

Successful Incidences of Controlling Multidrug-Resistant, Extensively Drug-Resistant, and Nosocomial Infection *Acinetobacter baumannii* Using Antibiotic Stewardship, Infection Control Programs, and Environmental Cleaning at a Chinese University Hospital

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Objective: We estimated the efficacy of antimicrobial stewardship (AMS), infection control programs (ICP), and environmental cleaning (ENC) for controlling the resistance of *Acinetobacter baumannii* (AB) and controlling the incidence of multidrug-resistant AB (MDRAB), extensively drug-resistant AB (XDRAB), and nosocomial infection AB in the ICU (NIAB-ICU) at a university hospital.

Methods: The intervention included 4-year AMS+ICP and 3-year AMS+ICP+ENC between January 2012 and December 2019.

Results: A total of 2636 AB isolates were collected totally, and 64.98% of AB isolates were MDR and 29.97% were XDR. Preintervention and postintervention incidences of MDRAB, XDRAB, and NIAB-ICU by AMS+ICP measures ranged from 84.96% to 71.98%, 41.96% to 33.13%, and 45.6% to 38%, respectively. However, all of them were not statistically changed ($P=0.085$, 0.072 , 0.061 , separately). The preintervention and postintervention incidences of MDRAB, XDRAB, and NIAB-ICU by AMS+ICP+ENC measures ranged from 71.98% to 36.55%, 33.13% to 19.88%, and 38% to 22.5%, respectively. Statistically significant declines were observed ($P=0.016$, 0.041 , 0.032 , separately). The defined daily doses (DDD) per 1000 patient-days (PD) decreased from 45 ± 3.3 to 30.81 ± 1.5 per 1000 PD across from 2012 to 2019, and a statistical decline was seen ($P=0.01$). Concurrently, the alcohol-based hand gel (ABHG) consumption per 1000 PD increased from 0.6 ± 0.05 L to 12.5 ± 2.3 L per 1000 PD, and a statistical increase was observed ($P=0.0001$). A statistically positive correlation was revealed between the DDD and incidence of MDRAB, XDRAB, and NIAB-ICU ($r=0.905$ and $p=0.002$; $r=0.939$ and $p=0.001$; $r=0.956$ and $p=0.0002$; respectively). Simultaneously, a statistically negative correlation was showed between the ABHG and incidence of MDRAB, XDRAB, and NIAB-ICU ($r=-0.858$ and $p=0.006$; $r=-0.888$ and $p=0.003$; $r=-0.882$ and $p=0.004$, separately).

Conclusion: The AMS, ICP, and ENC may be one of the most effective and best measures to address the increasing incidence of MDRAB, XDRAB, and NIAB-ICU currently.

Keywords: *Acinetobacter baumannii*, antibiotic resistance, antibiotic stewardship, infection control programs, environmental cleaning

Introduction

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Acinetobacter baumannii* (AB) is one of the most important nosocomial opportunistic pathogens;

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it has a unique ability for manifesting antimicrobial resistance.¹ The reported incidence of MDRAB and XDRAB infections has substantially increased over the past decades.² A rising incidence of carbapenem-resistant AB (CRAB), intrahospital and interhospital spread of CRAB, and a colistin-resistant AB complex has appeared in intensive care units (ICUs).^{3,4} It must be noted that a high mortality rate has been associated with infections caused by CRAB strains.⁵ The rapid spread of MDRAB and XDRAB in clinical settings has made choosing an appropriate antibiotic to treat these infections and executing contact precautions difficult for clinicians; indeed, institutional outbreaks caused by MDRAB and XDRAB are a tremendous public health problem.^{3,5} Although controlling the transmission of MDRAB and XDRAB is a high priority for hospitals, there is little information and data about MDRAB and XDRAB control.¹ The limited or even no effective treatment options make the clinical management of MDRAB and XDRAB infections particularly challenging.⁶

Despite several recommendations over the years, infection control programs (ICPs) and antimicrobial stewardship (AMS) have been implemented in several hospitals to promote the appropriate use of antimicrobials and prevent MDRAB. The interventions vary widely by region and effect.⁷ A few studies have revealed how education for ICPs, hand hygiene campaigns, and the judicious use of carbapenem may decrease the nosocomial incidence of CRAB and MDRAB.^{8–10} However, more and more studies have shown that the drug resistance of AB has generally increased; the prevalence of CRAB has increased worldwide, and numerous hospital outbreaks in ICUs have been reported.^{11–14} Some studies have even suggested enhanced stewardship programs are urgently needed and have been developed to avoid the spread and potential outbreaks by MDRAB, especially in high-resistance endemic settings.^{15,16}

Consequently, the relative efficacy of ICP and AMS is still inconclusive and controversial when it comes to controlling MDRAB and XDRAB.^{11,12}

Environmental cleaning (ENC) is an important component of a comprehensive strategy to control healthcare-associated infections, especially in wards such as the ICU, where patients are compromised.^{17,18} One study showed that comprehensive measures with environmental cleaning in a NICU environment were effective and significantly reduced the incidence rate of methicillin-resistant *Staphylococcus aureus*.¹⁹

A systematic review showed some strategies were differential for certain bacteria in ICUs, and when ENC was added to standard care + AMS, there was a significant reduction in the acquisition of MDR-AB. Hence, it is necessary to deeply evaluate the most effective prevention strategies.¹¹

Therefore, the purpose of our study is to estimate the efficacy of AMS, ICP, and ENC for controlling the resistance trend of AB and controlling the incidence of MDRAB, XDRAB, and nosocomial infection of AB in ICU (NIAB-ICU). The study was conducted from January 2012 to December 2019 at a tertiary hospital center.

Methods

The 4th Affiliated Hospital of Harbin Medical University, a 2600-bed teaching hospital located in northeastern China, has a 30-bed medical ICU and a 20-bed surgical ICU. Because of an increased incidence of MDRAB, XDRAB, and NIAB-ICU, ICP and AMS have been executed at this hospital since 2013. Active and exhaustive ENC has been implemented strictly since 2016. Therefore, we retrospectively estimated the efficacy of the intervention measures, including ICP, AMS, and ENC, between January 2012 and December 2019.

