Antibiotics prescription for targeted therapy of pediatric invasive pneumococcal diseases in China: a multicenter retrospective study

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Abstract

Background: *Streptococcus pneumoniae* (*S. pneumoniae*) is a major cause of bacterial meningitis, septicemia and pneumonia in children. Inappropriate choice of antibiotic can have important adverse consequences for both the individual and the community.

Objective: To evaluate antibiotics therapy for children with IPD (invasive pneumococcal diseases) in China.

Methods: A multicenter retrospective study was conducted in 14 hospitals from 13 provinces in China. Antibiotics prescription, clinical features and resistance patterns of IPD cases from January 2012 to December 2017 were collected. Appropriateness of targeted antibiotics therapy was assessed.

Results: 806 IPD cases were collected. The non-susceptibility rates of *S. pneumonia* to penicillin and cefotaxime were 40.9% and 20.7% respectively in 492 non-meningitis cases, whereas those were 73.2% and 43.0% respectively in 314 meningitis cases. Carbapenems were used in 21.3% of non-meningitis cases and 42.0% of meningitis cases. For 390 non-meningitis cases with isolates susceptible to cefotaxime, vancomycin and linezolid were used in 17.9% and 8.7% of cases respectively. For 179 meningitis cases with isolates susceptible to cefotaxime, vancomycin and linezolid were prescribed in 55.3% and 15.6% of cases respectively. Overall, therapies resulted inappropriate in 361 (44.8%) of 806 IPD cases, including 232 (28.8%) cases with inappropriate use of carbapenems, 169 (21.0%) cases with inappropriate use of vancomycin and 62 (7.7%) cases with inappropriate use of linezolid.

Conclusions: Antibiotic regimens for IPD definite therapy were often excessive with extensive prescription of carbapenems, vancomycin or linezolid in China. Antimicrobial stewardship programs should be implemented to improve antimicrobial use.

Introduction

Streptococcus pneumoniae is a major cause of bacterial meningitis, septicemia and pneumonia worldwide [1]. With the application of *S. pneumoniae* conjugate vaccine, the incidence of IPD has decreased in developed countries [2]. However, the pneumococcal conjugate vaccine is not universally used in China. *S. pneumoniae* is one of the most common pathogens and can cause infectious diseases, especially pneumonia, in Chinese children under 5 years of age [3]. A multicenter study of bacterial meningitis in Chinese children showed that *S. pneumoniae* was still the most common pathogen, occurring in up to 46.5% of cases [4].

Unnecessary or inappropriate choice of antibiotic can have important consequences for both the individual and the community, including modification of the enteric microbial ecology and the emergence of antimicrobial resistance. The issuance of guidelines for antibacterial use in clinical practice by the National Health Commission (NHC) of China in October 2004 encouraged more rational use of antibiotics [5]. The guidelines divide antibiotics into non-restricted use (i.e., recommended first-line drugs), restricted use and special use grades. Carbapenems, vancomycin and linezolid, which were often used in therapy of IPD in China [6, 7, 8], were classified as special use grades according to the NHC guidelines [5]. Data on

appropriateness assessment of antibiotics prescription for IPD in China is rare. The main purpose of this retrospective study was to evaluate the antibiotics therapy for pediatric IPD in China.

Methods

Study design and setting

A multicenter retrospective study was conducted in China. Hospitals included in this study should met following criteria: (1) a hospital must have adequate research capabilities to conduct the study, especially laboratory facilities for bacterial culture and the ability to assess susceptibility to antimicrobials; and (2) a hospital must be willing to participate in this research and have enough time to do this study. 14 hospitals (13 tertiary hospitals and 1 secondary hospital) joined our study. The selected hospitals consisted of 4 in north China, 4 in east China, 3 in south China and 3 in the northwest China. Demographic data, clinical features, laboratory findings, antibiotics prescription and clinical outcome of all patients with IPD in these hospitals were collected by local researchers. We considered clinical status on the day of discharge as the clinical outcome.

Study population

Inclusion criteria: (1) The admission day was between January 1, 2012 and December 31, 2017. (2) Hospitalized children younger than 18 years old with diagnosis of IPD in selected hospitals. (3) Clinical data should be available. Invasive pneumococcal infection was defined as illness in which *S. pneumoniae* was isolated from a normally sterile body site.

Exclusion criteria: (1) Less than two days of targeted antibiotic therapy for IPD. (2) Evidence of co-bacterial infection in IPD case.

Antimicrobial susceptibility testing

To rule out repeated strains, only one representative strain from each case was included. When both the blood and cerebrospinal fluid (CSF) cultures were positive in a case, we used only the strain from the CSF sample for antimicrobial susceptibility testing. According to the performance standards for antimicrobial susceptibility testing of the Clinical and Laboratory Standards Institute in 2008, we determined the penicillin susceptibility of *S. pneumoniae* by the minimum inhibition concentration. If an *S. pneumoniae* strain was isolated from a patient without meningitis, we defined its penicillin susceptibility by the parenteral nonmeningeal breakpoint (susceptible, ≤ 2.00 mg/l; intermediate, 4.00 mg/L; resistant, ≥ 8.00 mg/l) and cefotaxime/ceftriaxone/cefepime meningitis breakpoint (susceptible, ≤ 1.0 mg/L; intermediate, 2.0 mg/L; resistant, ≥ 4.00 mg/L). If an *S. pneumoniae* strain was isolated from a patient with pneumococcal meningitis, we defined its penicillin susceptibility by the parenteral meningeal breakpoint (susceptible, ≤ 0.06 mg/l; resistant, ≥ 0.12 mg/l) and cefotaxime/ceftriaxone/cefepime meningeal breakpoint (susceptible, ≤ 0.50 mg/L; intermediate, 1.00 mg/L; resistant, ≥ 2.00 mg/L).

