Infection and Drug Resistance

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ORIGINAL RESEARCH

Antimicrobial Resistance Among Pathogens Causing Bloodstream Infections: A Multicenter Surveillance Report Over 20 Years (1998–2017)

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Purpose: Bloodstream infections (BSIs) are a common consequence of infectious diseases and cause high morbidity and mortality. Appropriate antibiotic use is critical for patients' treatment and prognosis. Long-term monitoring and analysis of antimicrobial resistance are important in guiding physicians to choose appropriate antibiotics and understand the changes in antimicrobial resistance and infection control. Here, we report a retrospective study on the trends of antimicrobial resistance in the common BSI-associated pathogens.

Methods: The identification of strains and antimicrobial susceptibility tests were performed in each anticipating hospital independently. Data from the Hubei Province Antimicrobial Resistance Surveillance System (HBARSS) from 1998 to 2017 were retrospectively analyzed using WHONET 5.6 software.

Results: Data from HBARSS (1998–2017) revealed that 40,518 Gram-positive bacteria and 26,568 Gram-negative bacteria caused BSIs, the most common of which were *Staphylococcus aureus* and *Escherichia coli*. *Salmonella typhi* was a predominant BSI-associated pathogen in 1998–2003. Antimicrobial susceptibility data showed that the resistance rates of *E. coli* and *Klebsiella pneumoniae* to cefotaxime were significantly higher than those to ceftazidime. The proportion of strains of special antimicrobial resistance phenotypes including difficult-to-treat resistance (DTR), carbapenem-resistant (CR), extended-spectrum cephalosporin resistant (ECR) and fluoroquinolone resistant (FQR) in *E. coli* was 0.18%, 0.26%, 13.95%, 22.78% while in *K. pneumoniae* was 11.95%, 14.00%, 31.91% and 11.40%, respectively. In 2013–2017, *K. pneumoniae* showed resistance levels reaching 15.8% and 17.5% to imipenem and meropenem, respectively, and *Acinetobacter baumannii* showed high resistance rates ranging from 60 to 80% to common antibiotics. The detection rate of *Salmonella typhi* resistance to third-generation cephalosporins and fluoroquinolones was less than 5%. Control of methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major challenge, and in 2009–2017, the MRSA detection rate was 40–50%.

Conclusion: Prevalence of CR *K. pneumoniae* has increased significantly in recent years. Resistance rates of *A. baumannii* to common antimicrobial agents have increased exponentially, reaching high levels. MRSA remains a challenge to control. For *K. pneumoniae,* DTR, CR, ECR and FQR were antimicrobial resistance phenotypes that could not be ignored while for *E. coli* DTR and CR were rare antimicrobial resistance phenotypes. CR *K. pneumoniae, A. baumannii* and MRSA present major challenges for controlling BSIs.

Keywords: Hubei Province Antimicrobial Resistance Surveillance System, HBARSS, antimicrobial resistance, bloodstream infections, methicillin-resistant *Staphylococcus aureus*, MRSA, carbapenem-resistant

Introduction

Antimicrobial resistance is a major health-related issue of global concern. Long-term monitoring of bacterial resistance is important for implementing effective control measures.[1] Standardized and rational use of antibiotics can effectively reduce the occurrence of antimicrobial resistance.[1] The report of antimicrobial resistance surveillance, including

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antimicrobial resistance genotypes and molecular epidemiological data, was very valuable for the global infection control strategy.[2] At present monitoring systems for antimicrobial resistance in China operate at the national, provincial and hospital levels.[3]

Hubei Province is located in central China and has 13 prefectural administrative regions under its jurisdiction. The Statistics Bureau of Hubei Province reports that in 1998, the permanent population of Hubei Province was 58.91 million, and by the end of 2018, this number was 59.17 million. Of this population, 35.68 million people lived in towns, and 23.49 million people lived in villages.[4] The Hubei Province Antimicrobial Resistance Surveillance System (HBARSS) was founded in 1998 and initially consisted of 15 tertiary hospitals in different regions of Hubei Province. The number of network hospitals of HBARSS accounted for 13% of the general hospitals in Hubei province, while HBARSS covered 49.7% of the population in the whole province. Hospitals were added in 2003 and 2005, and 17 tertiary hospitals formed a monitoring network in Hubei Province. Since 2009, the monitoring network has been extended to secondary and tertiary hospitals across the entire province, and more than 50 hospitals have joined the monitoring network to date. The proportion of network hospitals from the registered hospitals for all of Hubei Province reached 14.45% (50/346) in 2018.

