

MDR/XDR *Acinetobacter baumannii* hospital infection associated with high mortality: A retrospective study in the PICU

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Research article

Keywords: MDR/XDR, *Acinetobacter baumannii*, Risk Factors, Mortality, Pediatric Intensive Care Units

Posted Date: December 23rd, 2019

DOI: <https://doi.org/10.21203/rs.2.19520/v1>

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Version of Record: A version of this preprint was published on August 12th, 2020. See the published version at <https://doi.org/10.1186/s12879-020-05321-y>.

Abstract

Background

Multiple drug-resistant (MDR) and extensively drug-resistant (XDR) *Acinetobacter baumannii* presents challenges for clinical treatment and causes high mortality in children. We aimed to assess the risk factors for MDR/XDR *Acinetobacter baumannii* (MDR/XDR-AB) infection and for 28-day mortality in this patient population.

Methods

This retrospective study included 102 pediatric patients who developed MDR/XDR-AB infection in the pediatric intensive care unit (PICU) of Shanghai Children's Hospital in China from January 2015 to December 2017. Clinical presentations and outcome of the patients were analyzed.

Results

Of the 102 patients (63 males and 39 females; mean age: 51.79 months), There were 63 (61.77%) male in the case group. The 28-day mortality rate was 29.41%. 18(17.64%) had bloodstream infections;4(3.92%) for which cerebrospinal fluid (CSF) cultures were positive; 14(13.73%) of them got positive cultures in aseptic fluid; 10 (9.8%) had central line-associated bloodstream infections; lower respiratory isolates (56/102) accounted for 54.9% of all patients. Multivariate logistic analysis indicated that high serum level of BUN (RR, 1.216, 95%CI, 1.27-2.616; P = 0.001) and high serum level of Cr (RR, 1.823, 95%CI, 0.902-0.980), were associated with high risk of mortality in MDR/XDR-AB infected patients.

Conclusion

MDR/XDR-Ab infection is a serious concern in pediatric patients with high mortality (29.41%). Mortality rate is higher in blood stream infection and central nervous system infection. Acute kidney injury is associated with high risk of mortality. Early use of tigarecycline might be involved in improving MDR/XDR-AB bacteremia.

Introduction

Acinetobacter baumannii is a Gram-negative coccobacillus that has a remarkable Ability to acquire antibiotic resistance which embarrassed for decades for causing persistent nosocomial infections.(1, 2) The propensity of *A. baumannii* to be multidrug-resistant (MDR) or extensively drug-resistant (XDR) presents therapeutic challenges.(3, 4) Invasive operations such as intra trachea mechanical ventilation, inserted invasive devices, intensive care unit stay, recent surgery, use of broad-spectrum antibiotics, ineffective management, and septic shock at diagnosis are reported as risk factors for colonization or infection by MDR *A. baumannii* and higher mortality(5, 6).

The incidence of MDR/XDR-AB is higher in children in pediatric intensive care unit (PICU) than in other patients on concern of severe underlying diseases, immune deficiency, and invasive operations.(7) the

mortality rate varies from 18.26–88.7% depending on the infection source.(7–9) The problems for pediatrician in China are polymyxins cannot be obtained, tigecycline only became available in late 2016, and had limited experience in manage these young patients.(10) (11)

Few studies have evaluated the risk factors for *A. baumannii* infection in Chinese pediatric patients. The objective of our study was to describe severe infections with MDR/XDR AB, as well as to investigate risk factors for mortality, in PICU patients.

Material And Methods

This retrospective study included pediatric patients who developed MDR/XDR-AB infection in the pediatric intensive care unit (PICU) of Shanghai Children’s Hospital in China.