Data of antibiotics prescription

The antibiotics prescription before the culture result was considered as empiric antibiotics therapy. Targeted/definitive antibiotics therapy was defined as antibiotics prescription for treatment of IPD after culture result.

Appropriateness of targeted antibiotics therapy were assessed by two pediatric infectious disease specialists according to 2016 European Society of Clinical Microbiology and Infectious Diseases guideline for diagnosis and treatment of acute bacterial meningitis [9] and Red Book: 2018–2021 Report of the Committee on Infectious Diseases [10]. In this study, we focused on use of carbapenems, vancomycin and linezolid which are classified as special use grades according to the NHC guidelines and frequently prescribed for IPD targeted therapy in China.

The definitive prescription of carbapenems was considered inappropriate if it met one of following listed criteria: 1) if the organism is nonsusceptible to carbapenems, carbapenem was still used in targeted therapy;2) if the organism is susceptible to penicillin or cephalosporins, carbapenem was still used in targeted therapy without any other reasons, such as hypersensitivity reactions to penicillins or cephalosporins. The definitive prescription of vancomycin or linezolid was considered inappropriate if it met following criteria: if the organism is susceptible to penicillin or cephalosporins, vancomycin or linezolid was still used in targeted therapy without any other reasons, such as hypersensitivity reactions to beta-lactam antibiotics.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as median and interquartile range (IQR). Categorical variables were compared using the chi-square or Fisher's exact tests. Continuous variables were compared by Student's t test or Mann–Whitney U test according to their distribution. Two-tailed P value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 17.0 software (IBM Corporation).

Results

Demographic data

Data of IPD cases from January 2012 through December 2017 was available in 8 hospitals, cases from January 2014 through December 2017 available in 3 hospitals and cases from January 2015 through December 2017 available in other 3 hospitals. Overall, 860 IPD cases were collected in 14 hospitals. Forty-nine patients were excluded for less than two days of targeted antibiotic therapy for IPD. Other 5 patients who had evidence of co-bacterial infection were also excluded. Thus, we included 806 children with IPD in our study. The ratio of M/F was 1.56:1. The median age of these patients was 1.3 years (interquartile range 0.8–3.1 years). There was no statistical significance in age and gender in different regions of China (Table 1).

Table 1
Characteristics of children presenting with IPD from different regions of China

	All Patients n = 806	North n = 368	East n = 161	South n = 237	Northwest n = 40	p
Median age, y (interquartile range)	1.3 (0.8–3.1)	1.3 (0.7–3.2)	1.6 (0.8–3.5)	1.3 (0.8–2.9)	1.1 (0.7-3.0)	0.287
Male	491 (60.9)	217 (59.0)	113 (70.2)	139 (58.6)	22 (55.0)	0.058
Underlying disease	101 (12.5)	59 (16.0)	25 (15.5)	14 (5.9)	3 (7.5)	0.001
ICU admission	241 (29.9)	124 (33.7)	41 (25.5)	63 (26.6)	13 (32.5)	0.144
Tracheal intubation	112 (13.9)	71 (19.3)	20 (12.4)	17 (7.2)	4 (10.0)	0.000
Death	92 (11.4)	54 (14.7)	18 (11.2)	16 (6.8)	4 (10.0)	0.023
Meningitis	314 (39.0)	145 (39.4)	61 (37.9)	90 (38.0)	18 (45.0)	0.845
Spn not susceptible to penicillin	431 (53.5)	212 (57.6)	64 (39.8)	135(57.0)	20 (50.0)	0.001
Spn not susceptible to cefotaxime	237 (29.4)	127 (34.5)	34 (21.1)	61 (25.7)	15 (37.5)	0.005

Spn, *Streptococcus pneumonia.*

Clinical findings

In our study, 101 (12.5%) cases had an underlying disease or causation (leukemia, 3.0%; trauma or surgery within one month before onset, 2.6%; congenital heart disease 2.4%; nephrotic syndrome, 2.1%; immunodeficiency, 1.6%; neuroblastoma, 0.5%; bone marrow transplant, 0.4%). Blood cultures were positive in 622 cases and CSF cultures were positive in 254 cases. There were 70 cases with positive pleural effusion cultures and 22 with positive cultures of other sites (ascites, 10 cases; joint effusion, 9 cases; bone marrow, 2 cases; subdural effusion, 1 case). A total of 121 cases had positive cultures of both blood and CSF.

Pneumococcal meningitis was diagnosed in 314 patients. Among 492 non-meningitis cases, there were 282 cases with bacteremic pneumonia, 176 cases of bacteremia without focal infection and 34 cases with other types of infection (peritonitis, 10 cases; osteoarticular infection, 9 cases; cellulitis, 7 cases; otitis media, 5 cases; infective endocarditis 2 cases; pericarditis, 1 case).

Two hundred and forty-one patients were admitted in ICU and 112 patients need tracheal intubation. Sixty-two (2.0%) of 314 patients with meningitis died and 57 (18.2%) presented with sequelae (28 with seizures, 8.9%; 20 with hearing loss, 6.4%; 2 with paralysis, 0.6%; and 9 with intellectual disability, 2.9%). Thirty (6.1%) of 492 patients with non-meningitis disease died. There were 4 patients with lung bullae and 2 patients with bronchiectasis in non-meningitis cases. The proportion of patients with underlying disease, tracheal intubation and death differed by regions (all P values 0.05) (Table 1).The proportion of patients with underlying disease in the north and the east were higher than that in the south and the northwest (all P values 0.05). The proportion of patients with tracheal intubation was highest in the north(P values 0.05).

Antimicrobial susceptibility testing

All the isolates from 806 patients underwent penicillin and cefotaxime susceptibility testing. We found 201 (40.9%) *S. pneumoniae* isolates with non-susceptibility to penicillin (90 intermediate and 111 resistant) and 102 (20.7%) isolates with non-susceptibility to cefotaxime (50 intermediate and 52 resistant) in non-meningitis cases. While in meningitis cases, there were 230 (73.2%) *S. pneumoniae* isolates resistant to penicillin and 135 (43.0%) isolates with non-susceptibility to cefotaxime (83 intermediate and 52 resistant) **(Fig. 1)**.

