pathogens by age.

Age group	Gender	Strains	Ratio (%)	Male: Female
Newborns	Male	50	1.3	108:100
	Female	48	1.2	
Children	Male	314	7.9	140:100
	Female	224	5.6	
Adults	Male	2086	52.6	167:100
	Female	1246	31.4	
Total		3968	100	161:100

Table 6. Antimicrobial resistance rates of CNS isolated from CSF, SPARSS, 2017-2021 (%).

Antibiotic	2017		2018		2019		2020		2021		Average	
	MR	MS	MR	MS	MR	MS	MR	MS	MR	MS	MR	MS
Ciprofloxacin	67.6	9.2	69	16	65.4	12.1	67.8	16.3	61.2	18.4	66.5	14.3
Clindamycin	51	21.3	58.9	28.6	56.9	31	59.5	35.9	60.4	33.3	57.6	30.5
Erythromycin	84.7	56.1	84.9	62.5	85.9	69.3	85.5	60.6	84	61.1	85.1	62.2
Gentamicin	40.4	8.3	42.4	6.7	27.3	4.7	34.9	3.8	34.3	7.2	35.6	6
Linezolid	0	0	0	0	0	0	0	0	0	0	0.3	0.5
Levofloxacin	66.9	6.5	68.4	15.2	65.4	11.2	65	16.3	63.8	11.1	66	12.2
Moxifloxacin	66.5	7.8	70	17.4	64.4	12.2	64.2	15.4	64.6	11	66.1	12.7
Q/D	6.7	5.3	15	14.9	18.4	10.9	18.8	11.1	16.7	9.8	14.5	10.2
Rifampin	12.8	3.2	18.5	0.8	9	1.2	11.7	2.3	8.3	1.2	11.8	1.7
SXT	63.1	22.7	53.9	26.9	52.3	24.1	59.1	28.9	53.8	21.4	56.2	24.9
Tetracycline	28.4	18.7	27.6	15.5	29.6	20.6	28.8	14.5	18.1	15.3	26.6	16.9
Tigecycline	0	0	0	0	0	0	0	0	0	0	0	0
Vancomycin	0	0	0	0	0	0	0	0	0	0	0	0

MR: MRCNS; MS: MSCNS.

Table 7. Antimicrobial resistance rates of *A. baumannii* isolated from CSF, SPARSS, 2017-2021 (%).

Antibiotic	2017 (n = 67)	2018 (n = 56)	2019 (n = 72)	2020 (n = 52)	2021 (n=54)	Average
Amikacin	41.8	34.8	31.5	15.8	44.8	35.8
Ceftazidime	80.0	66.6	68.5	70.3	71.7	71.9
Ciprofloxacin	71.2	53.5	63.8	62.5	65.1	64
Ceftriaxone	97.8	97.4	93.6	96.7	93.1	95.8
Cefoperazone/Sulbactam	80.8	63.9	64.4	69.2	61.1	64.9
Cefepime	78.4	65.9	64.4	71.4	70.8	70.5
Gentamicin	57.4	56.8	51	46.6	54.8	57.3
Imipenem	78.3	60	65.5	68.3	68.8	71.2
Levofloxacin	64.5	55.5	61	62.5	66.7	65.5
Meropenem	76.2	52.2	58.8	63.6	68	68
Ampicillin/Sulbactam	77.8	69.7	60.0	72	66.7	69.7
SXT	46.6	44.2	57.6	47.6	54.5	54.3
Tobramycin	41.7	50	50.9	43.6	48.6	47.3
Tigecycline	5.0	19.4	34.1	14.7	12.5	20.5
Polymixin B	0	0	0	0	0	0
Piperacillin/Tazobactam	73.5	61.5	72.1	70	71.8	73.0

N: number of strains isolated from patients of all ages.

Table 8. Antimicrobial resistance rates of *K. pneumoniae* isolated from CSF, SPARSS, 2017-2021 (%).

