Combined Use of Antibiotics as a Risk Factor for Health Care–Associated Infections: A Case-Control Study

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Research

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Abstract

Background

Antibiotics are among the most frequently prescribed medications. Many studies suggest an increased risk of health care–associated infections (HAIs) among antibiotic users. However most related studies have focused only on a single type of HAIs, but considering the complexity and extent of the subject, it is necessary to conduct extensive research. We conducted a case-control study to determine the association between antibiotic combination therapy and risk of HAIs.

Methods

Retrospective case-control study in a teaching hospital in Northwest China. Cases of 216 patients were diagnosed as HAIs during hospitalization between January 2019 and December 2019. Use antibiotics on admission and before the occurrence of HAIs were compared with 428 patients without HAIs during the same period, and matched by department.

Results

Ninety-one of 216 health care–associated infections, 157 of 428 Patients without health care–associated infections prescribed antibiotics on admission and before the occurrence of HAIs. After multi-variable analysis, Compared with patients without HAIs, the OR for antibiotics combination exposure in cases was 5.43 [95% confidence interval (CI) 2.62-11.24], and the OR for antibiotics exposure in cases was 0.23 (95% CI 0.12-0.43).

Conclusions

Combined use of antibiotics increases the risk of HAIs. In addition, Use of antibiotics before the diagnosis of HAIs is conducted associated with HAIs, and is the main protective factor.

Background

Health care–associated infections(HAIs), also known as hospital-acquired infection, HAIs a kind of infection, which is contracted from the environment or staff of a healthcare facility [1]. HAIs are well-described major adverse events in hospitals, threatening patient safety and challenging public health [2-6]. Human suffering is an immediate implication of these infections, given that they reduce the quality of life of patients and their relatives [7, 8]. HAIs also affect hospitals in mainland China. The social and financial burden of HAIs will be a challenge in the next decades for a number of reasons [9]. In addition, the outbreak of HAIs has seriously affected the reputation of the hospital, so it is particularly important to prevent and control HAIs.

Antibiotics are one of the most widely prescribed drugs and the first successful drugs that can cure diseases and effectively treat many infections. Furthermore, antibiotic resistance has drawn attention

from infectious diseases specialists, the Centers for Disease Control and Prevention, the World Health Organization, and U.S. and European governments [10-12]. The major risk factors associated with HAIs were low albumin, tracheostomy, prior hospital stay, central venous catheter insertion, urinary system disease, high blood glucose are associated, and intensive care unit (ICU) admission [13-15]. In addition, antibiotic exposure has been considered a risk factor for HAIs in previous studies [11, 16, 17]. However most related studies have focused only on a single type of HAIs, but given the complexity and extent of the subject, it is necessary to conduct extensive research. Until recently, there is some lack of knowledge about the relationship between combined antibiotic exposure and HAIs. A case-control study was undertaken to answer this question.

The aim of this study was to comprehensively analyze the association between antibiotics or combination of antibiotics and the risk of HAIs in a retrospective case-control study.

Materials And Methods

Setting

This study was carried out at affiliated hospital of Northwest Minzu University, a 1010-bed university teaching hospital in Northwest China. All 216 patients identified as HAIs between 1st January 2019 and 31st December 2019 (cases) were identified from report cases. Sixteen patients were excluded which did not meet the diagnostic criteria for HAIs.

Controls were selected at random from the patients who were not diagnosed with HAIs (the controls are stratified according to the quarterly distribution of cases and the sampling rates for the first quarter, second quarter, third quarter, and fourth quarter are 25%, 15%, 20%, and 40%, respectively) and were matched to cases based on department(at a ratio of 1:2)(Figure 1). Controls were excluded if it meets the diagnostic criteria for HAIs when viewing the cases. Case patients and controls were also excluded if their case data were incomplete. Total of 428 qualified controls were selected. Clinical datas were extracted from paper and electronic hospital case notes, and inspection records. The study was approved by the affiliated hospital of Northwest Minzu University Research Ethics Committee.

Exposures

Documented prescription of antibiotics (Contains β-lactams, macrolides, lincomycin, peptides and quinolones, etc.) or antibiotic combination (the simultaneous or sequential use of two or more antibiotics) on admission and before of hospital infection diagnosis was recorded. Antibiotics taken 1 to 2 days before the diagnosis of HAIs were not analyzed because it is in the incubation period of potential infection.