The penicillin non-susceptibility rate of *S. pneumoniae* in IPD cases differed by region (57.6% in the north, 57.0% in the south, 50.0% in the northwest, 39.8% in the east) (Table 1) and penicillin non-susceptibility rate in the north region and south region were higher than that in the east region (north 57.6% vs east 39.8%, p = 0.001; south 57.0% vs east 39.8%, p = 0.001). The cefotaxime non-susceptibility rate also differed by region and cefotaxime non-susceptibility rate in the north region were higher than that in south region and the east region (north 34.5% vs south 25.7%, p = 0.023; south 34.5% vs east 21.1%, p = 0.002).

The resistance rates of *S. pneumoniae* to meropenem, erythromycin, clindamycin, tetracycline, sulfamethoxazole, chloramphenicol and levofloxacin were 40.6% (238/586), 97.4% (760/780), 96.0% (509/530), 91.1% (666/731), 71.4% (657/469), 9.9% (71/716) and 2.3% (14/604) respectively. No *S. pneumoniae* isolates were resistant to vancomycin and linezolid **(Fig. 1)**.

Antibiotics prescription

Empiric antibiotics therapy

Twenty-five patients had antibiotics susceptibility of *S. pneumonia* when they were admitted in hospital. These 25 patients got targeted antibiotics therapy directly. So, 781 patients with IPD got empiric antibiotics therapy, including penicillins monotherapy (64, 8.2%), cephalosporins monotherapy (427, 54.7%), carbapenem monotherapy (90, 11.5%), cephalosporin plus vancomycin (52, 6.7%), carbapenem plus vancomycin (122, 15.6%), cephalosporin plus linezolid (5, 0.6%), carbapenem plus linezolid (7, 0.9%), cephalosporin plus teicoplanin (3, 0.4%)and macrolides monotherapy (11, 1.4%) (Table 2). The empiric antibiotics prescription had no significant difference between regions except penicillin. Penicillin monotherapy was the most commonly used for empiric therapy of IPD in the east region, compared with other regions (Table 2).

Table 2
Empiric antibiotics therapy of 781 patients with IPD from different regions of China

	All Patients n = 781	North n = 349	East n = 158	South n = 236	Northwest n = 38	p
Penicillins monotherapy	64 (8.2)	18 (5.2)	23 (14.6)	21 (8.9)	2 (5.3)	0.006
Cephalosporin monotherapy	427 (54.7)	199 (57.0)	78 (49.4)	131 (55.5)	19 (50.0)	0.396
Carbapenem monotherapy	90 (11.5)	43 (12.3)	17 (10.8)	25 (10.6)	5 (13.2)	0.895
Cephalosporin plus vancomycin	52 (6.7)	25 (7.2)	7 (4.4)	18 (7.6)	2 (5.3)	0.566
Carbapenem plus vancomycin	122 (15.6)	47 (13.5)	29 (18.4)	36 (15.3)	0 (0)	0.142
Cephalosporin plus linezolid	5 (0.6)	4 (1.1)	0 (0)	1 (0.4)	0 (0)	0.278
Carbapenem plus linezolid	7 (0.9)	5 (1.4)	1 (0.6)	1 (0.4)	0 (0)	0.475
Cephalosporin plus teicoplanin	3 (0.4)	3 (0.9)	0 (0)	0 (0)	0 (0)	0.183
Macrolides monotherapy	11 (1.4)	5 (1.4)	3 (1.9)	3 (1.3)	0 (0)	0.715

Definitive antibiotics therapy

Definitive antibiotics therapy strategy in non-meningitis cases included penicillins monotherapy (54, 11.0%), cephalosporin monotherapy (220, 44.7%), carbapenem monotherapy (47, 9.6%), cephalosporin plus vancomycin (9.3, 46 %), carbapenem plus vancomycin (46, 9.3%), cephalosporin plus linezolid (28, 5.7%), carbapenem plus linezolid (12, 2.4%), vancomycin monotherapy (18, 3.7%), linezolid monotherapy (13, 2.6%) and other prescriptions (8, 1.6%) **(**Table 3**)**. Thus, cephalosporin was prescribed in 295 (60.0%) cases and was most common antibiotic used in non-meningitis cases, followed by vancomycin (113 cases, 23.0%), carbapenems (105 cases, 21.3%), penicillin (59 cases, 12.0%),linezolid (55 cases, 11.2%)and teicoplan (3 cases, 0.6%) **(Fig. 2)**. Among 390 non-meningitis cases whose isolates were susceptible to cefotaxime, carbapenems, vancomycin and linezolid were prescribed in 83 (21.3%) cases, 70 (17.9%) cases and 34 (8.7%) cases respectively **(Fig. 3)**.

Table 3

Appropriateness of antibiotic prescription for targeted therapy of non-meningitis IPD

Table 7. Number of cases included in each hospital	
Hospital	Number of cases
Beijing Children's Hospital	179
Hebei Children's Hospital	173
Children's Hospital Affiliated to Zhengzhou University	112
Shenzhen Children's Hospital	97
Jiangxi Provincial Children's Hospital	63
Nanjing Children's Hospital Affiliated to Nanjing Medical University	44
Children's Hospital of Jinan	32
Hunan Children's Hospital	28

Spn, *Streptococcus pneumonia.*

a: 2 patients with penicillins plus vancomycin, 1 patient with penicillins plus linezolid, 1 patient with Cephalosporin plus teicoplanin and 1 patient with teicoplanin monotherapy.

b: 1 patient with penicillins plus linezolid and 1 patient with teicoplanin monotherapy.