Identification of MDR/XDR-AB was confirmed by positive blood, sputum, aseptic fluid or catheter culture as well as symptoms and signs of infection. Susceptibility testing to the tested antibiotics was determined according to the Clinical and Laboratory Standards Institute (CLSI) interpretive criteria for disk diffusion method(12). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. (13). Diagnosis of ventilation-associated-pneumonia (VAP) was made according to the recommendation by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). VAP involving XDR AB was defined as clinical evidence of pneumonia along with a positive bronchoalveolar lavage fluid (BALF) or tracheal aspiration culture of XDR AB from 48 h after intra-tracheal intubated mechanical ventilation. Tracheal aspirate specimens were qualified for performing cultures as at least 25 neutrophils and less than 10 epithelial cells per low-power field on Gram staining.

Clinical conditions and outcomes

Clinical, biological and treatment data were obtained retrospectively from the patients’ medical records. Underlying illnesses at the time of admission to the PICU were classified and pediatric risk of mortality \square (PRISM \square) scores were measured at the time of PICU admission. The 28-day mortality was defined as the mortality within 28days stay or left PICU.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation, and comparative analysis was conducted using an independent sample nonparametric test. The chi-square test or Fisher’s exact test was conducted. The Mann-Whitney test was used for continuous variables. Variables showing $p < 0.05$ in a univariate analysis were included in a multivariate analysis, which was performed by stepwise logistic regression. All statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical manifestations

During the study period of January 1, 2015 and December 31, 2017, a total of 102 episodes of MDR/XDR *Acinetobacter baumannii* in 102 patients were identified, their demographics and clinical features were summarized in Table 1. The overall incidence of MDR/XDR AB was 0.48 cases/1000 patient-days, and we observed a continually increased distribution of cases during the study period. Both the incidence and mortality were growing higher in the latest 6 months (Table 2). In 18 cases (17.65%), surveillance blood cultures became positive after clinical manifestation appeared, while 9 catheter (8.82%) and 16(15.68%) aseptic fluid were identified MDR/XDR AB positive. 19 (18.63%) episodes had tracheal aspirate cultures positive, and the other 37 (36.27%) had positive sputum cultures for MDR/XDR AB. The mean age was 51.79 months and male predominated (61.76%). 51 patients had surgery (50%) and 70 treated with corticosteroids (68.6%), all these patients received broad-spectrum antibiotics treatment for more than one week.

Table 1
 The Basic Characteristics of XDR Acinetobacter baumannii patients

Characteristics (n,%)		Survivors (n = 72,70.59%)	Nonsurvivors (n = 30,29.41%)	Odds Ratio (95%CI)	P value
Age, mean ± SD, month		30 (9.6, 88.75)	42 (9.825, 102.75)		0.504
Male/Female (n=)		44/28	19/11		0.83
Underlying disorders	Pneumonia(n,%)	61, 84.7%	25, 83.3%	0.902 (_0.284,2.862)	0.86
	Meningitis(n,%)	1, 1.38%	6, 20%	17.75 (2.033,154.993)	< 0.001*
	Leukemia/ Solid tumor(n,%)	6, 8.33%/ 10, 13.89%	6, 20%/ 11, 33.3%	4.577 (1.84, 51.383)	< 0.001
	Trauma(n,%)	3, 4.17%	0, 0%	0.557 (0.547, 0.567)	0.553
	Sepsis(n,%)	65, 90.27%	25, 83.33%	0.538 (0.156, 1.855)	0.321
	Peritonitis(n,%)	8, 11.11%	8, 26.67%	2.909 (0.975, 8.68)	0.049*
	Cardiovascular disease(n,%)	8, 11.11%	5, 16.67%	1.35 (0.401, 0.454)	0.627
	Hepatic disorder(n,%)	5, 6.94%	2, 6.67%	0.814 (0.149, 4.462)	0.813
	Others(n,%)	10, 13.89%	5, 16.67%	1.24 (0.385, 3.994)	0.718
WBC count(*10 ⁹ /L)	M(Q1,Q3)	7.99 (5.81, 13.62)	5.1 (1.64, 14.78)		0.046*
Neutropenia(*10 ⁹ /L)	M(Q1,Q3)	4.88 (3.51, 9.1)	3.37 (0.61, 11.05)		0.158
CRP(mg/L)	M(Q1,Q3)	37 (10, 74)	27 (16, 94.5)		0.406
PCT (ng/L)	M(Q1,Q3)	0.48 (0.18, 5.08)	1.56 (0.53, 8.27)		0.066
Lactate(mmol/L)		3.12 ± 2.9	3.09 ± 2.42		0.955
PRISM		6.73 ± 5.19	8.3 ± 4.76		0.183