Bloodstream infections (BSIs) are a major cause of morbidity and mortality in adults and children.[5,6] Solid tumors, combined septic shock, indwelling catheters and continuous venovenous hemofiltration were independent risk factors affecting the prognosis of BSI patients.[7] Appropriate use of antibiotics is critical for their treatment and prognosis. At present, China is one of the largest users of antibiotics worldwide,[8] and antibiotic overuse remains a serious problem worldwide.[9] Here, we report a 20-year analysis of HBARSS for 1998–2017. Our findings provide a reference for monitoring changes of antimicrobial resistance and management of antibiotics.

Materials and Methods

Study Design and Procedures

To effectively analyze the accumulated susceptibility data and determine the trend in antimicrobial resistance for the major pathogens, only data from the initial 15 hospitals in 1998–2002, 16 hospitals in 2003–2004 and 17 hospitals in 2005–2017 were analyzed. Each network hospital independently cultured, identified and conducted antimicrobial susceptibility testing of the strains, and the data were submitted to HBARSS annually. Whonet 5.6 software was used to analyze the data of antimicrobial resistance tests.

Blood culturing was performed on patients who satisfied the clinical standards.[10] Automated blood culture instruments, including the BD 9120, 9240 and FX 400 (BD Co., NJ, USA) or the 3D 120, 240 and 720 (Bio Mérieux, Lyon, France), were used in each hospital in the monitoring network. Strains were identified following each laboratory's protocol, which combined various automated instruments or an IVD-MALDI Biotyper (Bruker, Karlsruhe, Germany) with manual biochemical experiments. Either the disk-diffusion method or an automated instrument was used for the antimicrobial susceptibility tests. From 1998–2010, all hospitals used the disk-diffusion method for antimicrobial susceptibility testing. From 2011–2017, six hospitals used automated instruments, and 11 used the disk-diffusion method. Automated instruments for antimicrobial sensitivity testing included the Vitek-2 Compact system (Bio Mérieux, Lyon, France) and the domestic antimicrobial sensitivity testing system (Dier, Zhuhai, China). Antimicrobial susceptibility tests were performed strictly in accordance with Clinical Laboratory Standards Institute (CLSI) standards. Each hospital routinely carried out indoor quality control and participated in the External Quality Assessment of the Ministry of Health of China. Laboratory quality control experiments strictly followed the CLSI guidelines of the corresponding year, and standard strains were tested once weekly.

Because *CoNS*, Corynebacterium, Bacillus, Propionibacterium and other potential skin contaminants frequently contaminate blood cultures, whether these organisms were colonizing, pathogenic or contaminating bacteria was determined from the available clinical data.[11]

Definition of Specific Antimicrobial Resistance Phenotypes

In this study difficult-to-treat resistance (DTR) was defined as resistant in vitro to all ß-lactam categories, including carbapenems and fluoroquinolones. Carbapenem resistant (CR) was defined as resistant in vitro to imipenem and

meropenem. Extended-spectrum cephalosporin resistant (ECR) was defined as resistant in vitro to ceftazidime, cefotaxime and cefepime. Fluoroquinolone resistant (FQR) was defined as resistant in vitro to ciprofloxacin and levofloxacin.

Statistical Analysis

Data were analyzed using WHONET 5.6 software. When multiple specimens were collected from the same patient simultaneously, only the first isolate of a given species from a patient was analyzed according to CLSI M-39.[12] Interpretation criteria for the antimicrobial susceptibility results were based on CLSI 2020 Guidelines.[13]

Ethical Statement

The study protocol was approved by the Tongji Hospital ethics committee for research in health. The Tongji Hospital ethics committee also approved the waiver of informed consent to participate in this study due to its retrospective design. All patient data were anonymous prior to the analysis.

Results

Distribution of Pathogenic Bacteria

From 1998–2017, 40,518 Gram-positive bacterial strains and 26,568 Gram-negative bacterial strains were isolated from BSIs via HBARSS. The ratio of Gram-positive to Gram-negative bacteria was approximately 3:2 (Figure 1). The most common Gram-positive bacteria were coagulase-negative *Staphylococcus* (*CoNS), Staphylococcus (S.) aureus, Streptococcus viride, Enterococcus faecalis* and *Enterococcus faecium* (N>1000), while *Escherichia (E.) coli, Klebsiella (K.) pneumoniae, Salmonella (S.) typhi, Pseudomonas (P.) aeruginosa, Stenotrophomonas (S.) maltophilia and Acinetobacter (A.) baumannii* (N>1000) were the most common Gram-negative bacteria.

