

# A multicenter epidemiology study on the risk factors and clinical outcomes of nosocomial intra-abdominal infections in China: results from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) 2007–2016

Jiangang Zhang  
Chunjiang Zhao  
Hongbin Chen  
Henan Li  
Qi Wang  
Zhanwei Wang  
Feifei Zhang  
Hui Wang

On behalf of the CARES  
Network

Department of Clinical Laboratory,  
Peking University People's Hospital,  
Beijing, China

Correspondence: Hui Wang  
Department of Clinical Laboratory,  
Peking University People's Hospital,  
No. 11 Xizhimen Nandajie, 100044  
Beijing, China  
Tel/Fax +86 10 8832 6300  
Email whuibj@163.com

**Objective:** This study aimed to determine the risk factors for intra-abdominal infections (IAIs), assess the clinical outcomes of IAIs, and investigate the spectrum and antimicrobial resistance of major pathogens causing IAIs.

**Patients and methods:** This prospective observational study enrolled patients from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) program between 2007 and 2016. Data on the clinicopathological factors and causative pathogens were collected. The results of antimicrobial susceptibility tests were interpreted according to the minimum inhibitory concentration (MIC) interpretive breakpoints recommended by the Clinical and Laboratory Standards Institute in 2017.

**Results:** A total of 2,756 patients were included. The 30-day all-cause mortality was 9.5% (262/2,756). Multivariable analysis showed that the following independent risk factors were associated with the 30-day mortality: age >60 years, pulmonary disease, tracheal cannula, infection occurring in intensive care unit (ICU), prior admission within 3 months, antibiotic use before infection, recent use of immunosuppressants, and multidrug-resistant organisms. In addition, 2,913 clinical isolates were collected. The Gram-negative and Gram-positive bacteria accounted for 70.8% and 29.2% of all isolates, respectively. The most common pathogens were *Escherichia coli* (33.4%), *Klebsiella pneumoniae* (10.8%), and *Enterococcus faecium* (10.7%). *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the most common non-*Enterobacteriaceae* Gram-negative pathogens. *E. faecium*, *Enterococcus faecalis*, and *Staphylococcus aureus* were the most common Gram-positive pathogens. *E. coli*, *A. baumannii*, and *Enterobacter cloacae* were more commonly found in ICU patients than in non-ICU patients. Overall, the antibiotics tested in the CARES exhibited diminished susceptibility to pathogens over the study period, especially extended spectrum  $\beta$ -lactamase producing isolates.

**Conclusion:** Considering the current data set and high-level resistance of intra-abdominal pathogens to various antibiotics, further monitoring of the epidemiology of IAIs and their susceptibility to antibiotics through the CARES is warranted.

**Keywords:** intra-abdominal infections, risk factors, clinical outcomes, antimicrobial susceptibility, epidemiology

## Introduction

The Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) was launched in 2007 to investigate the antimicrobial susceptibility of causative patho-

gens in nosocomial infections in China. This nationwide surveillance program focuses on nosocomial infections, including bloodstream infections, hospital-acquired pneumonia, and intra-abdominal infections (IAIs), and currently includes 15 tertiary care hospitals.

IAIs are frequently encountered in clinical practice in hospital and healthcare settings. The etiology of these infections, usually polymicrobial in nature, can be diverse and often involves microorganisms derived from the intestinal microbiota.<sup>1</sup> IAIs are the second most common cause of infectious mortality in intensive care units (ICUs) and commonly result in high mortality and morbidity rates.<sup>2,3</sup> This study aimed to investigate the prevalence, risk factors, and outcomes of nosocomial IAIs in patients admitted to 15 Chinese teaching hospitals involved in the CARES between 2007 and 2016.