*p < 0.05

Characteristics (n,%)	Survivors (n = 72,70.59%)	Nonsurvivors (n = 30,29.41%)	Odds Ratio (95%CI)	P value
Shock	18, 25%	16, 53.33%	3.429 (1.403, 8.382)	0.006*
PaO2/FiO2	269 ± 113.55	220.96 ± 150.16		0.139
Exposure factors				
Steroid (n=, %)	49, 68.06%	21, 70%	1.619 (0.662, 3.963)	0.289
Immune suppressor (n=, %)	11, 15.27%	8, 26.67%	2.017 (0.718, 5.665)	0.263
Length of hospital day(day,M(Q1,Q3))	28 (17, 49.5)	36 (26.75, 45.25)		0.212
Length of broad- spectrum antibiotic therapy (day,M(Q1,Q3))	22 (12, 43)	31.5 (24.75, 41.5)		0.123
Length of mechanical ventilation(day, M(Q1,Q3))	6 (1, 15)	10 (6, 25)		0.02*
Length of CRRT/ECMO(h, M(Q1,Q3))	0 (0, 0)	0 (0, 6)		0.02*
Central vein catheter (n=, %)	69, 95.83%	30, 100%	1.435 (1.26, 1.634)	0.256
Arterial catheter (n=, %)	58, 80.56%	29, 96.67%	7.0 (0.877, 55.872)	0.036*
Intra trachea intubation (n=, %)	57, 79.17%	29, 96.67%	7.632 (0.96, 60.662)	0.027*
Operation (n=, %)	31, 43.06%	20, 66.67%	2.645 (1.085, 6.448)	0.03*
*p < 0.05				

Table 2

□Type of initial infection and the infection trends over the years

	2014–2015 (n =15)	2016 (n =18)	2017 (n =34)	2018 (n =34)
Bloodstream (n)	4	3	5	6
Central nervous infection(n)	1	0	1	2
Pneumonia (n)	4	8	23	21
Central-catheter associated (n)	0	3	3	3
Aseptic fluid (n)	6	4	2	2
28-day mortality (n,%)	6(40%)	4(22.22%)	7(20.59%)	13(38.24%)

Organ function and immune status of MDR/XDR AB. infected patients

Table 3. listed the organ function of patients at diagnose of MDR/XDR AB infection, as the concern of the importance of immunologic function in the process of anti-inflammatory pathophysiological, the indicators of immune function as well as serum cytokine levels were recorded in Table 4. It seems that no significant differences lies in the organ functions at diagnose of MDR/XDR AB infection, but non-survival patients appeared to have a lower NK cell activity ($5.23\% \pm 3.62\%$ vs. $9.17\% \pm 6.58\%$, $P = 0.005$), higher CD4⁺ T cell ratio ($39.074\% \pm 12.18\%$ vs. $31.84\% \pm 11.46\%$, $P = 0.03$), at the same time, a higher serum level of interleukin-8 (IL-8, 315.85 ± 552.09 pg/ml vs. 21.08 ± 51.59 pg/ml, $P = 0.01$) was noticed, which revealed a stronger inflammatory response in this group of patients.