Antimicrobial Susceptibility of Gram-Negative Bacteria

Both *E. coli* and *K. pneumoniae* showed higher resistance to the third-generation cephalosporin, cefotaxime, than to ceftazidime. The resistance rates of *E. coli* to ceftazidime and cefotaxime were 10.5–30.1% and 31.75–67.3%, respectively, whereas those of *K. pneumoniae* were 24–31.6% and 41.7–49.7%, respectively. The resistance rate of *E. coli* to fluoroquinolones was significantly higher than that of *K. pneumoniae*. The resistance rates of *E. coli* to ciprofloxacin and levofloxacin were 47.3–55.6% and 45.2–52.8%, respectively, and those of *K. pneumoniae* were 18.1–27.7% and 11.9–25.5%, respectively. The resistance rate of *K. pneumoniae* to carbapenems was significantly higher than that of *E. coli*. The resistance rates of *K. pneumoniae* to imipenem and meropenem were 2.4–15.8% and 1.8–17.5%, respectively, whereas those of *E. coli* were 0.8–2.3% and 0.8–1.3%, respectively (Table 1). *S. typhi* showed resistance to third-generation cephalosporins and fluoroquinolones, but the resistance rate was less than 6%. The resistance rate of *S. typhi* to ampicillin increased significantly from 6.9% in 1998–2002 to 38.5% in 2013–2017 (Table 2).

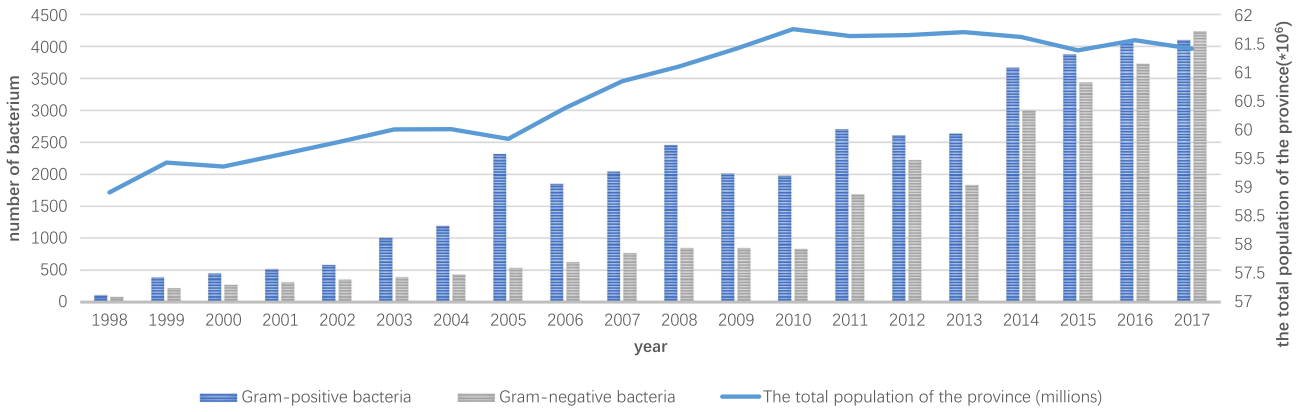

Figure 1 Demographic data and pathogens of BSI in Hubei Province.

Table 1 Resistance Rates of *Escherichia coli* and *Klebsiella pneumoniae* to the Common Antibiotics

	Escherichia coli								*Klebsiella pneumoniae*							
	1998–2002		2003–2007		2008–2012		2013–2017		1998–2002		2003–2007		2008–2012		2013–2017	
	n	R(%)	n	R(%)	n	R(%)	n	R(%)	n	R(%)	n	R(%)	n	R(%)	n	R(%)
Penicillins																
Piperacillin (100ug)	343	71.1	948	79.4	2652	81.1	4883	79	90	56.7	278	48.9	738	49.7	1960	52
β-Lactam combination agents																
Ampicillin clavulanic acid (20/10ug)	328	22	859	17.2	2468	17.7	4968	14.1	95	28.4	262	17.6	701	19.5	2005	29.6
Cefoperazone sulbactam (75/75ug)	/	/	930	9.2	2479	5.5	2962	7.6	48	18.8	259	12	688	9.3	1260	30.8
Piperacillin Tazobactam (100/10ug)	/	/	/	/	2062	4.7	6619	3.7	/	/	120	20.8	587	9.9	2560	20.4
Cephems (including cephalosporins I, II, III, and IV)																
Cefuroxime (30ug)	304	31.9	893	57.7	2520	68.4	5228	61.5	82	42.7	270	42.2	715	44.1	1889	45.8
Ceftazidime (30ug)	352	10.5	1015	17.7	2904	30.1	7137	26.6	96	24	290	25.9	810	27.7	2680	31.6
Cefotaxime (30ug)	356	31.7	989	56.6	2611	67.3	4467	62.5	97	42.3	288	41.7	695	44.3	1814	49.7
Cefepime (30ug)	/	/	973	33.4	2812	48.8	7122	41.3	38	39.5	279	29	780	30.1	2688	33.6
Cefoxitin (30ug)	/	/	824	12.7	2393	11.5	5136	7.5	/	/	239	18	674	13.9	1866	25.2
Monobactams																
Aztreonam (30ug)	329	14.6	969	25.6	2684	40.9	5704	37	90	34.4	278	25.9	745	30.2	2283	35.2
Carbapenems																
Imipenem (10ug)	341	2.3	1011	1.8	2850	1	7173	0.8	88	9.1	289	2.4	802	3.7	2685	15.8
Meropenem (10ug)	/	/	366	0.8	1988	1.2	6331	1.3	/	/	113	1.8	567	4.4	2372	17.5
Aminoglycosides																
Amikacin (30ug)	352	9.1	964	6	2870	6.2	6900	2.4	95	23.2	280	6.8	806	5.7	2620	12.7
Gentamicin (10ug)	352	47.4	992	55.1	2775	52.5	7152	39.5	96	35.4	285	23.2	793	25.7	2694	28.8
Fluoroquinolones																
Ciprofloxacin (5ug)	360	52.8	973	55.6	2448	54.3	7091	47.3	97	18.6	285	19.3	722	18.1	2668	27.7
Levofloxacin (5ug)	/	/	702	52.8	2190	54.6	6448	45.2	/	/	193	11.9	601	13.5	2511	25.5
Folate pathway antagonists																
Trimethoprim/sulfamethoxazole (1.25/23.75ug)	351	72.1	980	72.2	2636	62.8	7101	56.6	95	44.2	288	46.9	723	38.7	2673	31.6