Bacterial Isolates

AB, which was included in our study, was confirmed infection from the patient's clinical case and clinician. Clinical isolates from samples including blood, respiratory tract, urinary tract, wound surface, and other sources were obtained for every year. Isolate identification and antimicrobial susceptibility testing of AB were performed using VITEK II (bioMérieux, Marcy L'Etoile, France). Hand cultures from health care workers were also estimated for those working in the ICU. Environmental cultures were conducted for a diverse group of sites, including surrounding curtains, bedrails, bedside tables, respiratory equipment ventilator tubes, blood pressure cuffs, infusion pumps, stethoscopes, suctioning equipment, washbasins, computer keyboards, and monitors. The environmental and hand cultures were sampled using a sterile premoistened cotton swab, which was inoculated onto MacConkey agar plates. Isolates were transferred to the coordinating laboratory, subcultured on suitable media, and reserved in skim milk at -80°C until the minimum inhibitory concentration (MIC) was determined.

Antimicrobial Sensitivity and Resistance

The *in vitro* activity of regularly utilized antimicrobial agents was determined by broth microdilution in line with the guidelines of the Clinical and Laboratory Standards Institute (CLSI).^{20,21} The interpretive standards for the MIC of the antibiotics were determined based on the CLSI breakpoints.²¹ Classification of the AB isolates as a MDR or XDR was based on the EUCAST Expert Rules.²² Nosocomial infection with AB in the ICU was defined using the Centers for Disease Control and Prevention's definitions of nosocomial infections.^{20,23} The seven types of antibiotic agents tested in the current study were extended-spectrum cephalosporins (ceftazidime), carbapenems (imipenem and meropenem), quinolones (ciprofloxacin), β -lactam/ β -lactamase inhibitor combinations (piperacillin/tazobactam and cefoperazone/sulbactam), aminoglycosides (gentamicin and amikacin), glycopeptides (colistin), and tetracyclines (tigecycline). Colistin was examined in line with the recommendations of the CLSI-European Committee on Antimicrobial Susceptibility Testing (EUCAST).²³

Environmental Cleaning

According to the literature,²⁰ an exhaustive environmental cleaning program was established since 2016 at the 4th Affiliated Hospital of Harbin Medical University. The disinfectants used were hypochlorite-based disinfectants; a wipe disinfectant containing benzalkonium chloride and propane-1,2-diol was used for the handling of nondisposable medical products in which this disinfectant was not appropriate. Disposable medical products were discarded once the patient did not need them anymore, here by following the Centers for Disease Control's recommendations,²⁰ and nondisposable products were disinfected following the procedures previously illustrated. Two detailed checklists were established to verify the environmental decontamination sequence: one for the medical equipment sterilization and the other for the general environmental cleaning. These checklists had to be signed by the cleaning staff after executing any sterilization procedure, and the frequency was twice a day; the qualification rate was analyzed weekly. The infection control specialist met with the cleaning staff several times a week for feedback of the monitoring results and educational aims. Each ICU ward was closed in sequence periodically for a terminal sterilization at least three times every year. In addition, the bedside and room of a patient

with MDRAB or XDRAB infection underwent terminal cleaning after discharge.

Infection Control Projects

According to the literature,²¹ a comprehensive ICP has been implemented since 2013 at the 4th Affiliated Hospital of Harbin Medical University, as follows:

1. Illustrations for hand hygiene were provided via an education plan. An alcohol-based hand gel (ABHG) was available at all bedsides in the ICUs. Dispensers for ABHGs were fixed in every room and aisle to sustain and promote fundamental hygiene. Education of the hospital staff and campaigns to increase hand hygiene adherence were also conducted.
2. Hand hygiene adherence was continuously monitored by blinded nurses who were working in each ICU. Cultures from the hands of the medical staff who had cared for the infected patients and the environment were analyzed at three time points during their ICU stay to investigate cross-infection and the spread of infection to the staff. Monthly, the individual results were reported to the health care workers and the administration staff.
3. Illustrations for contact with and the seclusion of patients infected with MDRAB and XDRAB were provided. A list of infected patients for seclusion and cautionary contact was also created. The list was kept secret. Furthermore, the list also applied to the next hospital stay until colonization was removed.
4. Active surveillance for MDRAB and XDRAB colonization was conducted. All patients admitted to adult ICUs were screened weekly. Surveillance cultures were obtained by rectal and pharyngeal swabs. Positive monitoring was performed in all the patients who were admitted to the ICU for more than 2 days during an ongoing transmission.
5. Environmental cleaning for wards that infected patients might have touched was implemented according to the guidelines of the Centers for Disease Control and Prevention.²⁴ Environmental cleaning and disinfectants for any equipment were applied for an adequate period to achieve sterilization, based on the manufacturer's guidelines.
6. Regular meetings for the healthcare workers of affected areas were held every 2 to 4 weeks during

the first year of intervention and every 2 to 3 months afterwards; these were compulsory for ICU staff. In addition, all staff members were periodically informed about the evolution of rates as part of the educational program (monthly in ICUs, quarterly in other units).

Antimicrobial Stewardship

Based on the literature,²¹ antibiotic usage was strictly restricted through AMS since 2013 at the 4th Affiliated Hospital of Harbin Medical University, antibiotic use classification management included the following system:

1. Special usage classification of antibiotics: Limited clinical data are available on the efficacy or safety of new antibiotics or their superiority. These drugs are expensive, and hence, their use must be strictly controlled. The prescription of special usage classification antimicrobial agents requires approval from a respiratory medicine or infectious diseases physician. Doctors qualified at the sub senior level or above were granted special usage of such antibiotics and could prescribe them after examination.
2. Restricted usage classification of antibiotics: There are limitations based on the safety, cost, efficacy, and so forth of the drug for antibiotics that have a significant influence on pathogen resistance. A prescription for the restricted usage classification of antimicrobial agents requires approval from an respiratory medicine or infectious diseases physician. Doctors at an intermediate level or above were granted restricted usage of the antibiotics and could prescribe them after examination.
3. Unrestricted usage classification of antibiotics: This is applicable in the case of antibiotics that have been proven to be inexpensive, effective, and safe in clinical practice for a long time; they also have little influence on bacterial resistance. The doctors were granted unrestricted usage of the antibiotics and could prescribe them after examination.