## Patients and methods

### Study centers and patients

A total of 15 study centers were included in the CARES, and this prospective observational study enrolled 2,756 patients with nosocomial IAIs from the CARES program between 2007 and 2016. The criteria for IAI diagnosis were as follows:

1. Presence of organisms cultured from purulent material sampled from the intra-abdominal space during surgical operation or needle aspiration.
2. Presence of abscess or other evidence of IAI observed during surgical operation or histopathologic examination.
3. Presence of at least two of the following signs or symptoms with no other recognized cause: fever ( $>38^{\circ}\text{C}$ ), nausea, vomiting, abdominal pain, or jaundice. In addition, at least one of the following criteria is matched:
  - a. Organisms cultured from drainage of a surgically placed drain (such as closed-suction drainage system, open drain, or T-tube drain).
  - b. Organisms observed on Gram's stain of drainage or tissue obtained during surgical operation or needle aspiration.
  - c. Organisms cultured from blood and radiographic evidence of infection (eg, abnormal findings on ultrasound, computed tomography, magnetic resonance imaging, radiolabel scans, or abdominal X-ray radiographs).<sup>4</sup>

According to the Infectious Diseases Society of America guideline, nosocomial infection includes cases involving patients with positive culture results from a normally sterile site obtained  $>48$  hours after hospital admission.<sup>5</sup> This study aimed to investigate the nosocomial IAIs, so patients with positive culture results from intra-abdominal body sites

obtained  $\leq 48$  hours after admission were excluded. Then all patients enrolled in this study were considered as nosocomial IAIs. Patients with incomplete data were also excluded. All data included were confirmed by chart review.

### Bacterial isolates

All isolates were collected from 15 tertiary care hospitals and cultured from specimens obtained from intra-abdominal body sites (eg, appendix, peritoneum, colon, bile, pelvis, or pancreas).<sup>6,7</sup> Acceptable specimens included tissue, fluid, or deep wound cultures obtained intra-operatively as well as fluid from paracentesis or percutaneous aspiration of abscesses.<sup>8,9</sup> Isolates recovered from blood, urine, and perirectal abscess sources outside the intra-abdominal body sites were excluded.<sup>3</sup>

### Antimicrobial susceptibility testing

Antimicrobial susceptibility was determined by the agar dilution method and broth microdilution method (only for tigecycline), and the results were interpreted according to the minimum inhibitory concentration (MIC) interpretive breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) in 2017.<sup>10</sup> The tested antimicrobial agents included amikacin, ampicillin, ceftazidime, chloramphenicol, cefotaxime, erythromycin, cefepime, ceftioxin, levofloxacin, moxifloxacin, minocycline, rifampicin, sulfamethoxazole, teicoplanin, vancomycin (National Institute for Food and Drug Control of China, Beijing, China), ciprofloxacin (Bayer AG, Leverkusen, Germany), ceftriaxone (Hoffman-La Roche Ltd., Basel, Switzerland), cefoperazone/sulbactam, piperacillin/tazobactam, tigecycline (Pfizer, Inc., New York, NY, USA), imipenem (Merck & Co., Inc., Whitehouse Station, NJ, USA), and meropenem (Sumitomo Dainippon Pharma, Osaka, Japan). The tigecycline test was performed according to the Food and Drug Administration standards. The double-disk synergy test was used to determine extended spectrum  $\beta$ -lactamase (ESBL) production among isolates of *Escherichia coli* and *Klebsiella pneumoniae* as recommended by the CLSI.<sup>10</sup> The reference isolates *E. faecalis* ATCC 29212, *S. aureus* ATCC29213, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as quality control isolates.

### Statistical analyses

The chi-squared test or Fisher's exact test was used to compare the categorical variables, and Student's *t*-test was used to compare the continuous variables. To control the effects of confounding variables and identify the independent risk factors associated with death, a stepwise conditional logistic regression analysis was performed.<sup>11</sup> All variables with a *P*-value  $< 0.10$

in univariate analysis were included in the multivariate logistic model.<sup>12</sup> OR and 95% CI were calculated. *P*-values <0.05 were considered statistically significant, and all tests were two-tailed. The WHONET software (version 5.6, <http://www.whonet.org/software.html>) and SPSS (version 22.0) software program (IBM, Armonk, NY, USA) were used for data analyses.

## Ethical statement

This study was approved by the research ethics board at Peking University People's Hospital. Informed consent was not needed due to that the medical records and patient information were anonymously reviewed and collected in this observational study.

## Results

### Baseline data

A total of 2,756 patients were included in this study: 2,494 patients (90.5%) in the survival group and 262 patients (9.5%) in the nonsurvival group. In the survival group, the median age was 57 years (range, 1–94 years) and 1,509 (60.5%) of them were men. In the nonsurvival group, the median age was 62 years (range, 1–92 years) and 150 (57.3%) of them were men. The 30-day all-cause mortality was 9.5% (262/2756). The main demographic and clinical features of all patients are summarized in Table 1.