Note: "/" indicated that the antibiotics had not been tested.

Table 2 Resistance Rates of *Salmonella typhi* to the Common Antibiotics

	1998–2002		2003–2007		2008–2012		2013–2017	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Penicillins								
Ampicillin (10ug)	202	6.9	116	15.5	69	26.1	52	38.5
Fluoroquinolones								
Ciprofloxacin (5ug)	194	4.1	119	4.2	66	3	54	3.7
Levofloxacin (5ug)	34	0	65	1.5	59	0	37	2.7
Folate pathway antagonists								
Trimethoprim/sulfamethoxazole (1.25/23.75ug)	182	22	121	25.6	66	10.6	57	8.8
Cephems								
Ceftazidime (30ug)	192	3.6	109	1.8	62	3.2	42	0
Cefatriaxone (30ug)	41	2.4	62	1.6	38	5.3	23	0
Cefotaxime (30ug)	196	6.1	104	1.9	58	8.6	32	3.1
Phenicols								
Chloramphenicol (30ug)	83	6	68	7.4	33	9.1	41	7.3

Most resistance rates of *P. aeruginosa* to common antibiotics were less than 30%. The resistance rates of *A. baumannii* to common antimicrobial agents increased significantly from less than 50% in 2003–2007 to 55–70% in 2008–2012 (except to cefoperazone sulbactam) and to 60–80% in 2013–2017. From 1998 to 2017, the detection rates of extensively drug-resistant *A. baumannii* and *P. aeruginosa* were 34.38% (493/1434) and 7.45% (140/1879), respectively (Table 3). *S. maltophilia* was not resistant to ceftazidime in 1998–2012 but then showed a resistance rate of 58.1% in 2013–2017 (Table 4).

Epidemiology of Methicillin-Resistant *Staphylococcus aureus* (MRSA)

The MRSA detection rate was 10–30% in 1998–2003, which increased to 20–70% in 2004–2007 and 40–50% in 2009–2017 (Figure 2). The resistance rate of MRSA to common antibiotics was significantly higher than that of MSSA. The resistance rate of MRSA to trimethoprim/sulfamethoxazole decreased significantly from 69.9% in 1998–2002 to 3.8% in 2012–2017, and that of MSSA decreased significantly from 29.2% in 2003–2007 to 3.3% in 2013–2017 (Table 5).

Distribution of Specific Antimicrobial Resistance Phenotypes

For *E. coli*, DTR and CR were rare drug-resistant phenotypes, accounting for 0.18% (21/11597) and 0.26% (30/11597) respectively. While ECR and FQR were the main drug-resistant phenotypes, accounting for 13.95% (1618/11597) and 22.78% (2642/11597) respectively. But for *K. pneumoniae, ECR* were the most common drug-resistant phenotype, accounting for 31.91% (622/3949). The distribution proportion of DTR, CR and FQR was almost equal, accounting for 11.95% (233/3949), 14.00% (273/3949) and 11.40% (450/3949) respectively (Figure 3).