Data collection

Datas were obtained from patients' medical records, and relative datas were recorded on structured abstraction forms. Variables analyzed as possible confound included demographics (age, sex, marital

status, ethnic, education and hospital length of stay); invasive procedures (urinary catheter insertion, mechanical ventilation, etc.) during hospitalization; exposure (greater than two day) to antimicrobials (β-lactams, macrolides, lincomycin, peptides and quinolones, etc.) after admission and before the occurrence of nosocomial infection.

Statistical analysis

Demographic characteristics of the cases and controls were presented using descriptive statistics. Continuous variables were presented as mean ± SD, and we used t-tests for comparisons. As the results of the length of hospital stay of the datas for the two groups showed non-normal distribution, they were compared with the median, and the data for two groups were compared using the Wilcoxon rank-sum test. We presented categorical variables as numbers and percentages, and compared percentages using the chi-square test. Multivariate logistic regression models were used to compare each case group and control group. A forward elimination process was used, and adjusted odds ratios and 95% confidence intervals were calculated. Results of the regression models are presented as ORs along with 95% confidence intervals (CIs). A factor was considered to be statistically significant if the 95% CI of the corresponding OR did not contain 1.

A two-tailed P value of less than 0.05 was considered to show statistical significance, and statistical analyses were performed using SPSS Statistics 23 (IBM Corp, Armonk, NY, USA).

Patient involvement

No patients were involved in the design or implementation of the study, or writing up the results.

Results

During the study period, 216 cases were identified and selected with 428 controls for analyses. The clinical characteristics of these patients are shown in Table1. The mean age of case patients (66 years) was higher than that of the control groups (60years). The gender, ethnic, education, and marital status were similar for case patients and controls. The median hospital length of stay of case patients(20days) was longer than that of control groups(10days).The percentages of patients with a urinary catheter ,Ventilator or central catheter (urinary catheter, 42.6%; Ventilator,19.9%;central catheter, 13.9%) were higher in the cases than in the control groups (urinary catheter,7.5%;Ventilator, 0.7%;central catheter,0.7%) ($P<0.001$ for the three comparisons).

The results of antibiotics exposure are summarized in Table3. Total of 214 HAIs cases (91 cases before the diagnosis of HAIs, 123 cases after the diagnosis of HAIs) were exposed to antibiotic, compared with 157 of the non-HAIs controls. No significant difference in antibiotics exposure was found between HAIs cases and non- HAIs controls. In the cases, the percentage of patients with antibiotic combination therapy (antibiotic combination therapy, 33.3%) was higher than that of the controls (antibiotic combination therapy, 8.9%) ($P<0.001$). The OR for antibiotic combinations exposure in cases compared with non- HAIs

controls was 4.92 (95% CI3.17-7.63). The types of antibiotics and route of drug administration were similar for case patients and controls (P>0.05).

The adjusted odds ratios of HAIs associated with antibiotics and antibiotic combination exposure are displayed in Table3. After multivariate analysis, the OR for antibiotics exposure in cases compared with the controls was 0.18 (95% CI 0.09-0.35), which might be a protective factor. In addition, the OR for antibiotic combination exposure in cases compared with the controls was 3.34(95% CI 1.48-7.51), which was a risk factor for HAIs. At the same time, we also found that the odds ratio increases with age and length of residence.

Discussion

In univariate analysis, we found no statistically significant association between HAIs and exposure to antibiotics. However, after adjusting for confounding factors such as age and length of stay, use of antibiotics before the diagnosis of hospital infection may be associated with HAIs, and may be a protective factor. In addition, the combined use of antibiotics may increase the risk of hospital infections. This is a novel and important discovery, as antibiotics are widely overused [10, 18], HAIs are the main threat, and conventional control measures will require an unprecedented level of global cooperation.

Although prior studies have examined the relationship between HAIs and exposure to antibiotics, however, no study to date has systematically investigated the association between antibiotic exposure and HAIs. Thus, these previous results are questionable. Our discovery contrast with those of certain observational studies that have suggested antibiotic exposure is a risk factor for HAIs [19-22]. However, these results should be compared with caution because the infection sites and bacterial species in these studies are different. To date, datas from studies specifically focusing on risk factors of different types of hospital infections have been conflicting. A case-control study in a 600-bed tertiary-care teaching hospital setting demonstrated that no cephalosporin class was independently associated with ESBLs BSI; however, in a secondary model considering all oxyimino-cephalosporins as a single variable, a significant association was demonstrated [19]. Additionally, a retrospective observational cohort study conducted at the Hospital de Clínicas de Porto Alegre showed that the use of antibiotics within the last 10 days before the diagnosis of hospital-acquired pneumonia was the only independent predictor of infection with multidrug-resistant bacteria [21]. Also a recent study showing that prior use of antibiotics is the main factor for the presence of infection healthcare–associated endocarditis [23]. In addition, some studies did not clarify the relationship between hospital infection and antibiotics exposure [13-15]. Disagreement in the findings may be due to differences in type of HAIs, adjusted covariates, patient population, and confounding by determination of antibiotic exposure time.