On a hospital-wide basis, the prescription of restricted antimicrobial agents requires approval from a respiratory medicine or infectious diseases physician. An online antimicrobial control system has been deployed since 2013. Through the hospital information system, the respiratory medicine or infectious diseases physician can review the reports of cultures, the clinical and laboratory presentation,

and the images of each patient to whom special use of antimicrobial agents and the restricted antibiotics have been prescribed. Should a denial be made, the antimicrobial is discontinued by the hospital information system and notified immediately to modify the prescription.

Data Collection

The incidence density rate of hospital-onset MDRAB or XDRAB was defined as the per-patient number of first MDRAB or XDRAB isolates from clinical specimens and active surveillance testing at ≥ 3 calendar days after admission to the ICU; this was done after excluding patients with a history of colonization or infection.²⁵ Multiple positive isolates from one patient were considered as a single sample. Isolates were defined as susceptible, resistant, or intermediate to an antibiotic for statistical analysis. The ABHG consumption was calculated as the number of liters per 1000 patient-days (PD) and utilized as a marker for adherence to ICP rules. Antibiotic consumption was calculated as the defined daily dose (DDD) per 1000 PD, which is in line with the suggestions from the World Health Organization.²⁶ Data on antibiotic consumption were obtained from the hospital pharmacy service.

Statistical Analysis

Analyses were performed using SPSS v.17 (IBM, Armonk, NY). The chi-square test was utilized to compare the incidence density rate of susceptibility and resistance to AB, MDRAB, XDRAB, and NIAB-ICU during the study period. A *t* test was used to compare the variations of ABHG consumption and antibiotic consumption. A Pearson correlation coefficient was applied to confirm the correlation between the incidence rate of MDRAB, NIAB-ICU, and XDRAB and the ABHG consumption and the DDD. All examinations were two-tailed, and $P < 0.05$ was considered to indicate statistical significance.

Results

In total, between January 2012 and December 2019, 2636 AB clinical isolates were collected. Overall, 64.98% (1713) of the AB clinical isolates assessed were MDRAB, and 29.97% (790) were XDRAB. The number of AB clinical isolates obtained annually varied between 286 and 402.

Table 1 reveals that the AB clinical isolates were mainly isolated from the patient's respiratory tract sample,

Table 1 Patients Characteristics of 2636 AB Clinical Isolates from 2012 to 2019

Characteristics	Rate% (n)	MDR	XDR
		Rate% (n)	Rate% (n)
Samples			
Respiratory tract	79.5 (2096)	67.18 (1408)	30.06 (630)
Blood	6.5 (172)	64.53 (111)	29.07 (50)
Wound surface	6 (158)	62.66 (99)	28.48 (45)
Urinary tract	4 (105)	47.62 (50)	31.43 (33)
Other	4 (105)	42.86 (45)	30.48 (32)
Wards			
ICU	68 (1794)	65.33 (1172)	39.97 (717)
General ward	16 (421)	64.13 (270)	8.8 (37)
Outpatient department	0 (0)	0 (0)	0 (0)
Surgery department	16 (421)	64.37 (271)	8.6 (36)
Emergency department	0 (0)	0 (0)	0 (0)
Age, 60.8 (40–90)y			
≤17	0 (0)	0 (0)	0 (0)
18–64	35 (923)	65 (600)	29.9 (276)
≥65	65 (1713)	64.97 (1113)	30.01 (514)
Sex			
Female	48 (1265)	64.98 (822)	29.89 (378)
Male	52 (1371)	64.98 (891)	30.05 (412)

Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant.

ICU ward, and patients over 65 years old, accounting for 79.5% (2096), 68% (1794), and 65% (1713), respectively.

Table 2 presents the data related to antibiotic susceptibility and resistance of the AB clinical isolates. Colistin and tigecycline were the most effective antibiotics assessed: 99.6% and 98.83% of the AB isolates showed in vitro susceptibility to colistin and tigecycline, respectively, and 0.4% and 1.17% of the AB isolates showed resistance to colistin and tigecycline, respectively. In contrast, ciprofloxacin and piperacillin/tazobactam were the least effective antibiotics evaluated: only 10.9% of the AB clinical isolates were susceptible, and 79% were resistant to ciprofloxacin; in addition, 13.82% were susceptible and 81.07% were resistant to piperacillin/tazobactam. Colistin and tigecycline remained the most effective antibiotics assessed, with 98.5% and 95% of the MDRAB clinical isolates showing in vitro susceptibility to colistin and tigecycline, separately. Furthermore, colistin and tigecycline were the most effective antibiotics assessed for XDRAB, with 91.4% and 82% of the XDRAB clinical isolates showing in vitro susceptibility to colistin and tigecycline, respectively.

The resistance of the AB clinical isolates, stratified by study year, is presented in Table 3 and Figure 1. Over the

8-year study period, colistin and tigecycline were found to be stable and to have the lowest resistance among the antimicrobial agents. After the AMS and ICP interventions were implemented in 2013 and the ENC intervention was executed in 2016, the resistance of other antimicrobial agents to the AB clinical isolates, except for colistin and tigecycline, obviously decreased.

The sensitivity of the AB clinical isolates, stratified by study year, is presented in Table 4 and Figure 2. Over the 8-year study period, colistin and tigecycline were found to be stable and to have the highest susceptibility among the antimicrobial agents. After the AMS and ICP interventions were implemented in 2013 and the ENC intervention was executed in 2016, the susceptibility of the other antimicrobial agents to the AB clinical isolates, except for colistin and tigecycline, significantly improved.