### Species distribution of isolates

A total of 2,913 clinical isolates were collected from intra-abdominal body sites. The species distribution of these isolates is listed in Table 2. Gram-negative bacteria accounted for 70.8% and Gram-positive bacteria accounted for 29.2% of the isolates. The most common species were *E. coli* (973, 33.4%), *K. pneumoniae* (314, 10.8%), and *Enterococcus faecium* (312, 10.7%), followed by *P. aeruginosa* (230, 7.9%), *Acinetobacter baumannii* (186, 6.4%), *Enterococcus faecalis* (175, 6.0%), *Staphylococcus aureus* (140, 4.8%), and *Enterobacter cloacae* (104, 3.6%).

The species distribution of microorganisms collected from patients hospitalized in the ICU and non-ICU wards is presented in Table 3 (only species with ≥40 isolates are listed). *E. coli*, *A. baumannii*, and *E. cloacae* were more commonly found in ICU patients than in non-ICU patients (*P*<0.001, *P*<0.001, and *P*=0.018, respectively).

### Risk factors associated with the 30-day mortality

The results for the stepwise conditional logistic regression analysis of the multiple risk factors associated with death

are presented in Table 4. In the univariate analysis, 30-day mortality was associated with the following 12 factors (*P*<0.10): age >60 years (*P*=0.001), pulmonary disease (18.0% vs 12.2%, *P*=0.015), liver disease (19.2% vs 14.5%, *P*=0.059), renal disease (14.2% vs 9.9%, *P*=0.053), central venous catheter (27.5% vs. 21.8%, *P*=0.045), tracheal cannula (20.6% vs 15.6%, *P*=0.053), nasogastric tube (36.0% vs 43.1%, *P*=0.024), infection occurring in ICU (33.7% vs 27.1%, *P*=0.029), prior admission within 3 months (32.1% vs 25.6%, *P*=0.028), antibiotics use before infection (50.5% vs 42.7%, *P*=0.017), recent use of immunosuppressants (14.1% vs 9.2%, *P*=0.022), and multidrug-resistant organisms (21.6% vs 14.9%, *P*=0.009).

Multivariate analysis demonstrated the following independent predictors of death: age >60 years (OR, 1.109; 95% CI, 1.072–1.325; *P*<0.001), pulmonary disease (OR, 1.608; 95% CI, 1.023–2.403; *P*=0.027), tracheal cannula (OR, 1.407; 95% CI, 1.081–1.973; *P*=0.035), infection occurring in ICU (OR, 1.338; 95% CI, 1.208–1.911; *P*=0.013), prior admission within 3 months (OR, 1.425; 95% CI, 1.118–1.967; *P*=0.021), antibiotics use before infection (OR, 1.377; 95% CI, 1.048–1.782; *P*=0.009), recent use of immunosuppressants (OR, 1.633; 95% CI, 1.047–2.624; *P*=0.015), and multidrug-resistant organisms (OR, 1.583; 95% CI, 1.098–2.301; *P*=0.002).

### Antimicrobial susceptibility of isolates and antimicrobial resistance trends

Susceptibility rates, MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC ranges of all isolates causing IAIs between 2007 and 2016 are shown in [Tables S1–S6](#). The antimicrobial resistance trends of the main pathogens causing IAIs between 2007 and 2016 are also presented in [Figures S1–S4](#).

#### Enterobacteriaceae species

In general, tigecycline showed the highest activity (99.8% susceptible) against *Enterobacteriaceae*, followed by imipenem (98.3%), meropenem (97.9%), and amikacin (93.4%). Antimicrobial agents with susceptibility <50% included cefepime (47.9%), ceftriaxone (33.9%), cefotaxime (32.9%), levofloxacin (30.5%), and ciprofloxacin (29.7%). In addition, there was an increasing trend of carbapenem-resistant *Enterobacteriaceae* species (mainly carbapenem-resistant *E. coli* and carbapenem-resistant *K. pneumoniae*) between 2007 and 2016. The increasing trend of carbapenem-resistant *K. pneumoniae* was more rapid than that of carbapenem-resistant *E. coli*.