Discussion

Surveillance data during 1998–2017 in Hubei Province showed that the most common BSI-associated Gram-negative and Gram-positive bacteria were *E. coli* and *S. aureus*, respectively. This finding was consistent with that of the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS) report for 2002–2009[14] but differed from reports from Malawi, Africa, which showed that non-typhoid *Salmonella, S. typhi* and *Streptococcus pneumoniae* were the main BSI-associated pathogens.[6] Our findings were consistent with the previous reports in China. A study on trends in antimicrobial resistance in BSI at the first affiliated hospital of Zhengzhou University in China indicated *E. coli, K. pneumoniae, S. aureus, A. baumannii* and *P. aeruginosa* were the most common pathogen.[15]

Our study showed that *S. typhi* was also a main BSI-associated pathogen in Hubei Province during 1998–2003. Typhoid fever is a poverty-related disease, mainly occurring in Africa and Asia, with a low incidence in economically

Table 3 Resistance Rates of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to the Common Antibiotics

	Acinetobacter baumannii								*Pseudomonas aeruginosa*							
	1998–2002		2003–2007		2008–2012		2013–2017		1998–2002		2003–2007		2008–2012		2013–2017	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Penicillins																
Piperacillin (100ug)	9	22.2	64	50	341	69.5	760	78.8	99	24.2	189	29.1	473	23.7	1065	21.4
β-Lactam combinationagents																
Cefoperazone sulbactam (75/75ug)	/	/	62	12.9	299	24.4	643	63.1	/	/	/	/	/	/	/	/
Piperacillin Tazobactam (100/10ug)	/	/	36	41.7	245	62	876	74.9	/	/	89	19.1	334	13.2	1046	15.6
Cephems																
Ceftazidime (30ug)	10	30	68	42.6	351	63	879	76.5	100	26	191	18.8	471	21	1079	19
Cefepime (30ug)	/	/	65	38.5	310	62.9	986	75.4	/	/	175	17.7	465	21.3	1081	19.9
Carbapenems																
Imipenem (10ug)	/	/	68	23.5	334	61.1	989	74.4	95	16.8	189	21.2	473	23.7	1079	30.6
Meropenem (10ug)	/	/	30	20	272	58.1	829	76.1	/	/	87	14.9	381	21.8	935	25.6
Aminoglycosides																
Amikacin (30ug)	10	20	64	39.1	351	59.8	916	67.7	101	16.8	186	17.7	480	20.2	1063	14.3
Gentamicin (10ug)	10	40	65	49.2	344	67.4	986	75.5	103	23.3	186	29.6	468	26.3	1075	21.2
Fluoroquinolones																
Ciprofloxacin (5ug)	10	40	63	31.7	317	57.7	969	74.5	98	17.3	187	17.1	423	18.4	1069	17.5
Levofloxacin (5ug)	/	/	46	28.3	273	57.9	928	69.6	/	/	107	21.5	326	13.8	939	17.3
Folate pathway antagonists																
Trimethoprim/sulfamethoxazole (1.25/23.75ug)	8	25	68	50	268	63.4	962	74.3	/	/	/	/	/	/	/	/

Note: "/" indicated that the antibiotics had not been tested.

Table 4 Resistance Rates of *Stenotrophomonas maltophilia* to the Common Antibiotics

	1998–2002		2003–2007		2008–2012		2013–2017	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Fluoroquinolones								
Levofloxacin (5ug)	16	6.2	191	1	266	1.9	520	4.2
Folate pathway antagonists								
Trimethoprim/sulfamethoxazole (1.25/23.75ug)	38	10.5	243	9.5	268	22.4	531	11.1
Cephems								
Ceftazidime (30ug)	41	0	171	0	102	0	365	58.1
Phenicols								
Chloramphenicol (30ug)	24	0	90	0	19	0	259	5

developed regions such as Europe and the United States.[16–20] Typhoid fever is transmitted mainly through contaminated food and drinking water.[21] The incidence of *S. typhi*-related BSIs in rural children was reported to be 2–3 times higher than that in urban children.[22] The different incidences in different areas may be related to local medical and health conditions and vaccination rates. These factors may also have contributed to the high incidence in Hubei Province during 1998–2003. Reports from Africa suggested that *S. typhi* and non-*S. typhi* were consistently the most common pathogens of BSIs.[6] *Salmonella* infections are frequently associated with human immunodeficiency virus infections, very young or elderly patients, clinical malaria and malnutrition, and can be fatal in up to 20–25% of patients.[23,24] Reports from Africa showed that *Salmonella* was often resistant to first-line antibiotics such as chloramphenicol, sulfonamide and ampicillin.[25,26] In our study, the resistance rate of *S. typhi* to ampicillin increased from 6.9% in 1998–2002 to 38.5% in 2013–2017, and resistance rates to other antibiotics were lower than 10% in 2013–2017. The significant increase of antimicrobial resistance to ampicillin might be related to the extensive use of ampicillin. Given the fact that the target of ampicillin is located in the cell wall, and human just lack the cell wall, the use of ampicillin for treatment is relatively safe, which leads to the extensive use of ampicillin in clinical treatment. Resistance to fluoroquinolones and third-generation cephalosporins has also been reported in several African countries.[27,28] Our data showed that *S. typhi* resistance to third-generation cephalosporins and fluoroquinolones has emerged, but in 1998–2017, the detection rate was less than 5%. The disadvantages of this study was that we did not detect the antimicrobial resistance gene of