As shown in Table 5 and Figure 3, after the AMS+ICP interventions were implemented in 2013, the percentage of MDRAB clinical isolates ranged between 84.96% and 71.98% from 2012 to 2016; this was not a statistically significant change ($P=0.085$). However, after the AMS+ICP+ENC interventions were strictly executed in 2016, the percentage of MDRAB clinical isolates ranged between 71.98% and 36.55% from 2016 to 2019, and a statistically significant

Table 2 Antimicrobial Susceptibility of AB Clinical Isolates Obtained from Patients at a Hospital Center in China, 2012–2019

Antimicrobial	All Isolates (n=2636)			Breakpoint Interpretations ^a				MDR-AB	XDR-AB
	MIC (μg/mL)		Range of Values					(n=1713)	(n=790)
	MIC ₅₀	MIC ₉₀	Min	Max	%R	%I	%S	%S	%S
Piperacillin/ Tazobactam	4	64	≤1	>128	81.07	5.11	13.82	2.3	0
Cefoperazone/Sulbactam	4	64	≤1	>128	40.2	17.2	42.6	20.5	0
Imipenem	0.5	8	≤0.03	>32	61.7	8.1	30.2	14	0
Tigecycline	1	2	≤0.06	>16	1.17	0	98.83	95	82
Colistin	1	2	≤0.06	>16	0.40	0	99.6	98.5	91.4
Gentamicin	2	8	≤0.5	>32	68.4	2.59	29.01	16.2	0
Meropenem	0.5	8	≤0.03	>32	58.3	6.2	35.5	16	0
Amikacin	4	16	≤1	>64	70.07	1.73	28.20	5	0
Ceftazidime	4	32	≤0.25	>32	74.82	7.7	17.48	6.8	0
Ciprofloxacin	0.25	4	≤0.06	>16	79.00	10.1	10.9	3.7	0

Notes: %S=%susceptible, %I=%intermediate, %R=%resistant; Breakpoint Interpretation: Amikacin S≤16μg/mL, I=32μg/mL, R≥64μg/mL, Ceftazidime S≤8μg/mL, I=16μg/mL, R≥32μg/mL, Ciprofloxacin S≤1μg/mL, I=2μg/mL, R≥4μg/mL, Colistin S≤2μg/mL, I=4μg/mL, R≥8μg/mL, Gentamicin S≤4μg/mL, I=8μg/mL, R≥16μg/mL, Meropenem S≤2μg/mL, I=4μg/mL, R≥8μg/mL, Piperacillin/Tazobactam S≤16/4μg/mL, I=32/4μg/mL, R≥128/4μg/mL, Cefoperazone/Sulbactam S≤16/4μg/mL, I=32/4μg/mL, R≥128/4μg/mL, Imipenem S≤2μg/mL, I=4μg/mL, R≥8μg/mL, Tigecycline S≤2μg/mL, I=4μg/mL, R≥8μg/mL.

Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant.

Table 3 Antimicrobial Resistance of AB Clinical Isolates

Antimicrobial Agents	Resistance % (n)								P value ^a
	2012	2013	2014	2015	2016	2017	2018	2019	
	(n=286)	(n=310)	(n=302)	(n=314)	(n=332)	(n=348)	(n=402)	(n=342)	
Amikacin	78.6 (225)	70.4 (218)	70.5 (213)	69.2 (209)	71.3 (237)	69.5 (242)	64.5 (224)	61.5 (210)	<0.001
Gentamicin	75.2 (215)	71.5 (222)	73.8 (223)	67.9 (205)	63 (209)	70 (244)	61.9 (215)	59.5 (203)	<0.001
Meropenem	68 (194)	65 (201)	60.6 (183)	57.5 (174)	61 (203)	56.5 (197)	54.3 (189)	49.5 (169)	<0.001
Piperacillin/Tazobactam	85.1 (243)	82.4 (255)	93.6 (283)	82.0 (248)	78.1 (259)	85 (296)	77.5 (270)	75.1 (257)	<0.001
Cefoperazone/Sulbactam	55.5 (159)	52.8 (164)	50.5 (152)	51 (154)	45.3 (150)	36 (125)	35.5 (123)	30.2 (103)	<0.001
Ceftazidime	88.2 (252)	89.2 (277)	87.6 (264)	85 (257)	78.3 (260)	76.2 (265)	71.6 (249)	68.7 (235)	<0.001
Ciprofloxacin	86.5 (247)	85.6 (265)	82.3 (248)	78.2 (236)	80.6 (267)	74.2 (258)	70 (244)	71.2 (243)	<0.001
Imipenem	70 (200)	64 (198)	60.2 (182)	65.4 (197)	62.8 (208)	54.9 (191)	55.4 (193)	52 (178)	<0.001
Colistin	1.04 (3)	0.6 (2)	1 (3)	0.3 (1)	0.3 (1)	0 (0)	0 (0)	0 (0)	NS
Tigecycline	2.1 (6)	2.3 (7)	1.7 (5)	1.9 (6)	1.5 (5)	0.6 (2)	0 (0)	0 (0)	NS

Note: ^aValue represent the difference of sensitive rate between year 2012 and year 2019.

Abbreviation: NS, not significant.

decline was observed ($P=0.016$). In the same way, the percentage of XDRAB clinical isolates ranged between 41.96% and 33.13% from 2012 to 2016, but this was not a statistically significant difference ($P=0.072$). However, after the AMS+ICP+ENC interventions were strictly executed in 2016, the percentage of XDRAB clinical isolates ranged between 33.13% and 19.88% from 2016 to 2019, which was a statistically significant decline ($P=0.041$). In the same light, the rate of NIAB-ICU ranged between 45.6% and 38% from 2012 to 2016, and this was not a statistically significant change ($P=0.061$); however, after the AMS+ICP+ENC interventions were strictly executed in 2016, the rate of NIAB-

ICU ranged between 38% and 22.5% from 2016 to 2019, which was a statistically significant reduction ($P=0.032$).

The consumption of antimicrobial agents is shown in Table 5. After the AMS and ICP interventions were strictly executed in 2013 and the ENC intervention was implemented in 2016, the DDD per 1000 PD of total antimicrobial agents decreased gradually from 45 ± 3.3 to 30.81 ± 1.5 between 2012 and 2019, meaning a statistically significant decline was observed ($P=0.01$). In the same way, the ABHG consumption per 1000 PD increased obviously from 0.6 ± 0.05 L to 12.5 ± 2.3 L between 2012 and 2019, and a statistically significant increase was observed ($P=0.0001$).