Antibiotic	2017 (n = 35)	2018 (n = 35)	2019 (n = 36)	2020 (n = 33)	2021(n = 32)	Average
Amikacin	22.2	3.7	16.0	10.3	17.9	14.0
Aztreonam	48.1	32.1	35.0	31.8	44.4	40.3
Ceftazidime	40.9	25	38.1	41.7	37.5	40.4
Ciprofloxacin	64.0	46.4	50.0	52.2	60.0	50.0
Ceftriaxone	51.9	33.3	46.2	50.0	56.0	48.2
Cefoperazone/Sulbactam	66.6	40.9	38.5	31.3	40.0	39.0
Cefotaxime	55.6	42.8	56.2	66.7	63.2	54.5
Cefuroxime	50.0	52.7	57.2	50.0	60.0	56.4
ESBL	26.3	29.6	32.1	41.7	41.7	33.6
Cefepime	42.8	16.6	34.6	37.9	31.0	33.1
Gentamicin	46.4	25.9	34.8	41.7	40.0	38.8
Imipenem	25.5	25.0	19.4	18.2	22.2	19.3
Levofloxacin	65.4	53.3	45.9	48.1	46.2	51.2
Meropenem	16.6	9.5	29.1	26.7	29.4	21.3
Ampicillin/Sulbactam	70.0	41.2	60.0	58.8	50.0	58.0
SXT	42.3	30.8	28.0	28.6	25.0	33.3
Tobramycin	57.7	36.4	36.3	40.9	36.0	43.6
Piperacillin/Tazobactam	40.7	16.6	26.9	31.0	25.0	33.0

Table 9. Antimicrobial resistance rates of *S. pneumoniae* isolated from CSF, SPARSS, 2017-2021 (%).

Antibiotic	2017 (n = 40)	2018 (n = 40)	2019 (n = 38)	2020 (n = 24)	2021 (n = 28)	Average
Clindamycin	100.0	87.5	90.9	92.9	94.1	92.6
Ceftriaxone	18.7	26.4	40.0	21.7	41.7	28.8
Cefotaxime	33.3	40.9	47.6	38.5	55.6	42.9
Erythromycin	100.0	100.0	97.0	95.2	95.2	98.0
Linezolid	0.0	0.0	0.0	0.0	0.0	0.0
Levofloxacin	2.7	2.6	0.0	0.0	0.0	1.3
Meropenem	30.3	23.3	26.9	27.8	29.4	27.5
Moxifloxacin	4.5	0.0	0.0	0.0	0.0	1.1
Penicillin G	62.5	81.8	67.7	66.7	68	69.5
SXT	59	65.8	74.2	76.2	69.2	68.9
Tetracycline	95.8	95.0	88.2	90.9	91.7	92.9
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0

quinupristin/dalfopristin (Q/D). Resistance rates for MRSA to SXT and Q/D were 14.7% and 24.2%, respectively, while MSSA showed the rates of 5.0% and 16.9%. No *S. aureus* resistant to vancomycin, linezolid, and tigecycline were detected. The detection rates of methicillin-resistant coagulase-negative staphylococci (MRCoNS) were 60.2% (210/349), 62.4% (231 /370), 59.2% (268/453), 54.6% (215/394) and 54.4% (242/445), with a five-year average of 58.0%. This represents a downward trend. MRCoNS showed sensitivity to tigecycline, vancomycin, and linezolid, but the resistance rate of MRCoNS to common antibiotics was higher compared to methicillin-sensitive coagulase-negative staphylococcus (MSCoNS).

A. baumannii isolated from CSF exhibited resistance rates exceeding 60% to ceftazidime, ceftriaxone, cefoperazone/sulbactam, cefepime, imipenem, ampicillin/sulbactam, and piperacillin/tazobactam. Notably, the resistance rates had a downward trend in recent years. *A. baumannii* was highly sensitive to tigecycline and polymyxin B (Table 7).

K. pneumoniae isolated from CSF demonstrated resistance rates exceeding 50% to cefuroxime, cefotaxime, ampicillin/sulbactam and levofloxacin. The proportion of extended-spectrum β-lactamases (ESBLs)-producing strains increased from 26.3% to 41.7%. Although carbapenem resistance showed a decline in 2018, The resistance rate of meropenem has been rising continuously through 2021 (Table 8). *S. pneumoniae* isolated from CSF exhibited increasing resistance trends to cefotaxime and ceftriaxone, while remained sensitive to vancomycin and linezolid, and the drug resistance rates to penicillin G were above 60.0%

Table 10. Antimicrobial resistance rates of *S. pneumoniae* isolated from CSF in Pediatric and Adult, SPARSS, 2017-2021 (%).