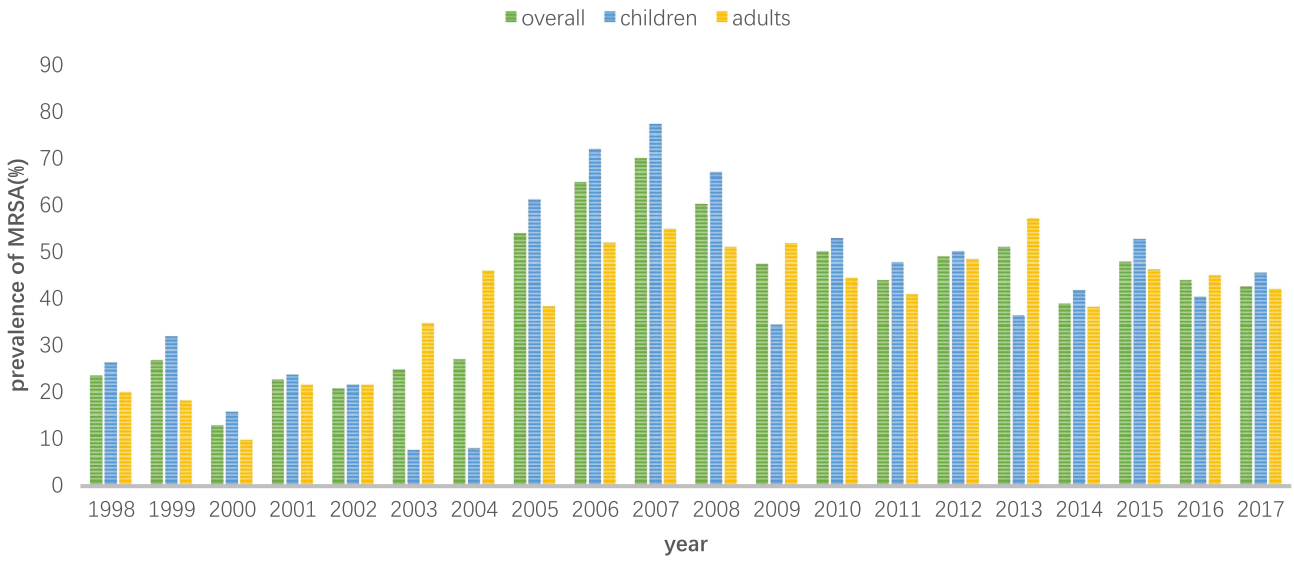

Figure 2 Prevalence of MRSA (%) in adults (≥18 years) and children (<18 years).

Table 5 Resistance Rates of MRSA and MSSA to the Common Antibiotics

	MRSA								MSSA							
	1998–2002		2003–2007		2008–2012		2013–2017		1998–2002		2003–2007		2008–2012		2013–2017	
	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)	n	R (%)
Aminoglycosides																
Gentamicin (10ug)	89	38.2	345	55.4	442	56.6	520	77.9	305	5.6	431	9.7	524	10.5	421	10.7
Fluoroquinolones																
Levofloxacin (5ug)	/	/	/	/	380	53.9	455	82.6	/	/	/	/	446	7.8	305	7.5
Folate pathway antagonists																
Trimethoprim/sulfamethoxazole (1.25/23.75ug)	83	69.9	379	64.9	435	41.1	504	3.8	300	26.7	449	29.2	501	22.2	397	3.3
Lincosamides																
Clindamycin (2ug)	72	61.1	388	67.5	462	63.6	514	55.3	265	30.6	446	28.7	541	21.4	401	19.5
Macrolides																
Erythromycin (15ug)	90	85.6	393	89.1	461	85.7	526	72.4	313	62.3	451	54.8	540	54.1	422	46.2
Oxazolidinones																
Linezolid (30ug)	/	/	/	/	/	/	487	0	/	/	/	/	/	/	376	0
Glycopeptides																
Vancomycin (30ug)	90	0	393	0	370	0	475	0	319	0	454	0	444	0	326	0
Teicoplanin (30ug)	/	/	360	1.1	434	1.2	491	0.2	/	/	424	0	476	0.2	329	0

Note: "/" indicated that the antibiotics had not been tested.