**Table 1** Demographic and clinical features of the 2,756 patients with IAIs in the study

| Variable                                 | Survival group (n=2494, 90.5%) |      | Nonsurvival group (n=262, 9.5% <sup>a</sup> ) |      | P-value |
|------------------------------------------|--------------------------------|------|-----------------------------------------------|------|---------|
|                                          | No.                            | %    | No.                                           | %    |         |
| <b>Demographics</b>                      |                                |      |                                               |      |         |
| Age, years, median (range)               | 57(1–94)                       | –    | 62(1–92)                                      | –    | –       |
| Gender, male                             | 1,509                          | 60.5 | 150                                           | 57.3 | 0.307   |
| <b>Comorbidities</b>                     |                                |      |                                               |      |         |
| Pulmonary disease                        | 450                            | 18.0 | 32                                            | 12.2 | 0.015   |
| Liver disease                            | 479                            | 19.2 | 38                                            | 14.5 | 0.059   |
| Renal disease                            | 353                            | 14.2 | 26                                            | 9.9  | 0.053   |
| Cardiovascular disease                   | 382                            | 15.3 | 40                                            | 15.3 | 0.997   |
| Neurological disease                     | 90                             | 3.6  | 15                                            | 5.7  | 0.105   |
| Cancer                                   | 423                            | 17.0 | 55                                            | 21.0 | 0.107   |
| Diabetes mellitus                        | 292                            | 11.7 | 37                                            | 14.1 | 0.256   |
| Agranulocytosis                          | 22                             | 0.9  | 5                                             | 1.9  | 0.144   |
| <b>Invasive procedures</b>               |                                |      |                                               |      |         |
| Splenectomy                              | 27                             | 1.1  | 5                                             | 1.9  | 0.259   |
| Tracheotomy                              | 208                            | 8.3  | 20                                            | 7.6  | 0.712   |
| Arterial catheter                        | 382                            | 15.3 | 37                                            | 14.1 | 0.619   |
| Central venous catheter                  | 685                            | 27.5 | 57                                            | 21.8 | 0.045   |
| Tracheal cannula                         | 514                            | 20.6 | 41                                            | 15.6 | 0.053   |
| Foley catheter                           | 1,075                          | 43.1 | 121                                           | 46.2 | 0.340   |
| Nasogastric tube                         | 898                            | 36.0 | 113                                           | 43.1 | 0.024   |
| <b>Other important clinical features</b> |                                |      |                                               |      |         |
| Infection occurred in ICU wards          | 841                            | 33.7 | 71                                            | 27.1 | 0.029   |
| Use of multiple antimicrobial agents     | 534                            | 21.4 | 66                                            | 25.2 | 0.173   |
| Surgical treatment                       | 1,372                          | 55.0 | 143                                           | 54.6 | 0.893   |
| <b>Past medical history</b>              |                                |      |                                               |      |         |
| Drinking history                         | 404                            | 16.2 | 41                                            | 15.6 | 0.831   |
| Smoking history                          | 464                            | 18.6 | 54                                            | 20.6 | 0.427   |
| Prior admission within 3 months          | 801                            | 32.1 | 67                                            | 25.6 | 0.028   |
| Antibiotic use before infection          | 1,259                          | 50.5 | 112                                           | 42.7 | 0.017   |
| Recent surgery                           | 1,200                          | 48.1 | 135                                           | 51.5 | 0.294   |
| Recent use of corticosteroids            | 481                            | 19.3 | 44                                            | 16.8 | 0.330   |
| Recent use of immunosuppressant          | 351                            | 14.1 | 24                                            | 9.2  | 0.022   |
| <b>Bacteria isolated from patients</b>   |                                |      |                                               |      |         |
| Gram-negative bacteria                   | 1,773                          | 71.1 | 182                                           | 69.5 | 0.579   |
| Multidrug-resistant organisms            | 538                            | 21.6 | 39                                            | 14.9 | 0.009   |
| <b>Sources of the IAI</b>                |                                |      |                                               |      |         |
| Peritoneum and peritoneal cavity         | 496                            | 19.9 | 59                                            | 22.5 | 0.314   |
| Abdominal and pelvic organs              | 1905                           | 76.4 | 189                                           | 72.2 | 0.130   |

Note: <sup>a</sup>9.5% is 30-day all-cause mortality.