Table 7. Number of cases included in each hospital	
Baoding Children' s Hospital	27
Xi'an Children's Hospital	25
Hangzhou Children's Hospital	22
Urumqi Children's Hospital	15
Maternal and Child Health Care Hospital of Inner Mongolia	10
Children's Hospital of Shanxi	9

	All patients n = 492	**Spn susceptible to penicillin** n = 291	**Spn not susceptible to penicillin** n = 201			**p**
Definitive antibiotics therapy			susceptible to cefotaxime n = 99	not susceptible to cefotaxime n = 102	Subtotal n = 201	
Penicillins monotherapy	54 (11.0)	29 (10.0)	12 (12.1)	13 (12.7)	25 (12.4)	0.389
Cephalosporin monotherapy	220 (44.7)	155 (53.3)	47 (47.5)	18 (17.6)	65 (32.3)	0.000

Spn, *Streptococcus pneumonia.*

a: 2 patients with penicillins plus vancomycin, 1 patient with penicillins plus linezolid, 1 patient with Cephalosporin plus teicoplanin and 1 patient with teicoplanin monotherapy.

b: 1 patient with penicillins plus linezolid and 1 patient with teicoplanin monotherapy.

Table 7. Number of cases included in each hospital						
Carbapenem monotherapy	47 (9.6)	36 (12.4)	5 (5.1)	6 (2.0)	11 (5.5)	0.011
Cephalosporin plus vancomycin	46(9.3)	17 (5.8)	8 (8.1)	21 (20.6)	29 (14.4)	0.001
Carbapenem plus vancomycin	46 (9.3)	20 (6.9)	12 (12.1)	14 (13.7)	26 (12.9)	0.023
Cephalosporin plus linezolid	28 (5.7)	13 (4.5)	3 (3.0)	12 (11.8)	15 (7.5)	0.159
Carbapenem plus linezolid	12 (2.4)	5 (1.7)	5 (5.1)	2 (2.0)	7 (3.5)	0.342
vancomycin monotherapy	18 (3.7)	5 (1.7)	5 (5.1)	8 (7.8)	13 (6.5)	0.006
Linezolid monotherapy	13 (2.6)	5 (1.7)	2 (2.0)	6 (5.9)	8 (4.0)	0.124
Other prescriptions	8 (1.6)	6[a] (2.1)	0 (0)	2[b] (2.0)	2 (1.0)	-
Inappropriate use of						
carbapenems	99 (20.1)	61 (21.0)	22 (22.2)	16 (15.7)	38 (18.9)	0.576
vancomycin	70 (14.2)	45 (15.5)	25 (25.3)	0 (0)	25 (12.4)	0.345
linezolid	34 (6.9)	24 (8.2)	10 (10.1)	0 (0)	10 (5.0)	0.160
No. patients with inappropriate antibiotic use	161 (32.7)	105 (36.1)	40 (40.4)	16 (15.7)	56 (27.9)	0.056

Spn, *Streptococcus pneumonia.*

a: 2 patients with penicillins plus vancomycin, 1 patient with penicillins plus linezolid, 1 patient with Cephalosporin plus teicoplanin and 1 patient with teicoplanin monotherapy.

b: 1 patient with penicillins plus linezolid and 1 patient with teicoplanin monotherapy.

Definitive antibiotics therapy strategy in meningitis cases included cephalosporin monotherapy (39, 12.4%), carbapenem monotherapy (15, 4.8%), cephalosporin plus vancomycin (88, 28.0%), carbapenem plus vancomycin (94, 29.9%),cephalosporin plus linezolid (26, 8.3%), carbapenem plus linezolid (21, 6.7%), vancomycin plus rifampin (16, 5.1%), linezolid monotherapy (6, 1.9%) and other prescriptions (9, 1.6%) **(**Table 4**)**. The most common antibiotic used in meningitis cases was vancomycin (202 cases, 64.3%), followed by cephalosporin (157 cases, 50.0%), carbapenems (132 cases, 42.0%), linezolid (58 cases, 18.5%) and rifampin (25 cases, 8.0%) **(Fig. 2)**. Among 179 meningitis cases whose isolates were susceptible to cefotaxime, vancomycin carbapenems, and linezolid were prescribed in 99 (55.3%) cases, 75 (41.9%) cases and 28 (15.6%) cases respectively **(Fig. 3)**.

Table 4
Appropriateness of antibiotic prescription for targeted therapy of meningitis IPD

	All patients n = 314	**Spn susceptible to penicillin n = 84**	**Spn not susceptible to penicillin n = 230**			**p**
Definitive antibiotics therapy			susceptible to cefotaxime n = 95	not susceptible to cefotaxime n = 135	Subtotal n = 230	
Penicillins monotherapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Cephalosporin monotherapy	39 (12.4)	19 (22.6)	18 (18.9)	2 (1.5)	20 (8.7)	0.001
Carbapenem monotherapy	15 (4.8)	9 (10.7)	6 (6.3)	0 (0)	6 (2.6)	0.007
Cephalosporin plus vancomycin	88 (28.0)	18 (21.4)	26 (27.4)	44 (32.6)	70 (30.4)	0.116
Carbapenem plus vancomycin	94(29.9)	21 (25.0)	26 (27.4)	47 (34.8)	73 (31.7)	0.248
Cephalosporin plus linezolid	26 (8.3)	5 (6.0)	8 (8.4)	13 (9.6)	21 (9.1)	0.366
Carbapenem plus linezolid	21 (6.7)	5 (6.0)	7 (7.4)	9 (6.7)	16 (7.0)	0.753
Vancomycin plus rifampin	16 (5.1)	5 (6.0)	2 (2.1)	9 (6.7)	11 (4.8)	0.899
vancomycin monotherapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Linezolid monotherapy	6 (1.9)	2 (2.4)	1 (1.1)	3 (2.2)	4 (1.7)	1.000
Other prescriptions	9 (2.9)	0 (0)	1[a] (1.1)	8[b] (5.9)	9 (3.9)	-