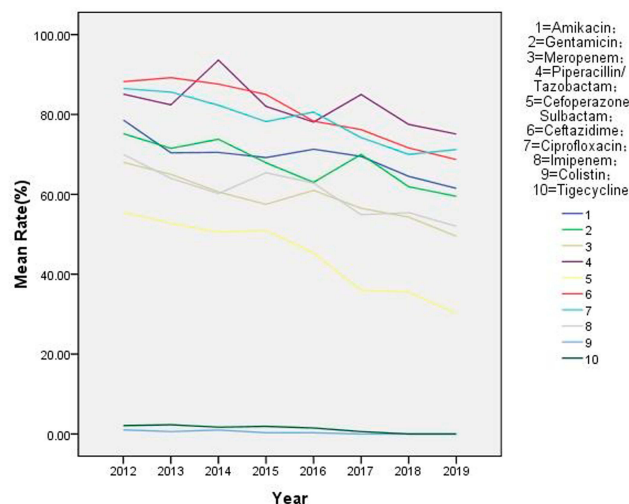


Figure 1 Antimicrobial resistance of AB clinical isolates obtained from patients at a hospital center in China, 2012–2019.

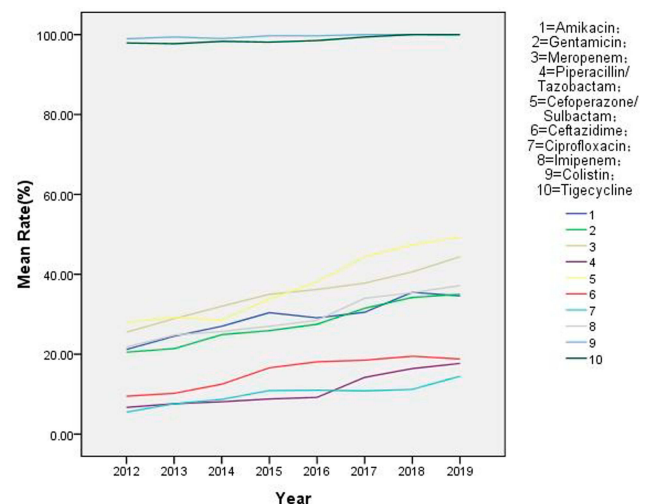


Figure 2 Antimicrobial susceptibility of AB clinical isolates obtained from patients at a hospital center in China, 2012–2019.

The Pearson correlation coefficient is shown in Tables 6–8, and Figure 4. Over the 8-year study period, a statistically significant positive correlation was found between the DDD and the incidence rate of MDRAB, XDRAB, and NIAB-ICU ($r=0.905$, $p=0.002$; $r=0.939$, $p=0.001$; $r=0.956$, $p=0.0002$; respectively). A statistically significant negative correlation was found between the ABHG and the incidence rate of MDRAB, XDRAB, and NIAB-ICU ($r=-0.858$, $p=0.006$; $r=-0.888$, $p=0.003$; $r=-0.882$, $p=0.004$; separately).

Discussion

Acinetobacter baumannii is one of the most important nosocomial infection pathogens.²⁷ The emergence of MDRAB and

XDRAB strains is becoming a major public health concern.²⁸ There is a high morbidity rate from AB infections in hospitals, especially in the ICU, and sputum is the most common sample type;²⁹ this is consistent with our research results. Our results further revealed that old age is a high risk group of AB nosocomial infection. A sex bias for AB nosocomial infection was reported,³⁰ but it was not shown in our study; this difference may be explained as regional and endemic.

Antibiotic exposure increases the acquisition of highly resistant AB. Thus, appropriate antibiotic use is imperative.³¹ Based on the local database of antibiotic resistance from the Taiwan Nosocomial Infection Surveillance System during the period 2003~2012, because of the overuse of carbapenems, the proportion of AB isolates that are resistant to

Table 4 Antimicrobial Susceptibility of AB Clinical Isolates

Antibiotics	Susceptibility % (n)								P value ^a
	2012 (n=286)	2013 (n=310)	2014 (n=302)	2015 (n=314)	2016 (n=332)	2017 (n=348)	2018 (n=402)	2019 (n=342)	
Amikacin	21.2 (60)	24.5 (76)	27 (81)	30.4 (95)	29.1 (96)	30.5 (106)	35.5 (143)	34.6 (118)	<0.001
Ceftazidime	9.5 (27)	10.2 (32)	12.5 (38)	16.6 (52)	18.1 (60)	18.5 (64)	19.5 (78)	18.8 (64)	<0.001
Ciprofloxacin	5.5 (16)	7.6 (24)	8.7 (26)	10.9 (34)	11.0 (37)	10.8 (38)	11.2 (45)	14.5 (50)	<0.001
Colistin	98.96 (283)	99.4 (308)	99 (299)	99.7 (313)	99.7 (331)	100 (348)	100 (402)	100 (342)	NS
Gentamicin	20.5 (57)	21.4 (66)	24.9 (75)	25.9 (81)	27.5 (91)	31.5 (110)	34.2 (137)	35 (120)	<0.001
Meropenem	25.5 (73)	28.9 (90)	32 (97)	35 (110)	36.2 (120)	37.8 (131)	40.6 (163)	44.4 (152)	<0.001
Piperacillin/Tazobactam	6.7 (19)	7.6 (24)	8.1 (24)	8.8 (28)	9.2 (31)	14.2 (49)	16.4 (66)	17.7 (61)	<0.001
Cefoperazone/Sulbactam	28.0 (80)	29.2 (91)	28.6 (86)	33.8 (106)	38.1 (126)	44.4 (155)	47.4 (190)	49.3 (169)	<0.001
Imipenem	21.8 (62)	24.8 (77)	25.7 (78)	27.0 (85)	28.5 (95)	34.0 (118)	35.4 (142)	37.2 (127)	<0.001
Tigecycline	97.9 (280)	97.7 (303)	98.3 (297)	98.1 (308)	98.5 (327)	99.4 (346)	100 (402)	100 (342)	NS

Note: ^aValue represent the difference of resistance rate between year 2012 and year 2019.

Abbreviation: NS, not significant.