Table 3

Organ function of patients at diagnose of MDR/XDR Acinetobacter baumannii infection

Organ		Survivors	Nonsurvivors	P value
Cardiovascular				
	MAP(mmHg) (mean \pm SD)	64.02 \pm 12.99	58.03 \pm 15.61	0.254
	EF(%)(mean \pm SD)	65.14 \pm 7.06	66.78 \pm 3.09	0.418
	CI(L/min.m2) (mean \pm SD)	3.94 \pm 1.11	5.83 \pm 3.47	0.267
	LA(mmol/L) (mean \pm SD)	3.12 \pm 2.9	3.09 \pm 2.42	0.309
Respiratory				
	PEEP(cmH2O) (mean \pm SD)	4.84 \pm 1.11	6.24 \pm 2.02	0.21
	Tidal volume(ml/kg) (mean \pm SD)	8.11 \pm 0.92	7.98 \pm 0.83	0.276
	PaO2/FiO2 (mean \pm SD)	220.96 \pm 150.16	269 \pm 113.55	0.139
	Plateau pressure (cmH2O) ((M(Q1,Q3))	10 (9, 12)	11 (10, 13)	0.191
Hepatic				
	TBIL(mmol/L) ((M(Q1,Q3))	3.25 (2.3, 5.175)	10.86(6.64, 18.85)	0.236
	ALT(U/L) ((M(Q1,Q3))	25.5 (14, 48)	20 (11.75, 34.75)	0.425
Renal				
	BUN(mmol/L) (mean \pm SD)	4.22 \pm 2.92	8.18 \pm 9.52	0.204
	Cr(umol/L) (mean \pm SD)	35.04 \pm 31.52	29.27 \pm 29.15	0.314
Nervous				
	Glasgow(mean \pm SD)	10.97 \pm 2.93	10.03 \pm 3.14	0.173
Gastric-intestine				
	Intra-abdominal pressure(cmH2O) (mean \pm SD)	7.46 \pm 4.15	8.95 \pm 5.01	0.303

Table 4

The immunologic function and serum cytokines levels in the patients

Characteristics	Survivors	Nonsurvivors	P value
NK (%) (mean \pm SD)	9.15 \pm 6.21	6.2 \pm 3.61	0.029*
IgG(g/L) (mean \pm SD)	10.37 \pm 4.59	10.56 \pm 4.84	0.78
IgA(g/L) (mean \pm SD)	1.01 \pm 0.92	0.94 \pm 0.86	0.77
IgM(g/L) (mean \pm SD)	1.03 \pm 0.65	0.66 \pm 0.45	0.02*
CD4 ⁺ (%) (mean \pm SD)	32.66 \pm 11.44	39.67 \pm 12.18	0.039*
CD8 ⁺ (%) (mean \pm SD)	28.72 \pm 13.83	31.38 \pm 10.29	0.43
CD19 ⁺ (%) (mean \pm SD)	31.38 \pm 10.29	23.74 \pm 17.18	0.17
IL-6(pg/ml) (M(Q1,Q3))	0.1(0.1, 22.25)	323.86 (0.1, 733.62)	0.14
IL-8(pg/ml) (M(Q1,Q3))	0.1 (0.1, 22.99)	15.25 (1.62, 47.22)	0.01*
IL-10(pg/ml) (M(Q1,Q3))	6.05 (0.1, 21.81)	16.13 (0.1, 55.07)	0.22
*p < 0.05			

Table 5

Logistic regression of risk factors

variable	OR (95%CI)	P value
BUN (mmol/L)	1.823 (1.270–2.616)	0.001*
Cr (mmol/L)	0.94 (0.902–0.980)	0.004*
P < 0.05*		

Drug resistance results of MDR/XDR AB

Bacteriological findings are summarized in Fig. 1. (Antimicrobial resistance in 102 *A. baumannii* clinical isolates). MDR/XDR AB. was resistant to carbapenems, aminoglycosides, most cephalosporins and sulfa drugs. Their resistance rates were more than 75%. Only tigecycline, polymyxin had a high sensitivity to MDR/XDR AB. (89.87%, 96.67%). The resistance rates of cefoperazone-sulbactam was 44%, while had an intermediary rate of 43%.