Antibiotic	Antimicrobial resistance rates (%)	
	Pediatric (N = 79)	Adult (N = 91)
Clindamycin	6.5	10.8
Clindamycin	91.8	93.3
Ceftriaxone	27.3	30.3
Cefotaxime	51.3	37.7
Erythromycin	98.6	97.5
Linezolid	0.0	0.0
Levofloxacin	0.0	2.7
Meropenem	22.8	31.4
Moxifloxacin	0.0	1.8
Penicillin G	80.0	60.5
SXT	64.9	73.4
Tetracycline	96.9	90.4
Vancomycin	0.0	0.0

(Table 9). The resistance rate to cefotaxime was 51.3% in children and 37.3% in adults. Children showed an 80% resistance rate to penicillin G compared to 60.5% in adults (Table 10).

E. coli isolated from CSF exhibited resistance rates exceeding 50% to cefuroxime, ceftriaxone, ampicillin/sulbactam, and SXT, over 70% to ciprofloxacin, cefazolin and levofloxacin, and over 80% to ampicillin, while showing low resistance to amikacin, imipenem and meropenem (Table 11). The resistance rate of adult isolates was higher than in children for most antibiotics (Table 12).

Discussion

Meningitis is a severe infectious disease characterized by acute onset and rapid progression, often leading to high mortality and disability rates. The prognosis is closely linked to the timely administration of effective antibacterial treatment. However, traditional CSF culture methods often yield low rates of

Table 11. Antimicrobial resistance rates of *E. coli* isolated from CSF, SPARSS, 2017-2021 (%).

Antibiotic	2017 (n = 34)	2018 (n = 27)	2019 (n = 33)	2020 (n = 31)	2021(n = 26)	Average
Amikacin	3.2	0	11.5	4.8	0	4.1
Ampicillin	90.3	85.7	87.5	89.3	89.5	89.4
Aztreonam	61.3	50	58.3	50	35	52.2
Ceftazidime	39.3	33.4	58.3	52.6	33.3	42.6
Ciprofloxacin	73.3	78.3	80	82.4	82.4	77.1
Ceftriaxone	64	54.5	87.5	59.1	61.9	65.8
Cefoperazone/Sulbactam	9.1	31.6	25	17.7	25	23.1
Cefotaxime	69.2	77.8	66.7	60	41.7	61.6
Cefuroxime	66.7	64.2	80	55.5	66.7	68.5
Cefazolin	76	77.8	88.9	76.9	85.7	81
ESBL	65	45	72.7	23.5	55.6	53.6
Cefepime	41.9	30.4	50	45.5	21.7	38.4
Gentamicin	45.2	42.9	36	57.9	36.8	45.2
Imipenem	3.2	0	7.7	13.6	4.3	4.8
Levofloxacin	75	82.6	92.3	85	85	80.2
Meropenem	0	0	5.9	5.3	0	5.2
Ampicillin/Sulbactam	84.6	64.7	72.7	73.4	71.5	72.8
SXT	50	54.2	76	61.9	73.9	62.8
Tobramycin	59.2	42.8	33.3	61.1	44.4	48.6
Piperacillin/Tazobactam	3.2	8.4	15.4	23.8	13	14.9