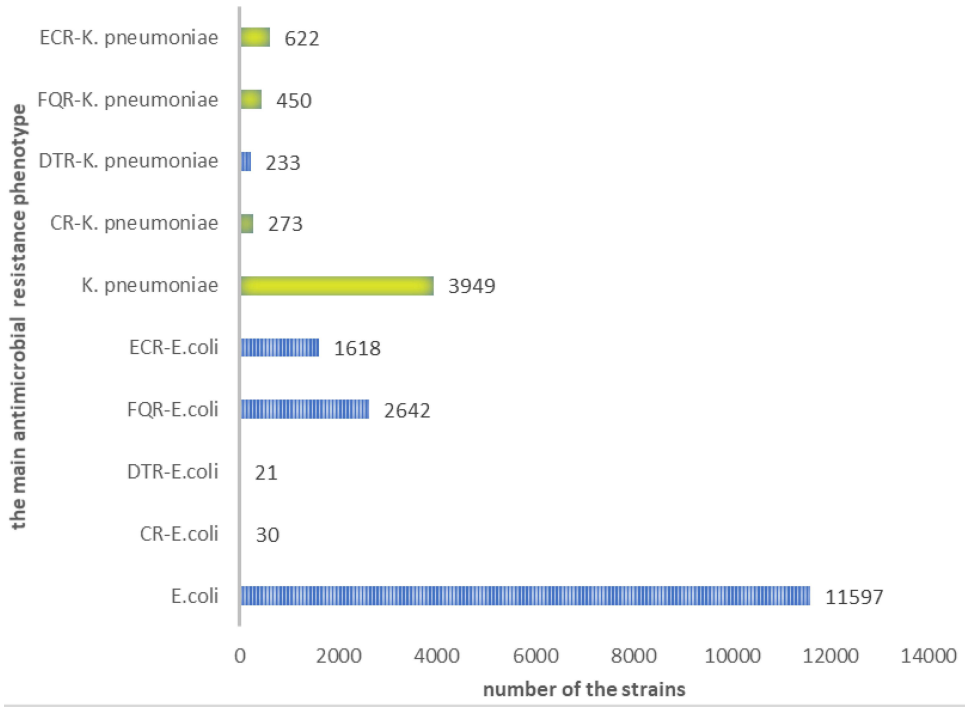

Figure 3 Distribution of the main antimicrobial resistance phenotypes.

Salmonella typhi. More and more studies showed that surveillance genomic data could accelerate understanding of virulence and antimicrobial resistance.[29,30]

Antibiotic susceptibility tests showed that the resistance rates of *E. coli* and *K. pneumoniae* to third-generation cefotaxime were significantly higher than those to ceftazidime, which is consistent with the 30-year data reported from CHINET in China.[3] Wang et al showed that CTX-M was the most important ESBL type in China and that cefotaxime resistance might be a sign of ESBL-producing bacterial strains.[31] *E. coli* and *K. pneumoniae* showed low resistance to amikacin, cefoperazone/sulbactam and imipenem; thus, these antibiotics might be used as empirical treatment options. Notably, in 2013–2017, the rates of *K. pneumoniae* resistance to imipenem and meropenem reached 15.8% and 17.5%, respectively. Studies have confirmed that mortality rates of patients infected with carbapenem-resistant (CR) *K. pneumoniae* strains are significantly higher than those of patients infected with carbapenem-sensitive strains.[32,33] CR *K. pneumoniae* strains often exhibit combined resistance to cephalosporins, fluoroquinolones, aminoglycosides, beta-lactamase inhibitors and other antimicrobial agents.[34] Few antimicrobial agents, including tigecycline and polymyxin, can be used to treat CR *K. pneumoniae*. [35] *K. pneumoniae* resistant to colistin has emerged and colistin resistance was mainly associated with deleterious mutations and transposon in the mgrB gene.[36] The resistance mechanism of *Enterobacteriaceae* to carbapenems is very complex. Producing carbapenemase including KPC, IMP, NDM-1, OXA-48 and AmpC enzyme, or Extended-Spectrum β-Lactamases (ESBLs) including TEM, SHV, CTX may be the primary mechanisms.[37] The study performed by Gao et al in our province showed that KPC-2 was the most common carbapenemase-resistant gene in *K. pneumoniae* to Carbapenems, whereas NDM-1 was more common in *E. coli*.[37]

This study revealed that *P. aeruginosa* and *A. baumannii* were the most common non-fermentative Gram-negative bacteria that caused BSIs. Susceptibility tests showed that resistance rates of *P. aeruginosa* to most antibiotics were less than 30%. However, these results differed from those reported in a multicenter epidemiological study on the risk factors and clinical outcomes of nosocomial intra-abdominal infections in China (the Chinese antimicrobial resistance surveillance of nosocomial infections [CARES] 2007–2016), which indicated that *P. aeruginosa* showed high resistance to a variety of antimicrobial agents, except amikacin, whose susceptibility rate was 83.4%.[38] The antimicrobial susceptibility profiles of *A. baumannii* isolates from BSIs were similar to those of *A. baumannii* isolates from abdominal infections. *A. baumannii* was alarmingly resistant to diverse antibiotics, including third-generation cephalosporins,