Outcomes

All the patients received active antibiotic treatment within 7 days. Regarding treatment given within 7 days, based on the in vitro susceptibility test, cefoperazone/sulbactam, tigecycline, polymyxin were the recommended antimicrobial agents for XDR *A. baumannii* eradication. Before Jan. 2017, the patients received cefoperazone/sulbactam combined with carbapenems after appearance of MDR/XDR AB during January to December 2017, as tigecycline became available, 28 patients were treated by tigecycline combined with cefoperazone/sulbactam or fosfomycin. Although 63.3% patients in the non-survival group treated by tigecycline (15.2% in survival group), it seems that a delayed applying of this antibiotic (0.56 ± 0.27 d vs. 7.07 ± 4.93 d after positive culture reports received, $p = 0.0025$). Totally, 72 patients (70.59%) improved and 30 patients (29.41%) dead.

Discussion

A. baumannii, an aerobic, gram-negative bacillus which is widely distributed in nature, is notorious for its remarkable Ability to acquire antibiotic resistance. As a result, it causes persistent hospital-acquired infections (1, 2). In our present study, the incidence of MDR/XDR- AB at our facility was 0.48 cases/1000 patient-days, which was consistent with the incidence range from 0 to 58 cases/1000 patient-days(15) and lower than the incidence of another PICU that literature reports(7). Patients in PICU always characterized by more severe underlying diseases, immune dysfunction and more complex medical history, all of these conditions will cause severe infection of *A. baumannii*. while MDR/XDR AB strains appeared.

From our single-center data, ventilator-associated pneumonia (VAP) occupied the major complication in pediatric critically ill patients who MDR/XDR AB infection with an incidence rate of 54.9% (56/102). Both blood stream and CNS infection caused relative high mortality. Due to an increase in invasive operations as well as the severity of primary conditions of critically ill patients, the overall incidence of MDR/XDR AB infection increased.

MDR/XDR AB is resistant to most pediatric antimicrobial agents, including penicillins, most cephalosporins, carbapenems, aminoglycosides, and sulfa drugs. XDR AB tends to develop resistance to multiple antimicrobial agents through degrading enzymes targeting β - lactams, increasing the expression of Ampc enzyme, modifying enzymes targeting aminoglycosides and alteration to the binding sites for quinolones, producing OXA-23 carbapenem enzyme, decreasing the expression of outer membrane pore channel protein, efflux pump system hyperactivity, and loss of PBPs. Additionally, MDR/XDR AB could induce drug resistance through plasmid integration, while causing multiple drug resistance plasmids(2, 16, 17). In our study, the susceptibility results showed that the drug resistance rates of MDR/XDR AB to beta-lactam antibiotics were more than 75% except for cefoperazone/sulbactam (44%). This phenomenon could be explained that sulbactam may be combined with the important PBPs or change the outer membrane permeability of G⁻ bacteria, thus making the beta-lactamase leakage while increasing the opportunity of other antibacterial drugs into biomass.(18) As the contribution of sulbactam, another antibiotic contains sulbactam-ampicillin/sulbatan, showed lower drug resistance rate (79%) than other beta-lactam antibiotics.

During the period of neither tigecycline nor polymyxin was available, a combination therapy of cefoperazone/sulbactam or fosfomycin and carbapenems was applied.

Since the safety of children's medication has been put in an important place, our choice of antibiotics faced a lot of limitations. Although no evidence in the literature that combination therapy is prior to single drug for infection with MDR/XDR AB, some in vitro studies have shown that certain drug combinations are synergistic(19, 20). In the study by Singkham-In U et al(21), the combination of 1 × MIC of imipenem (16–64 mg/L, and 128 mg/L of isolate A10) and 1 × MIC of fosfomycin (128–256 mg/L) showed synergism and bactericidal effect against most *A. baumannii* isolates. Fosfomycin, when combined with imipenem, may enhance the inhibition of bacterial cell wall synthesis. So from this point of view, the combination of fosfomycin and carbapenems in the past few years benefited a number of our patients. In our study, from Jan 2017, 28 patients received tigecycline treatment. Though it seemed that 63.3% patients in the non-survival group treated by tigecycline while 15.2% in survival group, what cannot be ignored was the initiation of tigecycline treatment in non-survival group was 6.5 day later ($0.56 \pm 0.27d$ vs. $7.07 \pm 4.93d$ after positive culture reports received, $p = 0.0025$) than survival group positive culture report received, which might have an impact on higher treatment failure rate.