Spn, *Streptococcus pneumonia.*

a: Carbapenem plus vancomycin and rifampin.

b: 2 patients with cephalosporin plus vancomycin and rifampin, 2 patients with cephalosporin plus linezolid and rifampin, 2 patients with linezolid plus rifampin, 1 patient with carbapenem plus vancomycin and rifampin and 1 patient with carbapenem plus linezolid and rifampin,

	All patients n = 314	Spn susceptible to penicillin n = 84	Spn not susceptible to penicillin n = 230			p
Inappropriate use of						
carbapenems	133 (42.4)	35 (41.7)	40 (42.1)	58 (43.0)	98 (42.6)	0.881
vancomycin	109 (34.7)	54 (64.3)	55 (57.9)	0 (0)	55 (23.9)	0.000
linezolid	28 (8.9)	12 (14.3)	16 (16.8)	0 (0)	16 (7.0)	0.044
No. patients with inappropriate antibiotic use	200 (63.7)	65 (77.4)	77 (81.1)	58 (43.0)	135 (58.7)	0.002
Spn, *Streptococcus pneumonia.*						
a: Carbapenem plus vancomycin and rifampin.						
b: 2 patients with cephalosporin plus vancomycin and rifampin, 2 patients with cephalosporin plus linezolid and rifampin, 2 patients with linezolid plus rifampin, 1 patient with carbapenem plus vancomycin and rifampin and 1 patient with carbapenem plus linezolid and rifampin,						

Appropriateness of definitive antibiotics therapy

According to the aforementioned selected appropriateness criteria for use of carbapenems, vancomycin and linezolid, therapies resulted inappropriate in 361 (44.8%) out of 806, including 232 (28.8%) cases with inappropriate use of carbapenems, 169 (21.0%) cases with inappropriate use of vancomycin and 62 (7.7%) cases with appropriate use of linezolid. There was inappropriate use of carbapenems, vancomycin or linezolid in 161 (32.7%) non-meningitis cases, including 99 (20.1%) cases with inappropriate use of carbapenems, 70 (14.2%) cases with inappropriate use of vancomycin and 34 (6.9%) cases with appropriate use of linezolid (Table 3). Inappropriate use of carbapenems, vancomycin or linezolid was found in 200 (63.7%) meningitis cases, including 133 (42.4%) cases with inappropriate use of carbapenems, 109 (34.7%) cases with inappropriate use of vancomycin and 28 (8.9%) cases with inappropriate use of linezolid (Table 4).

Inappropriate antibiotics therapy group of non-meningitis had higher proportion of patients with underlying disease, ICU admission, tracheal intubation and death (all P values 0.02), compared with appropriate antibiotics therapy group of non-meningitis (Table 5). Similarly, inappropriate antibiotics therapy group of meningitis also had higher proportion of patients with ICU admission, tracheal intubation and death (all P values 0.001), compared with appropriate antibiotics therapy group of meningitis (Table 5).

Table 5
Baseline characteristics of the patients with IPD (meningitis cases and non-meningitis cases) receiving appropriate/inappropriate antibiotic prescription

	Meningitis cases **n = 314**			**Non-meningitis cases** **n = 492**		
	Appropriate therapy n = 114	Inappropriate therapy n = 200	p	Appropriate therapy n = 331	Inappropriate therapy n = 161	p
Median age, y (interquartile range)	1.1 (0.6–3.6)	1.1 (0.5–3.2)	0.733	1.5 (0.9–3.1)	1.8 (1.0-3.1)	0.075
Male	69 (60.5)	123 (61.5)	0.865	202 (61.0)	97 (60.2)	0.868
Underlying disease	7 (6.1)	23 (11.5)	0.120	27 (8.2)	44 (27.3)	0.000
ICU admission	35 (30.7)	108 (54.0)	0.000	41 (12.4)	57 (35.4)	0.000
Tracheal intubation	9 (7.9)	59 (29.5)	0.000	14 (4.2)	30 (18.6)	0.000
Death	9 (7.9)	53 (26.5)	0.000	14 (4.2)	16 (9.9)	0.013
Spn not susceptible to penicillin	95 (83.3)	135 (67.5)	0.002	125 (60.5)	56 (32.3)	0.056

Inappropriate use rate of carbapenems (42.2% in the east, 30.0% in the northwest, 26.2% in the south,24.5% in the north), vancomycin (31.7% in the east, 19.8% in the north, 16.9% in the south, 12.5% in the northwest) and linezolid (11.1% in the north, 7.2% in the south, 1.9% in the east, 2.5% in the northwest) all differed by region (all P values 0.02) (Table 6). Inappropriate use rate of carbapenems and vancomycin was highest in the east. Nevertheless, inappropriate use rates of linezolid were higher in the north and the south than that in the east and the northwest (Table 6).

Table 6
Appropriateness of antibiotic prescription for targeted therapy of IPD from different regions of China