After multivariate analysis, the confounding factors of age, hospitalization and invasive procedures were adjusted, indicating that exposure to antibiotics is a protective factor for HAIs. Consider that if a patient uses antibiotics because of an infection in one part of the body, infections in other parts can be prevented, because the effect of antibiotics is usually systemic. However, unless the patient is very likely

to be infected, it is not recommended to use antibiotics in advance to prevent unknown infections, and the abuse of antibiotics can lead to the production of resistant bacteria.

This study showed that use of the combination antibiotic was strongly associated with HAIs. There is few research reports on whether combination antibiotic could be a risk factor for acquisition of HAIs, and the type of hospital infection is single. The study conducted at the University of Maryland Medical Center found previous in-hospital piperacillin-tazobactam use (current admission), and previous present admission in-hospital vancomycin use (current admission) as independent risk factors [24]. A case-control study in Southern Brazil showed that use of the combination antibiotic piperacillin-tazobactam within the previous 14 days was strongly associated with extended-spectrum-blactamase production in bloodstream infections due to Klebsiella pneumonia or Escherichia coli [20]. According to another study, prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or imipenem) was a risk factor associated with ventilator-associated pneumonia caused by potentially drug-resistant bacteria (OR,4.12; 95% CI, 1.2-14.2)[25]. In addition, a study conducted in China showed that the use of more than three antibacterial drugs in patients is an independent risk factor for piperacillin-tazobactam caused by carbapenem-resistant Klebsiella pneumonia [26]. Combining the above, whether it is a single infection type or a single antibiotic combination, and the results of this comprehensive study, the combination of antibiotics does increase the risk of HAIs. It is unclear why antibiotic combination is the risk of HAIs. One possible explanation is that the current state of antibiotic therapy has reached a critical point because indiscriminate usage is leading to both compromised immunity and increased resistance. Even the administration of combined broad-spectrum antibiotic therapy can lead to increased mortality in uninfected patients [27].

The major advantage of our study is that cases contain multiple types of infections, and the selection of controls is based on stratified sampling in different quarters and matched by department. This study focuses on the relationship between antibiotic combination exposure and the health care–associated infections. In addition, it is different from the previous analysis of only some fixed combination antibiotics. The focus of this study is the combination of different types of antibiotics. Furthermore, the diversified case mix is reassuring, and the results can be extended to similar centers, including patients of all ages and all educational backgrounds. All available records, including progress notes, prescription orders, medical advice and electronic records are reviewed. Inevitably, our study has several limitations. First, it was carried out in a single hospital, which may produce an impact on our results given variations in HAIs prevention and control practices among institutions. Regarding statistical analysis, what may threaten our results was confounding bias. For example, we couldn't align the cases and controls with underlying diseases, because the condition of patients with multiple underlying diseases was too complicated, although we tried to control this confounding bias through department matching. In addition, we were unable to identify any ‘over-the-counter’ use of antibiotics; however, ‘over-the-counter ‘ antibiotics basically did not happen because antibiotics were strictly controlled drugs, so would not have affected the study cohort. Finally, the patient's exposure to antibiotics before admission was not considered because there was no reliable record.

Conclusions

In conclusion, this study suggests that exposure to combined antibiotics is a risk factor for HAIs, not indicate an increased risk of HAIs associated with exposure to antibiotics before occurrence of HAIs. As far as the author knows, this is the first time this risk factor has been found in the population of a Chinese hospital. Applying evidence-based guidelines to the appropriate use of antibiotics may reduce the spread of bacteria without harming patients who really need this effective antibiotic treatment. However, excessive combined use of antibiotics may cause a series of harms, such as antibiotic resistance and the increased risk of hospital infections found in this study. Given this potential adverse effects, clinicians should use caution in prescribing combination antibiotic for patients at risk.

Abbreviations

health care–associated infections , HAIs.