A. baumannii was transported together by infiltrating neutrophils. Go Kamoshida et al (22) found that *A. baumannii* exploits human neutrophils by adhering to and inducing IL-8 release for bacterial portage. *A. baumannii* stimulation IL-8 plays a critical role in enhancing the migration of *A. baumannii*-adhering neutrophils, the migration of AB was suppressed when the infiltration of neutrophils was suppressed by inhibiting IL-8 (23). Through Toll-like receptor 4 (TLR4) and CD14, *A. baumannii* lipopolysaccharide leads the production of the neutrophil chemotactic factor IL-8 (2) and the proinflammatory cytokine TNF- α (24). In our MDR/XDR AB infected patients, a higher serum level of IL-8 ($0.1(0.1, 22.99)pg/ml$ vs. $15.25(1.62, 47.215)pg/ml$) was detected in the non-survival group, this phenomenon might explain that *A. baumannii* in this group seems to spread throughout the body more easily.

Studies have shown that purified TLR2 ligands from *A. baumannii* are immunostimulatory (25). CD4⁺ T cells play important role in the Th1/Th2 paradigm, participate in inflammation(26), AbOmpA of *A. baumannii* (AbOmpA) is a major porin protein in the outer membrane and is partly responsible for apoptosis of eukaryotic cells. Jun SikLee et al (27) co-cultured CD4⁺ splenic T cells with AbOmpA-treated DCs, and found AbOmpA directs CD4⁺ T cell differentiation towards a Th1 response. Most biofilms provide a mechanical barrier to phagocytosis much like a capsule. A small number of bacteria become biologically active by migration from the biofilm or by shearing forces that remove small clumps of the biofilm. These bacteria released from the biofilm can induce not only host responses but also act as the seeding colony for the establishment of another infectious focus (28). In our research, the patients in non-survival group appeared a higher CD4⁺ T cell ratio than survival patients, which revealed that a persistent neutrophil activation and accumulation in tissue that caused inflammation spread.

Our study had several limitations. First, because data were collected retrospectively from medical records, some parameters had to be inferred from the charts. Susceptibility testing had limitations, fosfomycin was

not included, which resulted in a lack of antibiotic susceptibility evidence when we made treatment decisions.

In conclusion, our study suggests that MDR/XDR-AB is an important opportunistic pathogen that causes nosocomial infection in PICU with a rather high mortality. The incidence increased in the last six months, ineffective management, immune dysfunction, co-infected with other pathogen contributed to the risk of death.

Declarations

Ethical approval and consent to participate: Not applicable

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Competing interests: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding: This study was supported by the Multicenter Clinical Research Program of Shanghai Jiao Tong University School of Medicine (DLY201618), funded by the Science and Technology Commission of Shanghai Municipality (18411951000).

Author's contributions: YCZ and YJS designed the study. JYS, TS managed data and its quality. JYS, YJS and CXW performed the statistical analysis. FW, YPZ and HJM participated in the data interpretation. JYS, TS, YC drafted the manuscript. CXW and YCZ contributed substantially to its revision. All authors read the manuscript carefully and approved the final version.

Acknowledgements: Not applicable.