Table 5 DDD, ABHG and the Rate of MDR-AB, XDR-AB and NIAB-ICU from 2012 to 2019

	2012	2013	2014	2015	2016	2017	2018	2019	P ^a	P ^b	P ^c
MDR rate (%)	84.96 (243)	80 (248)	77.81 (235)	71.97 (226)	71.98 (239)	59.77 (208)	47.01 (189)	36.55 (125)	0.085	0.004	0.016
XDR rate (%)	41.96 (120)	34.84 (108)	34.77 (105)	34.39 (108)	33.13 (110)	25 (87)	20.89 (84)	19.88 (68)	0.072	0.008	0.041
NIAB-ICU rate (%)	45.6 (212/465)	42.3 (212/502)	40.7 (224/551)	39.5 (236/598)	38 (228/602)	27 (158/586)	25.2 (148/588)	22.5 (135/601)	0.061	0.011	0.032
DDD (g/1000 patient-days)	45±3.3	44.19±2.8	43.37±1.9	39.52±1.6	38.55±2.2	30.26±1.6	25.95±1.3	30.81±1.5	0.72	0.01	0.58
ABHG (L/1000 patient-days)	0.6±0.05	3.8±0.5	5.7±0.9	8.5±1.3	9.8±1.5	10.9±1.9	11.2±2.1	12.5±2.3	0.001	0.0001	0.61

Notes: P^a value represent the difference of isolation rate between year 2012 and year 2016, P^b value represent the difference of isolation rate between year 2016 and year 2019, P^c value represent the difference of isolation rate between year 2012 and year 2019.

Abbreviations: MDR, multidrug resistant; XDR, extensively drug resistant; NIAB-ICU, nosocomial infection of AB in ICU; DDD, daily defined doses per 1000 patient-days; ABHG, alcohol-based hand gel liters per 1000 patient-days.

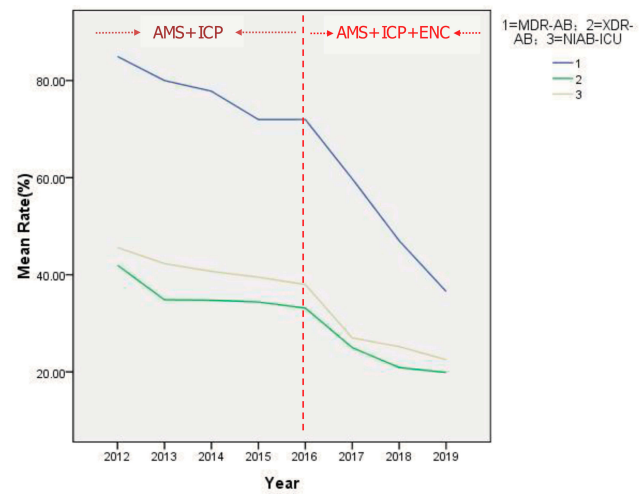


Figure 3 The trends of MDR-AB rate, XDR-AB rate and NIAB-ICU rate from 2012 to 2019. **Abbreviations:** AMS, antimicrobial stewardship; ICP, infection control programs; ENC, environmental cleaning; NIAB-ICU, nosocomial infection of acinetobacter baumannii in ICU.

imipenem or meropenem increased from 17.2% to 72.8%.³² Indeed, the proportion of AB clinical isolates resistant to imipenem or meropenem is similar to our research results. Cutting down on the unreasonable usage of antibiotics has been shown to improve patient prognosis and contain the adverse effects of antibiotic consumption.³³ Antibiotic application should be based on drug sensitivity and the prevalence of local resistant AB.³⁴ In our study, colistin and tigecycline were found to be the most effective antibiotics assessed, yet some drug sensitivity results are inconsistent with individual reports,^{35,36} which could be explained by differences in the habit, frequency, and region of antibiotic use. Antibiotic resistance is complex and driven by many interrelated factors, including expectations, time constraints, economic incentives, knowledge, attitudes, perceptions, cultural factors, health system characteristics, and regulations.^{37,38} Therefore, changing antibiotic prescription behavior is a complex initiative that requires a strategic intervention.³⁷

AMS has also been a cornerstone of controlling resistance AB. Many studies have found it crucial.³⁹ Australia's first National Antimicrobial Resistance policy for 2015~2019 mentions the demand for resources to sustain the implementation of AMS in all hospitals.⁴⁰ One study revealed that the incidence of MDRAB was addressed by controlling the inappropriate duration of antimicrobial treatments and the misuse of carbapenems.⁴¹ However, the values of DDD in our study are clearly higher than those reported in Australia

Table 6 The Correlation of Isolation Rates of MDR-AB with Consumption of Antimicrobial Agents and ABHG

	2012	2013	2014	2015	2016	2017	2018	2019	r	P
MDR rate (%)	84.96 (243)	80 (248)	77.81 (235)	71.97 (226)	71.98 (239)	59.77 (208)	47.01 (189)	36.55 (125)	0.905	0.002
DDD (g/1000 patient-days)	45±3.3	44.19±2.8	43.37±1.9	39.52±1.6	38.55±2.2	30.26±1.6	25.95±1.3	30.81±1.5		
ABHG (L/1000 patient-days)	0.6±0.05	3.8±0.5	5.7±0.9	8.5±1.3	9.8±1.5	10.9±1.9	11.2±2.1	12.5±2.3		

Abbreviations: DDD, daily defined doses per 1000 patient-days; ABHG, alcohol-based hand gel liters per 1000 patient-days; MDR, multidrug resistant.

Table 7 The Correlation of Isolation Rates of XDR-AB with Consumption of Antimicrobial Agents and ABHG

	2012	2013	2014	2015	2016	2017	2018	2019	r	P
XDR rate (%)	41.96 (120)	34.84 (108)	34.77 (105)	34.39 (108)	33.13 (110)	25 (87)	20.89 (84)	19.88 (68)	0.939	0.001
DDD (g/1000 patient-days)	45±3.3	44.19±2.8	43.37±1.9	39.52±1.6	38.55±2.2	30.26±1.6	25.95±1.3	30.81±1.5		
ABHG (L/1000 patient-days)	0.6±0.05	3.8±0.5	5.7±0.9	8.5±1.3	9.8±1.5	10.9±1.9	11.2±2.1	12.5±2.3		

Abbreviations: DDD, daily defined doses per 1000 patient-days; ABHG, alcohol-based hand gel liters per 1000 patient-days; XDR, extensively drug resistant.

and the Netherlands.^{21,42} This may be related to the insufficient of administration of antibiotic application.