pathogen detection [7]. Studies have demonstrated that administering antibacterial therapy up to 24 hours before lumbar puncture reduces the sensitivity of CSF culture from 88% to 70%, performing lumbar puncture within 24 hours of antibacterial treatment further diminishes sensitivity to 59% [8]. Additionally, factors such as sample retention time and detection thresholds further affect the positivity rate of CSF cultures [9]. The etiology of central nervous system(CNS) infections varies significantly based on temporal, geographical, age-related and demographic factors [10,11]. Thus, empirical clinical treatment is often necessary until the pathogen is identified. Analyzing the distribution and antimicrobial susceptibility of pathogens in CSF is therefore essential for guiding empirical antibiotic therapy. From 2017 to 2021, the number of SPARSS members included in the analysis increased from 40 to 58, while the proportion of pathogens isolated in CSF decreased from 0.6% to 0.4%. A total of 3968 pathogenic bacteria were isolated from CSF in this study. Of these, 70.6% were Gram-positive bacteria, 27.2% were Gram-negative bacteria, and 2.2% were fungi. The most frequently detected bacteria were CoNS (50.7%), *A. baumannii* (7.6%), *K. pneumoniae* (4.3%), *S. pneumoniae* (4.3%), *E. coli* (3.8%), and *S. aureus* (3.5%) (Table 4). Our analysis indicates that the distribution of pathogens in CSF varies by gender and season, with a higher proportion of strains among males and a peak in isolation rates during autumn. Notably, the male-to-female ratio among patients with bacterial meningitis varies by age group: 1.1:1 in newborns, 1.4:1 in children, and 1.7:1 in adults. This disparity may be linked to hormonal differences and inflammatory responses associated with the X chromosome, potentially leading to more robust immune responses in females [12].

CoNS emerged as the predominant pathogen causing CSF infections, consistent with the 50.3% reported by the national bacterial resistance monitoring network. Although the detection rate of MRCoNS has shown a downward trend, it remains significantly higher than that of *A. baumannii*, which accounts for 7.6% of isolates. CoNS are common skin and mucosal flora; thus, when isolating CoNS from CSF, it is crucial to rule out contamination. Clinicians should integrate clinical symptoms with other CSF examinations to confirm bacterial meningitis and enhance standardized sample collection and management practices.

The distribution of pathogens varies among different populations. In neonates, *E. coli* was the most common pathogen, aligning with several domestic reports [13-15], likely due to *E. coli* contamination in

Table 12. Antimicrobial resistance rates of *E. coli* isolated from CSF in Pediatric and Adult, SPARSS, 2017-2021 (%).

Antibiotic	Antimicrobial resistance rates (%)	
	Pediatric (N = 50)	Pediatric (N = 101)
Amikacin	2.2	5.2
Ampicillin	86.4	88.4
Aztreonam	42.2	58.6
Ceftazidime	36.6	48.5
Ciprofloxacin	73.2	81.6
Ceftriaxone	48.8	75.3
Cefoperazone/Sulbactam	9.6	27.4
Cefotaxime	52.6	69
Cefuroxime	72.2	70.7
Cefazolin	66.7	91.3
ESBL	42.9	58
Cefepime	28.3	44.3
Gentamicin	40	45.7
Imipenem	2.1	5.1
Levofloxacin	78	86.9
Meropenem	0	7.8
Ampicillin/Sulbactam	75.6	73.7
SXT	60.9	63.6
Tobramycin	43.9	51.5
Piperacillin/Tazobactam	4.4	16.5

the maternal reproductive tract during vaginal delivery [16]. In children, *S. pneumoniae* was the predominant pathogen, related to its colonization in the upper respiratory tract, with studies indicating that 30% of healthy children harbor *S. pneumoniae* in this area [17]. In adults, *A. baumannii* was the most common pathogen, potentially due to higher usage of preventive drugs and exposure to traumatic procedures [18]. The distribution of isolated fungi vary by population. In children, all isolated fungi were *Candida*, while in adults *C. neoformans* was the most frequently isolated species, followed by *Candida*. This pattern may be linked to the widespread use of broad-spectrum antibiotics, glucocorticoids, chemotherapeutic drugs and immunosuppressive drugs, as well as the increasing prevalence of immunodeficiency diseases and organ transplantation. Currently, the incidence of cryptococcal meningitis has significantly increased, surpassing viral and tuberculous meningitis [15].