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Figures

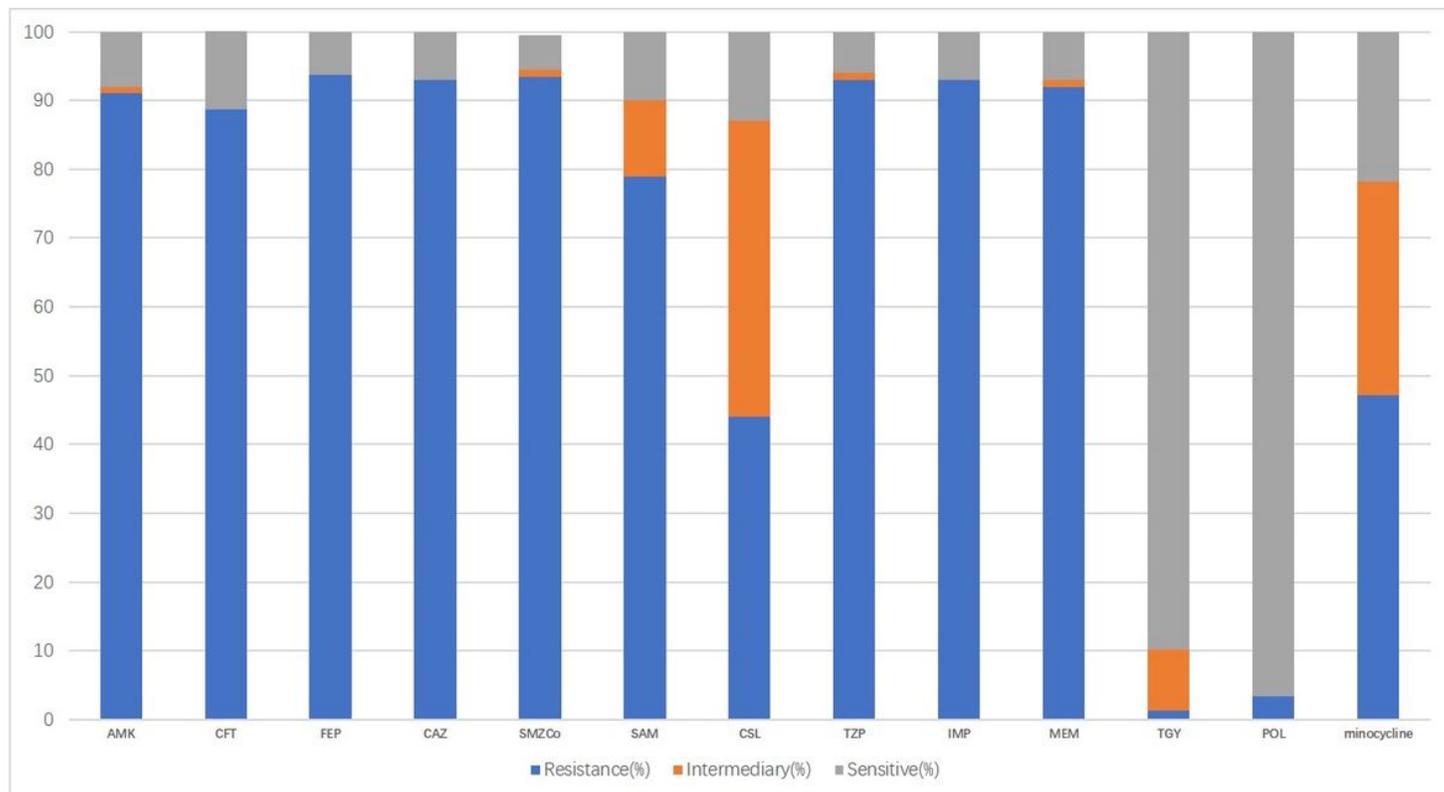


Fig. 1 – Antimicrobial resistance in 102 *A. baumannii* clinical isolates. (A) Blue for resistant, red for intermediate and green for sensitive. AMK = amikacin; CFT = ceftriaxone; FEP = cefepime; CAZ = ceftazidime; SMZCo = sulfamethoxazole; SAM = ampicillin/sulbactam; CSL = cefoperazone/sulbactam; TZP = piperacillin/tzobartan; IMP = imipenem; MEM = meropenem; TGY = tetracycline; POL = polymyxin; MNO = minocycline.

Figure 1

Summary of bacteriological findings