Abbreviations: IAI, intra-abdominal infection; ICU, intensive care unit.

### *E. coli*

A total of 973 isolates were collected, including 491 ESBL-positive isolates and 482 ESBL-negative isolates. For these isolates, meropenem, imipenem, and tigecycline showed the highest activity (all  $\geq 97.8\%$  susceptible) against *E. coli*. However, some antibiotics exhibited very poor potency. Notably, ceftriaxone and cefotaxime were the least active agents, only displaying 0.8% susceptibility against ESBL-positive isolates. In addition, there was a relatively smooth uptrend of ESBL-producing *E. coli* isolates from 47.4% in 2007 to 52.7% in 2016.

### *K. pneumoniae*

A total of 314 isolates were collected, including 77 ESBL-positive isolates and 237 ESBL-negative isolates. Meropenem, imipenem, and tigecycline showed highest activity (all  $\geq 92.0\%$  susceptible) against *K. pneumoniae*. In addition, there was a relatively smooth uptrend of ESBL-producing *K. pneumoniae* isolates between 2007 and 2016 (except in 2011).

### *P. aeruginosa* and *A. baumannii*

A total of 230 *P. aeruginosa* isolates and 186 *A. baumannii* isolates were tested. Almost all the isolates showed high-

level resistance to diverse antimicrobial agents. However, only amikacin exhibited good activity (83.4% susceptible) against *P. aeruginosa*.

With regard to *A. baumannii* isolates, tigecycline exhibited the highest activity (84.4% susceptible) among the tested antimicrobial agents. *A. baumannii* was alarmingly resistant to diverse classes of antibiotics including third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems.

Both *P. aeruginosa* and *A. baumannii* showed the same trend of an initial increase followed by a decrease in resistance

to carbapenems. Nonetheless, a high resistance to carbapenems was a big threat with both the organisms.

### *S. aureus*

A total of 140 *S. aureus* isolates were collected, including 89 methicillin-susceptible *S. aureus* (MSSA) isolates (63.6%) and 51 methicillin-resistant *S. aureus* (MRSA) isolates (36.4%). All these isolates were susceptible to teicoplanin and vancomycin. In addition, all MSSA isolates were susceptible to minocycline. In contrast, fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) exhibited very poor activity against MRSA isolates. Erythromycin exhibited poor activity against both MRSA (13.8% susceptible) and MSSA (37.2% susceptible) isolates. The MRSA isolates showed an increasing trend from 2011 to 2016.

### *E. faecalis* and *E. faecium*

A total of 175 *E. faecalis* and 312 *E. faecium* isolates were collected. All the isolates were susceptible to teicoplanin and vancomycin ( $\geq 97.4\%$  susceptible). Overall, *E. faecium* isolates had a high resistance (84.0% resistant) to ampicillin, whereas *E. faecalis* isolates were much more susceptible to ampicillin (93.5% susceptible). Only 1.9% of *E. faecium* isolates showed resistance to vancomycin with a decreasing trend in resistance between 2007 and 2016.

## Discussion

In this study, we investigated the risk factors for nosocomial IAI and the outcomes of these infections. We found that age  $>60$  years, pulmonary disease, tracheal cannula, infection occurring in ICU, prior admission within 3 months, antibiotics use before infection, recent use of immunosuppressants, and multidrug-resistant organisms were independent predic-