Antibiotic resistance is a major global concern, as antibiotic use not only inhibits bacterial growth but also contributes to resistance. To combat infections caused by drug-resistant pathogens, continuous monitoring of antibiotic susceptibility is recommended by the World Health Organization [19]. In our study, MRCoNS showed higher resistance rates to common antibiotics compared with the methicillin-sensitive CoNS (MSCoNS), but remained sensitive to tigecycline, vancomycin, and linezolid. Although CoNS were generally sensitive to linezolid, resistant strains have been reported both domestically and internationally. *A. baumannii*, the second most prevalent pathogen in CSF, exhibited resistance rates exceeding 60% against

cephalosporins, cephalosporin- β -lactamase inhibitor combinations and carbapenems, but showed low resistance to tigecycline and polymyxin. Treating CNS infection caused by *A. baumannii* is challenging, with the mortality rate ranging from 15% to 70%, notably higher in developing countries [20]. For severe multi-drug resistance, *A. baumannii* infections, treatment regimens combining polymyxin with tigecycline, sulbactam, or fosfomycin can be recommended [21-23]. For children, the regimen includes tigecycline combined with either meropenem or fosfomycin. In this study, *K. pneumoniae* was the third most common pathogen, with a notable increase in ESBLs-producing and carbapenem-resistant strains. The resistance rate to imipenem ranged from 18.2% to 25.5%, and resistance to meropenem increased from 16.6% to 29.4% by 2021. Due to the limited number of *Klebsiella pneumoniae* strains found in children, comparisons of drug resistance rates between children and adults have not been well established. *S. pneumoniae*, the fourth most common pathogen, showed more than 60% resistance to penicillin G and an upward trend in resistance to ceftriaxone and cefotaxime. Resistance rates to cefotaxime and penicillin G were higher in children (51.3% and 80.0%, respectively) compared to adults (37.3% and 60.5%, respectively), which may relate to the limited and excessive use of these drugs in children. No strains resistant to vancomycin and linezolid were found. *E. coli* showed resistance rates exceeding 50% to cefuroxime, ceftriaxone, ampicillin/sulbactam, and SXT, more than 70% resistance to ciprofloxacin, cefazolin, and levofloxacin, more than 80% resistance to ampicillin, lower resistance to amikacin, imipenem and meropenem, and the resistance rate of adults to most drugs is higher than that of children; Compared to *K. pneumoniae*, *E. coli* showed lower carbapenem resistance. *S. aureus* exhibited high resistance rates to erythromycin and penicillin G but was sensitive to tigecycline, linezolid, and vancomycin. Except for SXT and Q/D, MRSA showed higher resistance rates than MSSA. For most antibiotics, the drug resistance rate of *E. coli* and *S. pneumoniae* in adults is higher than that in children.

Based on the above monitoring data, for the treatment of pan-resistant or carbapenem-resistant *A. baumannii* infection, adults can be treated with the polymyxin-based combination of tigecycline or sulbactam or fosfomycin, and the treatment of pan-resistant *A. baumannii* in children is tigecycline combined with meropenem or fosfomycin; *Enterobacteriaceae* bacteria are sensitive to carbapenem antibiotics. Because imipenem is not easy

to pass through the blood-brain barrier, carbapenem antibiotics that can pass through the blood-brain barrier such as meropenem can be selected. However, the resistance rate of carbapenem antibiotics has increased in the past 5 years. As the last line of defense against Gram-negative bacteria infection, we should control the growth of resistance rate and strengthen the screening and control of carbapenem-resistant bacteria. Linezolid and vancomycin still maintain absolute advantages in treating common clinical infections of Gram-positive bacteria.

In conclusion, the current data suggest severe resistance among pathogens in CSF in Shandong Province, China, with significant variability in pathogen distribution across patient populations. Strengthening clinical monitoring of bacterial antibiotic resistance is crucial, particularly by establishing comprehensive surveillance of pathogen distribution and resistance patterns. This approach will guide the rational use of antimicrobials and promote accurate diagnosis and treatment of CNS infections.

Acknowledgements

This study was supported by the clinical promotion and research of precision diagnosis and treatment of infectious diseases in children carried out by the multidisciplinary collaboration from the Shandong Provincial Clinical Research Center for Children's Health and Disease (RC006) and the Science and Technology plan of Jinan Municipal Health Commission (2022-1-45 and 2022-2-149).

Availability of data and materials

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

Ethics statement

This study was reviewed and approved by the Ethical Review Committee of Children's Hospital Affiliated to Shandong University (approval no. SDFE-IRB/P-2022017). All procedures followed were in strict compliance with the Ethical Review of Biomedical Research Involving Human Subjects (2016), the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

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Conflict of interests: No conflict of interests is declared.