Declarations

Ethics approval and consent to participate:

The study was approved by the affiliated hospital of Northwest Minzu University Research Ethics Committee.

Consent for publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

Xiao-Liang Zhang analyzed and interpreted the patient data regarding the health care–associated infections and antibiotics exposure. Fang-Bin Li performed the datas collection, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table1. Baseline characteristics and outcomes for cases and controls

Characteristics	HAIs Cases(n=216)	Non- HAIs Controls(n=428)	P Value
Sex, n. (%)			
Male	134(62.0)	255(59.6)	0.547
Female	82(38.0)	173(40.4)	
Ethnic, n. (%)			
Han	209(96.8)	416(97.2)	
Muslia	1(0.4)	2(0.5)	0.944
Tibetan	6(2.8)	10(2.3)	
Education, n. (%)			
Undergraduate or above	30(13.9)	46(10.7)	
Junior college	28(13.0)	53(12.4)	0.265
Technical secondary school	16(7.4)	55(12.9)	
Senior middle school	78(36.1)	147(34.3)	
Other*	64(29.6)	127(29.7)	
Marital status, n. (%)			
Married	206(95.4)	401(93.7)	
Unmarried	9(4.2)	26(6.1)	0.478
Divorce	1(0.4)	1(0.2)	
Ventilator, no. (%)			
Yes	43(19.9)	3(0.7)	<0.001
No	173(80.1)	425(99.3)	
Urinary catheter, no. (%)			
Yes	92(42.6)	32(7.5)	<0.001
No	124(57.4)	396(92.5)	
Central catheter, no. (%)			
Yes	30(13.9)	3(0.7)	<0.001
No	186(86.1)	425(99.3)	
Bronchoscope, no. (%)			

Yes	21(9.7)	11(2.6)	<0.001
No	195(90.3)	417(97.4)	
Age, mean y±SD, years	66±15.9	60±18.1	<0.001
Median hospital length of stay (IQR), days	20(14-33.5)	10(7-14)	<0.001

*Including illiterate, elementary school, junior high school.

Y, mean;SD, standard deviation; IQR, interquartile range.

Values are numbers (percentages) unless stated otherwise.

Table2. Association Between Antibiotic Exposure and HAIs

Characteristics	HAIs Cases(n=216)	Non- HAIs Controls(n=428)	P [a] Value
Antibiotic exposure, n. (%)			
Yes	214(99.1)	157(36.7)	<0.001
No	2(0.9)	271(63.3)	
Antibiotic exposure before occurrence of HAIs, n. (%)			
Yes	91(42.1)	157(36.7)	0.18
No	125(57.9)	271(63.3)	
Antibiotic combination, n.(%)			
Yes	70(32.4)	38(8.9)	<0.001
No	146(67.6)	119(91.1)	
Types of antibiotics, n. (%)			
β-lactams	128(65.6)	130(67.4)	
Quinolone	49(25.1)	56(29.0)	0.13
Carbapenems	8(4.1)	2(1.0)	
Other [b]	10(5.2)	5(2.6)	
Route of drug administration, n. (%)			
Intravenous drip	87(95.6)	149(94.9)	
Mix [c]	3(3.3)	1(0.6)	0.10
Oral	1(1.1)	7(4.5)	

[a] P value calculated using χ2.

[b] Contains linezolid, metronidazole, etc.

[c] Two or more routes of administration.

Table3. The multiple logistic regression model adjusted the odds ratio of antibiotics and antibiotic combination exposure, and Identify variables associated with HAIs

Variable	HAIs Cases(n=216)	Non- HAIs Controls(n=428)	Adjusted Odds Ratio (95% CI)	P Value
Antibiotics	91	157	0.18(0.09-0.35)	<0.001
Antibiotic combination	70	38	3.34(1.48-7.51)	<0.001
Ventilator	43	3	11.74(1.99-69.38)	<0.001
Central catheter	30	3	2.31(0.49-10.88)	0.29
Urinary catheter	92	32	3.40(1.76-6.56)	<0.001
Age				
<40 years	15	52	Reference	—
40-50 years	17	62	1.22(0.43-3.46)	0.70
51-57 years	38	72	1.53(0.58-4.07	0.39
58-65 years	37	83	1.66(0.64-4.29)	0.30
66-72 years	23	42	3.35(1.17-9.55)	0.024
73-80 years	41	51	4.13(1.55-10.96)	0.004
≥81 years	45	66	2.48(0.94-6.60)	0.068
Hospital length of stay				
<7 days	1	95	Reference	—
7-14 days	45	216	32.65(3.46-307.87	0.0023
15-21 days	68	77	141.42(14.81->999.99)	<0.001
22-28 days	35	27	176.23(17.76->999.99)	<0.001
29-35 days	17	3	444.23(33.69->999.99)	<0.001
>35 days	50	10	550.83(50.57->999.99)	<0.001