**Table 2** Species distribution of the main pathogens in all IAI cases

| Species                            | N            | %           |
|------------------------------------|--------------|-------------|
| <b>Gram-negative bacteria</b>      | <b>2,063</b> | <b>70.8</b> |
| <i>Enterobacteriaceae</i>          | 1,559        | 53.5        |
| <i>E. coli</i>                     | 973          | 33.4        |
| <i>K. pneumoniae</i>               | 314          | 10.8        |
| <i>E. cloacae</i>                  | 104          | 3.6         |
| Others                             | 168          | 5.8         |
| Nonfermentative bacteria           | 454          | 15.6        |
| <i>P. aeruginosa</i>               | 230          | 7.9         |
| <i>A. baumannii</i>                | 186          | 6.4         |
| Others                             | 38           | 1.3         |
| Other Gram-negative bacteria       | 50           | 1.7         |
| <b>Gram-positive bacteria</b>      | <b>850</b>   | <b>29.2</b> |
| <i>Enterococcus</i>                | 539          | 18.5        |
| <i>E. faecalis</i>                 | 175          | 6.0         |
| <i>E. faecium</i>                  | 312          | 10.7        |
| Others                             | 52           | 1.8         |
| <i>Staphylococcus</i>              | 271          | 9.3         |
| <i>S. aureus</i>                   | 140          | 4.8         |
| <i>Staphylococcus haemolyticus</i> | 41           | 1.4         |
| <i>Staphylococcus epidermidis</i>  | 65           | 2.2         |
| Others                             | 25           | 0.9         |
| Other Gram-positive bacteria       | 40           | 1.4         |

**Abbreviation:** IAI, intra-abdominal infection.

**Table 3** Species distribution<sup>a</sup> of microorganisms collected from IAI patients hospitalized in ICU and non-ICU

| Species                | Total |      | ICU |      | Non-ICU |      | P-value |
|------------------------|-------|------|-----|------|---------|------|---------|
|                        | N     | %    | N   | %    | N       | %    |         |
| Total                  | 2,540 | 100  | 599 | 23.6 | 1941    | 76.4 |         |
| <i>E. coli</i>         | 973   | 38.3 | 186 | 19.1 | 787     | 80.9 | <0.001  |
| <i>K. pneumoniae</i>   | 314   | 12.4 | 76  | 24.2 | 238     | 75.8 | 0.837   |
| <i>E. faecium</i>      | 312   | 12.3 | 84  | 26.9 | 228     | 73.1 | 0.158   |
| <i>P. aeruginosa</i>   | 230   | 9.1  | 47  | 20.4 | 183     | 79.6 | 0.272   |
| <i>A. baumannii</i>    | 186   | 7.3  | 81  | 43.5 | 105     | 56.5 | <0.001  |
| <i>E. faecalis</i>     | 175   | 6.9  | 49  | 28.0 | 126     | 72.0 | 0.182   |
| <i>S. aureus</i>       | 140   | 5.5  | 34  | 24.3 | 106     | 75.7 | 0.921   |
| <i>E. cloacae</i>      | 104   | 4.1  | 14  | 13.5 | 90      | 86.5 | 0.018   |
| <i>S. epidermidis</i>  | 65    | 2.6  | 18  | 27.7 | 47      | 72.3 | 0.520   |
| <i>S. haemolyticus</i> | 41    | 1.5  | 10  | 24.4 | 31      | 75.6 | 0.950   |