MDRAB and XDRAB have a high potential to spread among ill patients in the wards, especially in the ICU.⁴³ Clonal dissemination provides evidence for the prevalence of multidrug-resistant AB among clinical isolates.²⁹ During nosocomial outbreaks, the colonization in the hospital environment was very important for the transmission of MDRAB, and environmental cultures revealed that numerous sites in ICUs were contaminated with MDRAB.⁴⁴ These reports suggested that the high incidence of MDRAB, XDRAB, and NIAB-ICU should be solved immediately, and the medical specialty must undertake most duties.⁴⁵

Early recognition and timely implementation of appropriate ICP were crucial in preventing outbreaks.⁴³ Our results suggest monitoring cultures are needed to obviously reduce the incidence of MDRAB, XDRAB and NIAB-ICU. One study showed that providing education about ICP may decrease the nosocomial incidence of CRAB.⁸ Another study showed that improved monitoring of hospital-acquired infections and effective ICP may be the best way to solve this problem.⁴⁶ A few studies also have shown that better hand hygiene, isolation of infected patients, environmental disinfection, and targeted surveillance can improve the success rate of controlling MDRAB infection.^{47,48}

Although ICP and AMS were essential for the control of MDRAB infections,¹ MDRAB and XDRAB are some

of the most difficult multidrug-resistant pathogens to achieve sufficient control. There are still many outbreaks of AB nosocomial infections reported, especially in ICUs,^{3,16,35,49-52} which indicated that it cannot achieve successful control only through AMS and ICP. This is consistent with what we observed in 2012~2016.

The comprehensive measures of a neonatal ICU with improved ENC practice have been shown to be effective and significantly in reducing the incidence of nosocomial infections.⁵³ Particular attention should be paid to effective ENC.⁵⁴ Disinfectants should be applied for an adequate period of time to achieve sterilization. The disinfection of potentially contaminated medical equipment should be done meticulously.⁵⁵ Special attention is required for the sterilization of mechanical ventilators. The ENC and ICP methods that were employed in the current study were based on the accepted tenets of unit closure, intense environmental cleaning, environmental cultures, and improved ICP by the staff.¹⁶ Hand hygiene compliance should be improved.⁵⁴ Testing of the cleaning processes caused the discovery of several leaks, and the environmental cultures provided important feedback for the ICU and cleaning staff. The leaks were addressed with education and checklists.

Curbing the development of resistance in AB is important in hospitals, but there are limited reports on MDRAB, XDRAB, and NIAB-ICU control measures. Although AMS, ICP, and ENC are coordinated strategies designed to promote the appropriate use of antimicrobials and avoid drug resistance of pathogens, their effectiveness have not

Table 8 The Correlation of Rates of NIAB-ICU with Consumption of Antimicrobial Agents and ABHG

	2012	2013	2014	2015	2016	2017	2018	2019	r	P
NIAB-ICU rate (%)	45.6 (212/465)	42.3 (212/502)	40.7 (224/551)	39.5 (236/598)	38 (228/602)	27 (158/586)	25.2 (148/588)	22.5 (135/601)		
DDD (g/1000 patient-days)	45±3.3	44.19±2.8	43.37±1.9	39.52±1.6	38.55±2.2	30.26±1.6	25.95±1.3	30.81±1.5	0.956	0.0002
ABHG (L/1000 patient-days)	0.6±0.05	3.8±0.5	5.7±0.9	8.5±1.3	9.8±1.5	10.9±1.9	11.2±2.1	12.5±2.3	-0.882	0.004

Abbreviations: DDD, daily defined doses per 1000 patient-days; ABHG, alcohol-based hand gel liters per 1000 patient-days; NIAB-ICU, nosocomial infection AB of ICU.

been fully evaluated. Hence, the current systematic review was performed to evaluate the relative efficacy of strategies for the prevention of MDR gram-negative bacteria in the ICU. When ENC was added to standard care + AMS, there was a significant reduction in the acquisition of MDRAB.¹¹ Because some strategies were differential for certain bacteria, the current study highlights the need for further evaluation of the efficacy of ASM+ICP+ENC.

We assessed the effectiveness of ASM+ICP and ASM+ICP+ENC measures in our study, respectively. Despite the downward trend, the incidences of MDRAB, XDRAB, and NIAB-ICU were not significantly controlled by ASM+ICP intervention measures. The results of our study are counter to those that have been reported in the literature,¹ the reason for this may be related to the different level of environmental disinfection. However, after the AMS+ICP+ENC intervention measures were strictly executed, a statistically significant decline in the percentage of MDRAB, XDRAB, and NIAB-ICU was observed. This is showed what we observed in 2016~2019. Our study results further suggest that a statistically significant positive correlation can be found between the DDD and the incidence rate of MDRAB, XDRAB, and NIAB-ICU. Simultaneously, a statistically significant negative correlation was found between the ABHG and the incidence rate of MDRAB, XDRAB, and NIAB-ICU. Nowadays, new antibiotics with resistance to AB are not being developed quickly enough. The control of drugs resistance to AB is imperative. Gajdacs M pointed out the main foci of our scientific advancements should be to preserve the drugs that we currently have (through the development of rapid and sensitive diagnostic tools to ensure their prudent use, and antibiotic stewardship practices).⁵⁶ Hence, our study results have revealed that the trends in the resistance of AB to antibiotics can be affected by AMS, ICP, and ENC. Our study findings suggest that controlling the increasing incidences of MDRAB, XDRAB, and NIAB-ICU by only combining AMS and ICP is far from enough. However, when ENC was added to AMS and ICP, there was a statistically significant decline in the incidence of MDRAB, XDRAB, and NIAB-ICU. Therefore, AMS, ICP, and ENC may be one of the most effective and best measures to address the increasing incidence of MDRAB, XDRAB, and NIAB-ICU.