	All Patients n = 806	North n = 368	East n = 161	South n = 237	Northwest n = 40	p
Penicillins monotherapy	54 (6.7)	20 (5.4)	20 (12.4)	13 (5.5)	1 (2.5)	0.019
Cephalosporin monotherapy	259 (32.1)	96 (26.1)	44 (27.3)	102 (43.0)	17 (42.5)	0.000
Carbapenem monotherapy	62 (7.7)	24 (6.5)	16 (9.9)	19 (8.0)	3 (7.5)	0.607
Cephalosporin plus vancomycin	134 (16.6)	72 (19.6)	20 (12.4)	33 (13.9)	9 (22.5)	0.086
Carbapenem plus vancomycin	140 (17.4)	51 (13.9)	49 (30.4)	31 (13.1)	9 (22.5)	0.000
Cephalosporin plus linezolid	54 (6.7)	38 (10.3)	1 (0.6)	15 (6.3)	0 (0)	0.000
Carbapenem plus linezolid	33 (4.1)	15 (4.1)	3 (1.9)	14 (5.9)	1 (2.5)	0.204
Vancomycin plus rifampin	16 (2.0)	13 (3.5)	1 (0.6)	2 (0.8)	0 (0)	0.038
Vancomycin monotherapy	18 (2.2)	9 (2.4)	3 (1.9)	6 (2.5)	0 (0)	0.556
Linezolid monotherapy	19 (2.4)	17 (4.6)	1 (0.6)	1 (0.4)	0 (0)	0.001
Other prescriptions	17 (2.1)	13[a] (3.5)	3[b] (1.9)	1[c] (0.4)	0 (0)	-
Inappropriate use of						
carbapenems	232 (28.8)	90 (24.5)	68 (42.2)	62 (26.2)	12 (30.0)	0.000
vancomycin	169 (21.0)	73 (19.8)	51 (31.7)	40 (16.9)	5 (12.5)	0.001
linezolid	62 (7.7)	41 (11.1)	3 (1.9)	17 (7.2)	1 (2.5)	0.000

a: 2 patients with cephalosporin plus vancomycin and rifampin, 2 patients with cephalosporin plus linezolid and rifampin, 2 patients with linezolid plus rifampin, 2 patients with carbapenem plus vancomycin and rifampin, 2 patients with teicoplanin monotherapy, 1 patient with carbapenem plus linezolid and rifampin, 1 patient with penicillins plus linezolid and 1 patient with Cephalosporin plus teicoplanin.

b: 3 patients with penicillins plus vancomycin,

c: 1 patient with penicillins plus linezolid.

	All Patients n = 806	North n = 368	East n = 161	South n = 237	Northwest n = 40	p
No. patients with inappropriate antibiotic use	361 (44.8)	169 (45.9)	88 (54.7)	90 (38.0)	14 (35.0)	0.006
a: 2 patients with cephalosporin plus vancomycin and rifampin, 2 patients with cephalosporin plus linezolid and rifampin, 2 patients with linezolid plus rifampin, 2 patients with carbapenem plus vancomycin and rifampin, 2 patients with teicoplanin monotherapy, 1 patient with carbapenem plus linezolid and rifampin, 1 patient with penicillins plus linezolid and 1 patient with Cephalosporin plus teicoplanin.						
b: 3 patients with penicillins plus vancomycin,						
c: 1 patient with penicillins plus linezolid.						

Table 7. Number of cases included in each hospital

Hospital	Number of cases
Beijing Children’s Hospital	179
Hebei Children's Hospital	173
Children's Hospital Affiliated to Zhengzhou University	112
Shenzhen Children's Hospital	97
Jiangxi Provincial Children's Hospital	63
Nanjing Children's Hospital Affiliated to Nanjing Medical University	44
Children's Hospital of Jinan	32
Hunan Children's Hospital	28
Baoding Children' s Hospital	27
Xi'an Children's Hospital	25
Hangzhou Children's Hospital	22
Urumqi Children's Hospital	15
Maternal and Child Health Care Hospital of Inner Mongolia	10
Children's Hospital of Shanxi	9

Discussion

Our study results highlight the problem of antibiotics use in the management of IPD in China. The retrospective study results revealed that up to 44.8% of the prescriptions were inappropriate and excessive. To our knowledge, this is the first multicenter study about appropriateness of antibiotic therapy for IPD in China.

We observed many inappropriate uses of carbapenems: 42.4% in meningitis cases and 20.1% in non-meningitis cases. According to the clinical application evaluation rules of carbapenems released by the NHC in 2018 [11], carbapenems should be reserved for severe infection caused by aerobic gram-negative bacilli with multiple drug resistance, severe mixed infection of aerobic bacteria and anaerobic bacteria such as *Bacteroides fragilis* and empiric treatment of infection in patients with severe immunodeficiency before

pathogen identified. Carbapenems use was often inappropriate in definitive antibiotics therapy for IPD unless other pathogens were detected for reasonable use. The spread of carbapenem-resistant Gram-negative bacteria (GNB) with the consequent change in institutional epidemiology continues to evolve rapidly worldwide [12]. Previous studies have showed that carbapenem resistance in GNB appeared to correlate with previous exposure to carbapenems [13, 14, 15, 16]. And with reduction in carbapenem use, the incidence of *Clostridioides difficile* infection decreased [17]. Inappropriate carbapenems use in targeted therapy for IPD should be reduced in China.

Vancomycin was used inappropriately in 34.7% of meningitis cases and 14.2% of non-meningitis cases, while inappropriate use of linezolid was found in 8.9% of meningitis cases and 6.9% of non-meningitis cases. According to guidelines, vancomycin and linezolid were only used in IPD patients with isolates not susceptible to β-lactams or patients allergic to β-lactams. In other words, vancomycin and linezolid should not be used in patients with *S. pneumoniae* susceptible to penicillins and cephalosporins unless there were reasons of drug allergy. Unnecessary or inappropriate use of vancomycin and linezolid can result in the emergence of antimicrobial resistance. Previous vancomycin use was a risk factor for vancomycin resistant enterococci (VRE) colonization which increased the risk of subsequent VRE infection [18]. Limiting empiric vancomycin exposure was associated with a decreased incidence of VRE [19]. A relationship was also found between appropriate linezolid use and the incidence of linezolid-resistant strains of *E. faecium, S. epidermidis* and *S. haemolyticus* [20]. To reduce inappropriate use of vancomycin and linezolid for patients with IPD in China, we should educate the clinicians that β-lactams rather than vancomycin or linezolid usually should be the first choice for treatment of *S. pneumoniae* susceptible to penicillins and cephalosporins.