aminoglycosides, fluoroquinolones and carbapenems.[38] In this study, resistance rates of *A. baumannii* to common antibiotics increased significantly in 1998–2017. In 2003–2007, the antimicrobial resistance rate of *A. baumannii* was less than 50%, but by 2013–2017, the resistance rate reached 60–80%. The emergence of multidrug-resistant *A. baumannii*, especially extensively drug-resistant and fully drug-resistant strains, has made clinical treatment difficult. A retrospective study from Oman indicated *A. baumannii* strains were highly resistant (50–83%) to most of the tested antibiotics, with the highest against ceftriaxone (83%) and ceftazidime (75%), and lowest against colistin (1%) and tigecycline (8%).[39] According to CLSI guidelines, *S. maltophilia* showed standard resistance levels to minocycline, levofloxacin and trimethoprim/sulfamethoxazole as determined by disk-diffusion tests, but MIC testing showed break points for ticarcillin/clavulanic acid, ceftazidime and chloramphenicol, minocycline, levofloxacin and trimethoprim/sulfamethoxazole.[13] Therefore, some hospitals could increase the antimicrobial sensitivity test results of some antibiotics after changing disk-diffusion tests to MIC tests. For example, for *S. maltophilia*, disk diffusion method had only three antimicrobial break points, while MIC method had six antimicrobial break points. As a result, clinicians had more choices in the empirical treatment. However, the disadvantage of the change of antimicrobial sensitivity test methodology was that the cumulative antimicrobial sensitivity data were inevitably biased when comparing data for many years. In this study, the resistance rate of *S. maltophilia* to ceftazidime increased to 58.1% in 2013–2017, whereas the resistance rates of *S. maltophilia* to other antimicrobial agents were less than 25%. Whether the increase in ceftazidime resistance was related to its wide clinical application requires further investigation and analysis.

Surveillance data on BSIs during 1998–2017 showed that the resistance rate of *A. baumannii* to common antibiotics has reached a high level, and the prevalence of CR *K. pneumoniae* has increased significantly, resulting in significant difficulties in clinical treatment. Our data show that vancomycin, teicoplanin, linezolid and trimethoprim/sulfamethoxazole can be used to treat MRSA. The resistance rate of MRSA to trimethoprim/sulfamethoxazole has decreased significantly, possibly related to the decreased of use of this antibiotics in recent years. Studies from China, South Korea and France have shown that the antimicrobial resistance rates of *S. aureus, K. pneumoniae, E. coli, P. aeruginosa* and *Candida albicans* also decreased with the decreased clinical use of these antimicrobial agents.[40–43] Tigecycline and polymyxin can be used to empirically treat CR *K. pneumoniae, E. coli* and *A. baumannii*.[44]

This study had several limitations. The BSI incidence in Hubei Province was often reported from single research centers. We failed to find accurate data on the BSI incidence for all of Hubei Province during 1998–2017. Previous reports lacked demographic data. One shortcoming of this study was that the accurate BSI incidence was not calculated for Hubei Province. Another limitation was that different hospitals used different strain identification methods, including manual biochemical experiments and an IVD-MALDI Biotyper, and these results were undistinguishable once combined. Different hospitals adopted different antimicrobial sensitivity test methods, and the same hospital may change the antimicrobial sensitivity test method used between 1998 and 2017. Although each hospital strictly followed the CLSI guidelines, the inconsistency of test methods and the difference of antimicrobial sensitive consumables may lead to deviation in the analysis of antimicrobial resistance. The weakness of the analysis of the resistance mechanism involved in Gram-negative resistance to beta-lactams and more particularly to carbapenems was also a limitation of this study. We will increase the content of antimicrobial resistance mechanism research in the future.

Conclusion

CR *K. pneumoniae, A. baumannii* and MRSA present major challenges to controlling BSIs. *S. typhi* resistant to the third generation cephalosporins and quinolones has emerged, but the drug resistance rates were all less than 5%. For *K. pneumoniae* DTR, CR, ECR and FQR were antimicrobial resistance phenotypes that could not be ignored while for *E. coli* DTR and CR were rare antimicrobial resistance phenotypes.

Abbreviations

BSI, Bacterial bloodstream infection; HBARSS, Hubei Province Antimicrobial Resistance Surveillance System; DTR, difficult-to-treat resistance; CR, Carbapenem-resistant; FQR, Fluoroquinolone resistant; ECR, Extended-spectrum cephalosporin resistant; CoNS, coagulase-negative staphylococcus; EARS-Net, European Antimicrobial Resistance Surveillance Network; CARES, Chinese antimicrobial Resistance surveillance of nosocomial Infections; MRSA,

Methicillin-resistant S. aureus; CDC, Centers for Disease Control and Prevention; CLSI, Clinical Laboratory Standards Institute.

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