Figures

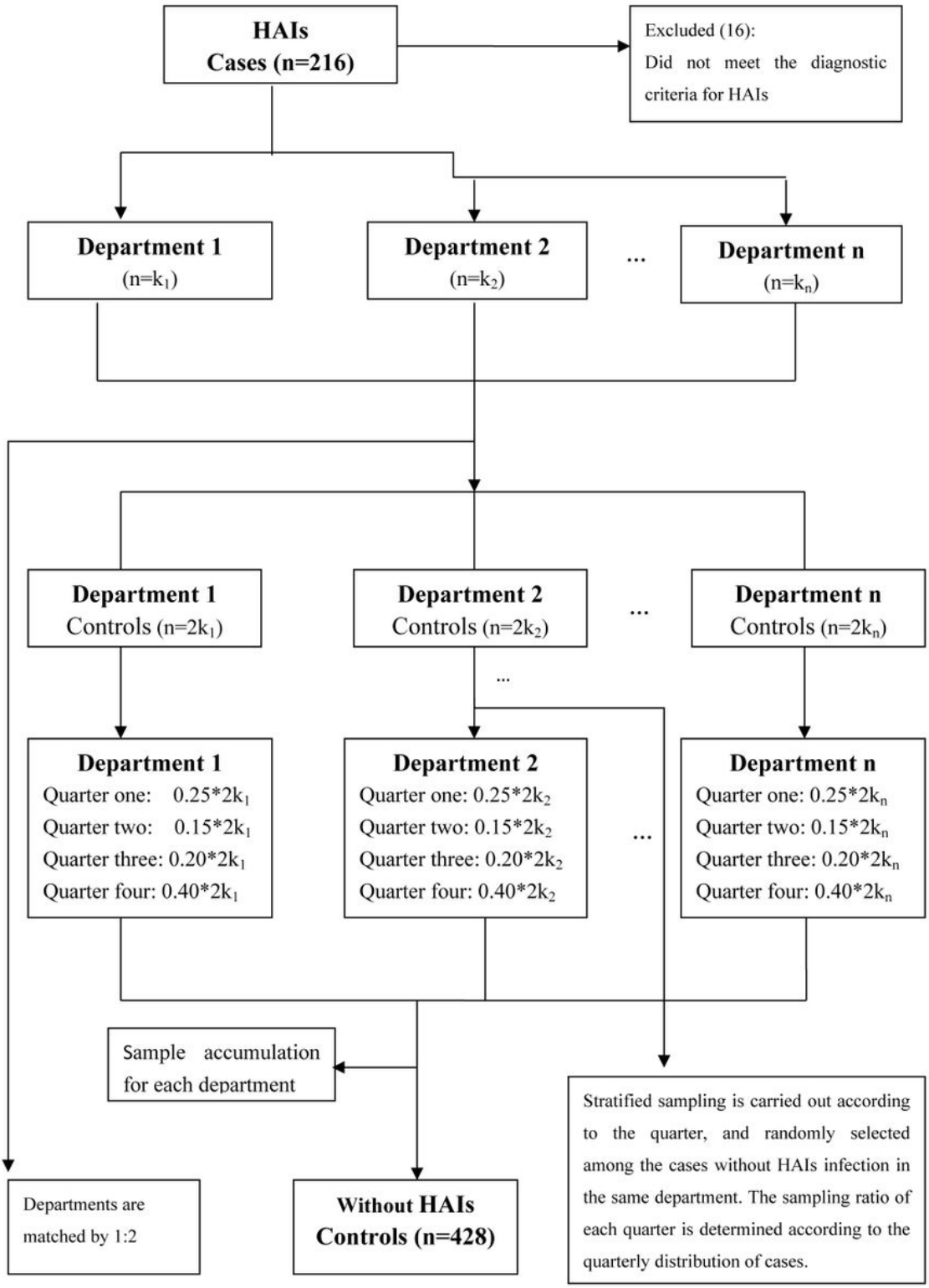

Figure 1

Summary of the control group selection process and reasons for excluding the studies. Abbreviation: HAIs, health care–associated infections.