Patients who get inappropriate use of vancomycin, linezolid or carbapenems in definite therapy had higher proportions of ICU admission, tracheal intubation and death. It means that more severe cases of IPD were prone to get excessive use of antibiotics such as vancomycin, linezolid and carbapenems. Clinicians used the antibiotics in IPD not only according the isolate susceptibility but also by judging the severity of patient. This situation looks like reasonable. But all patients in our study had definite diagnosis of IPD and patients with other bacteria co-infection were excluded. Thus, severity of patients in our case series should not be the reason for excessive use vancomycin, linezolid or carbapenems. Clinicians should modify antibiotics according to susceptibility testing results for definite therapy if there is no evidence of other bacteria co-infection.

Our study also show that inappropriate use rates of carbapenems, vancomycin or linezolid in definitive therapy differed by regions, although empiric antibiotics prescription had little difference. Inappropriate use rates of carbapenems and vancomycin were highest in the east, while inappropriate use rates of linezolid were higher in the north and the south. It seems that clinicians' compliance with the IPD guidelines was different in regions of China. Education of IPD guidelines should be implemented across China.

Our study has some limitations. First, some participating centers did not involve all the IPD patients through January 1, 2012 to December 31, 2017. However, our study is the largest study of IPD antibiotic treatments

in children. Second, the failure to collect the antibiotic dosage of definite therapy in this study might underestimate the inappropriate antibiotics use.

Through this national hospital-based survey, we found that antibiotic regimens for IPD definite therapy were often excessive with extensive prescription of carbapenems, vancomycin or linezolid. There is an urgent need for specific guidelines for IPD in China. Antimicrobial stewardship programs should be implemented to improve antimicrobial use.

Abbreviations

S. pneumoniae: *Streptococcus pneumoniae*; IPD: invasive pneumococcal diseases; NHC: National Health Commission; CSF: cerebrospinal fluid; VRE: vancomycin resistant enterococci.

Declarations

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Availability of Data and Materials

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

Authors’ Contributions

All the authors had access to the full data set and take responsibility for the integrity of the data and the accuracy of the data analysis **(Table 7)**. LG and YYH conceived and designed the study. ZL, LWH, WF, TK, ZQX, ZK, LSH, LJ, BJ, DHL, CXX, LJ, WYM, ZQ, MHX, LZ, DJK, ZCH, WKK, LAW, LSJ, WDM, CHJ, ZSY, LXD, YL, DF and CTM collected the data. CTM contributed to the analysis and interpretation of data and writing of the manuscript. LG, YHY and ZWS revised the manuscript. All authors reviewed and agreed the final manuscript.

Ethical Approval and informed consent

This study was reviewed and approved by the Ethics Committee of Beijing Children’s Hospital Affiliated to Capital Medical University (IEC-C-008-A08-V.05.1). All methods were performed in accordance with the relevant guidelines and regulations. Because this is a retrospectively study, we obtained the data of patients

from the Medical Records and Statistics Room and we analyzed the data anonymously; thus, informed consent was not required. The Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University approved the waiver for this study.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Transparency declarations

None to declare.