The main advantages of our study are the time series analysis and the prospective data collection, which permits the exact analysis in the ICP, AMS, and ENC intervention studies. In addition, obtaining a more effective solution for

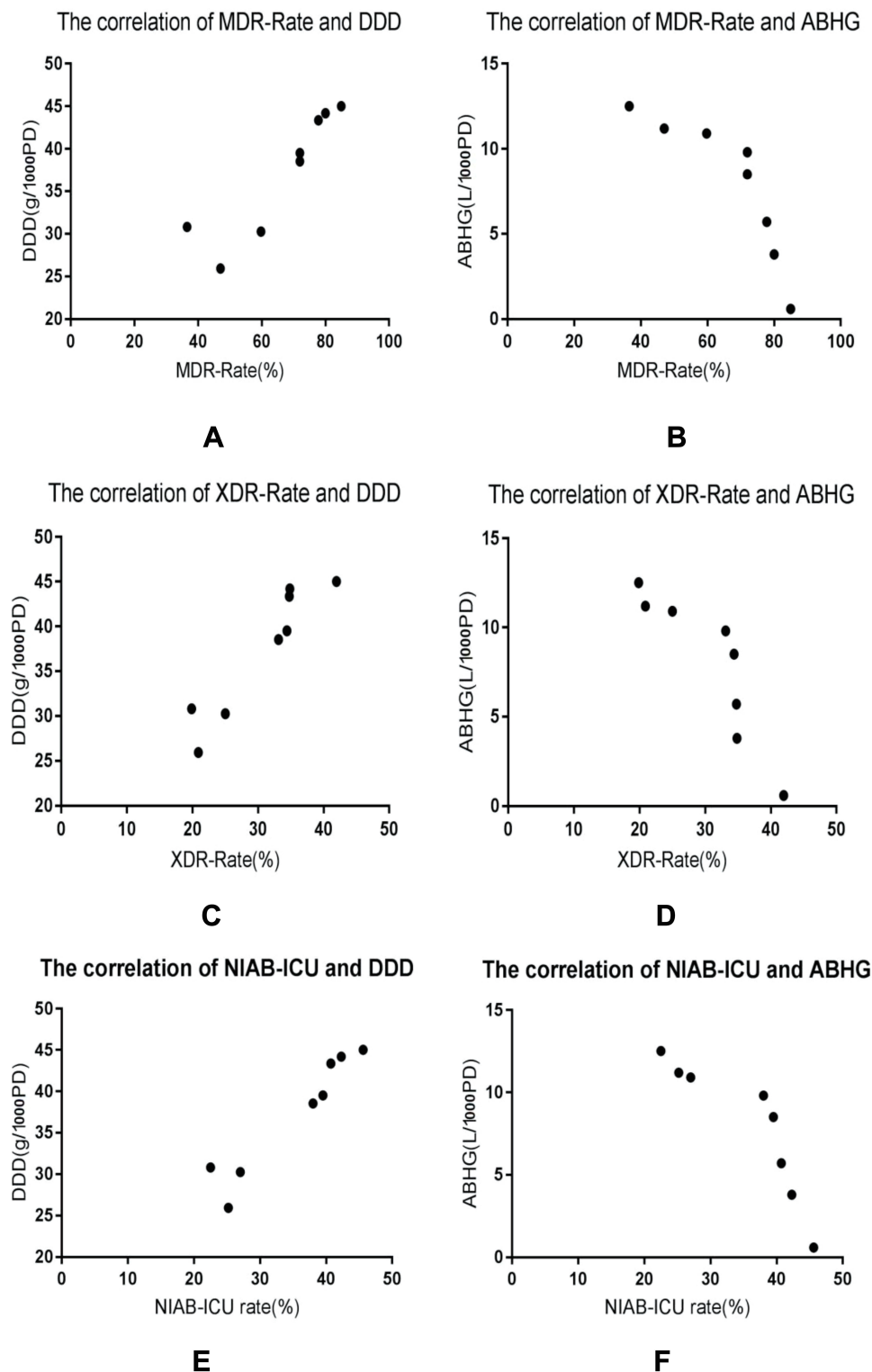


Figure 4 The correlations of isolation rates of MDR-AB, XDR-AB and NIAB-ICU with DDD and ABHG.

better controlling the incidence of MDRAB, XDRAB, and NIAB-ICU in hospitals needs a multidisciplinary and transversal team. However, our research has a few limitations. First, the design of the current study stops us from

realizing if adding any other methods would have led to removing MDRAB, XDRAB, and NIAB-ICU. Simultaneously, the period for observation may not be enough to demonstrate how long the effectiveness of

these interventions is maintained after the interventions. Afterwards, despite our study reporting data from the hospital, the application of these methods to other kinds of hospitals and units may need a modification to the local epidemic situation and hospital environment characteristics. Ultimately, testing the susceptibility and resistance to AB clinical isolates was not done for all the antimicrobial agents; therefore, the treatment of MDRAB and XDRAB was based on the local sensitiveness to the main antimicrobial agents and the local epidemiology.

Conclusion

In total, 2636 AB clinical isolates were collected, and 64.98% of the AB clinical isolates assessed were MDRAB, and 29.97% were XDRAB. AB clinical isolates were mainly isolated from the patient's respiratory tract sample, the ICU ward, and patients over 65 years of age. Colistin and tigecycline were the most effective antibiotics assessed: 99.6% and 98.83% of the AB isolates showed in vitro susceptibility to colistin and tigecycline, respectively. Our study findings suggest that controlling the increasing incidences of MDRAB, XDRAB, and NIAB-ICU by only combining AMS and ICP is far from enough. However, in our study, when ENC was added to AMS and ICP, there was a statistically significant decline in the incidence of MDRAB, XDRAB, and NIAB-ICU. Our study results further suggest that a statistically significant positive correlation can be found between the DDD and the incidence rate of MDRAB, XDRAB, and NIAB-ICU. Simultaneously, a statistically significant negative correlation was found between the ABHG and the incidence rate of MDRAB, XDRAB, and NIAB-ICU. Therefore, AMS, ICP, and ENC may be one of the most effective and best measures to address the increasing incidence of MDRAB, XDRAB, and NIAB-ICU.

Ethics and Consent Statement

This study has been reviewed and approved by the Research Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University (no. 2019-127). The patient had given his consent for publication of clinical details, and written informed consent was obtained. All authors have been personally and actively involved in substantive work leading to the report, and will hold themselves jointly and individually responsible for its content. All relevant ethical safeguards have been met in line with the Declaration of Helsinki.

Disclosure

The authors report no funding and no conflicts of interest for this work.

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