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Figures

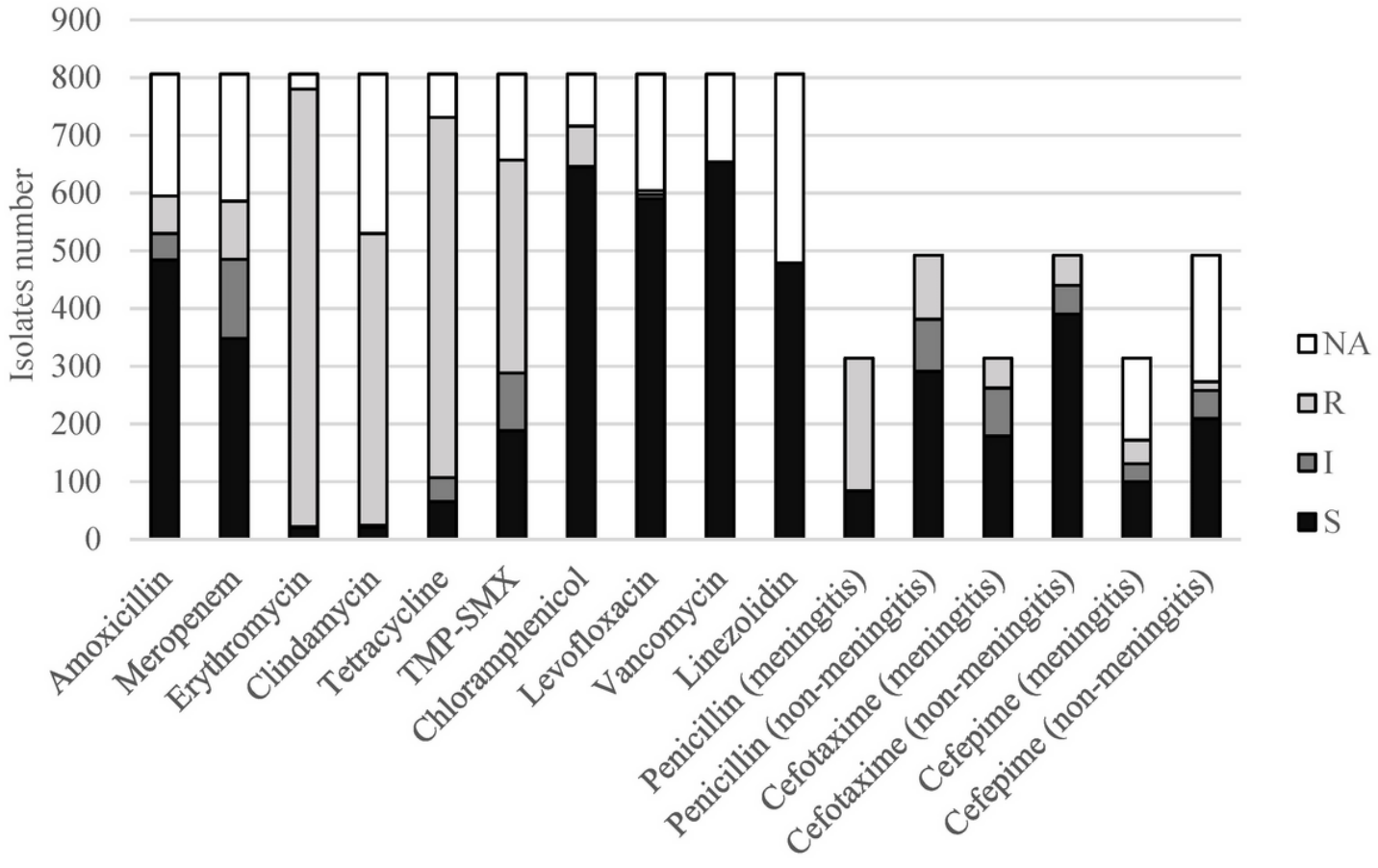

Figure 1

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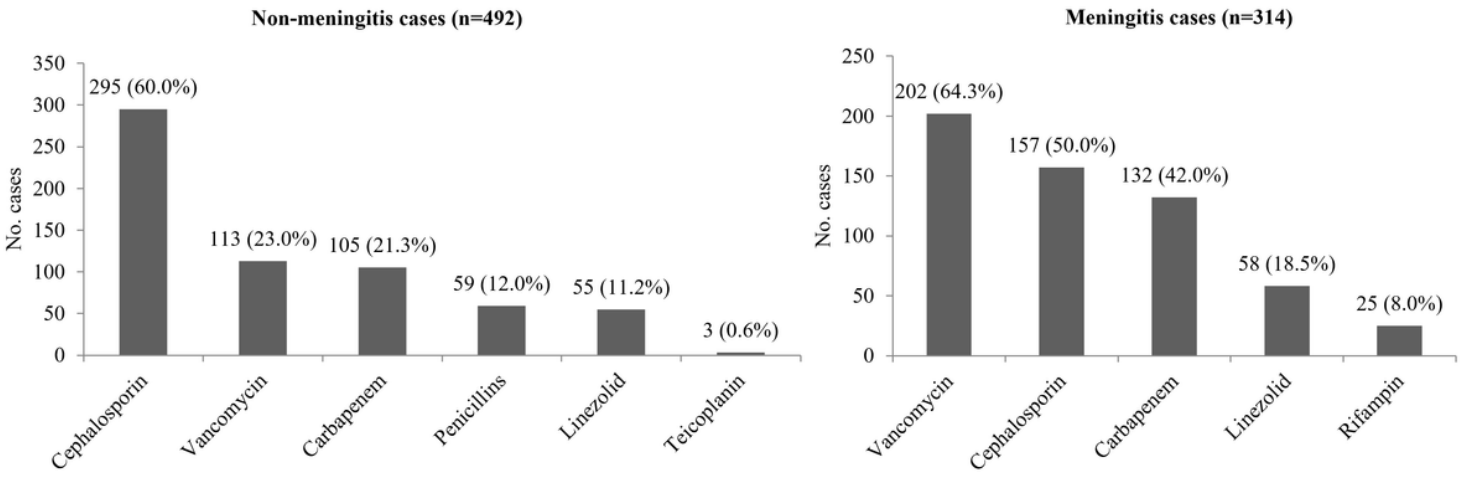

Figure 2

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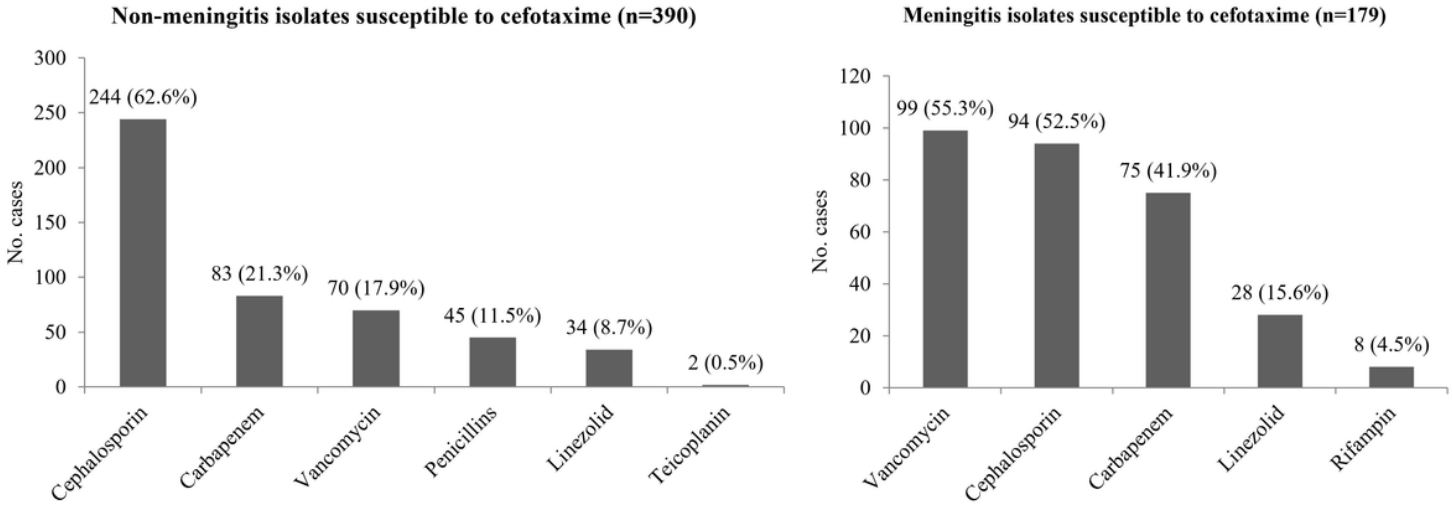

Figure 3

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