**Note:** <sup>a</sup>Only species with  $\geq 40$  isolates are listed in the table.

**Abbreviations:** IAI, intra-abdominal infection; ICU, intensive care unit.

**Table 4** Univariate and multivariate analyses of the risk factors associated with 30-day all-cause mortality

| Characteristics                          | Univariate analysis |             |         | Multivariate analysis |             |         |
|------------------------------------------|---------------------|-------------|---------|-----------------------|-------------|---------|
|                                          | OR                  | 95% CI      | P-value | OR                    | 95% CI      | P-value |
| <b>Demographics</b>                      |                     |             |         |                       |             |         |
| Age >60 years                            | 1.034               | 1.026–1.052 | 0.001   | 1.109                 | 1.072–1.325 | <0.001  |
| Gender, male                             | 1.144               | 0.883–1.479 | 0.307   |                       |             |         |
| <b>Comorbidities</b>                     |                     |             |         |                       |             |         |
| Pulmonary disease                        | 1.582               | 1.089–2.354 | 0.015   | 1.608                 | 1.023–2.403 | 0.027   |
| Liver disease                            | 1.401               | 0.988–2.027 | 0.059   | 1.497                 | 0.997–2.019 | 0.053   |
| Renal disease                            | 1.496               | 0.996–2.319 | 0.053   | 1.476                 | 0.991–2.239 | 0.051   |
| Cardiovascular disease                   | 1.004               | 0.710–1.445 | 0.997   |                       |             |         |
| Neurological disease                     | 0.617               | 0.359–1.117 | 0.105   |                       |             |         |
| Cancer                                   | 0.769               | 0.564–1.061 | 0.107   |                       |             |         |
| Diabetes mellitus                        | 0.807               | 0.562–1.179 | 0.256   |                       |             |         |
| Agranulocytosis                          | 0.458               | 0.180–1.367 | 0.144   |                       |             |         |
| <b>Invasive procedures</b>               |                     |             |         |                       |             |         |
| Splenectomy                              | 0.563               | 0.227–1.657 | 0.259   |                       |             |         |
| Tracheotomy                              | 1.101               | 0.694–1.818 | 0.712   |                       |             |         |
| Arterial catheter                        | 1.100               | 0.770–1.602 | 0.619   |                       |             |         |
| Central venous catheter                  | 1.362               | 1.007–1.862 | 0.045   | 1.307                 | 0.976–1.834 | 0.064   |
| Tracheal cannula                         | 1.399               | 0.996–2.000 | 0.053   | 1.407                 | 1.081–1.973 | 0.035   |
| Foley catheter                           | 0.883               | 0.684–1.141 | 0.340   |                       |             |         |
| Nasogastric tube                         | 0.742               | 0.574–0.962 | 0.024   | 0.796                 | 0.652–1.157 | 0.069   |
| <b>Other important clinical features</b> |                     |             |         |                       |             |         |
| Infection occurring in ICU               | 1.369               | 1.033–1.828 | 0.029   | 1.388                 | 1.208–1.911 | 0.013   |
| Use of multiple antimicrobial agents     | 0.813               | 0.608–1.098 | 0.173   |                       |             |         |
| Surgical treatment                       | 1.018               | 0.787–1.314 | 0.893   |                       |             |         |
| <b>Past medical history</b>              |                     |             |         |                       |             |         |
| Drinking history                         | 1.042               | 0.740–1.493 | 0.831   |                       |             |         |
| Smoking history                          | 0.881               | 0.645–1.216 | 0.427   |                       |             |         |
| Prior admission within 3 months          | 1.377               | 1.034–1.849 | 0.028   | 1.425                 | 1.118–1.967 | 0.021   |
| Antibiotics use before infection         | 1.365               | 1.056–1.768 | 0.017   | 1.377                 | 1.048–1.782 | 0.009   |
| Recent surgery                           | 0.872               | 0.849–1.677 | 0.294   |                       |             |         |
| Recent use of corticosteroids            | 1.184               | 0.639–1.523 | 0.330   |                       |             |         |
| Recent use of immunosuppressants         | 1.624               | 1.067–2.558 | 0.022   | 1.633                 | 1.047–2.624 | 0.015   |
| <b>Bacteria isolated from patients</b>   |                     |             |         |                       |             |         |
| Gram-negative bacteria                   | 1.081               | 0.817–1.422 | 0.579   |                       |             |         |
| Multidrug-resistant organisms            | 1.572               | 1.113–2.263 | 0.009   | 1.583                 | 1.098–2.301 | 0.002   |
| <b>Sources of the IAI</b>                |                     |             |         |                       |             |         |
| Peritoneum and peritoneal cavity         | 0.854               | 0.632–1.167 | 0.314   |                       |             |         |
| Abdominal and pelvic organs              | 1.249               | 0.935–1.657 | 0.130   |                       |             |         |

**Abbreviations:** IAI, intra-abdominal infection; ICU, intensive care unit.

tors of patient survival. Compared to other representative surveillance programs which monitor the epidemiology and trends in antibiotic resistance of intra-abdominal pathogens to currently used therapies, such as the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, this study collected the demographic and clinical data of the patients in detail and analyzed the risk factors and clinical outcomes of nosocomial IAIs in China. The data and results of this study may be helpful to the IAI treatment in clinic.

A total of 2,913 isolates were collected from 15 tertiary care teaching hospitals involved in the CARES between 2007 and 2016. We analyzed the updated epidemiology and antimicrobial susceptibility of the causative pathogens. The

epidemiological data from our study highlights the diversity of intra-abdominal pathogens, as many different species causing IAIs were isolated. Of these, the most common species were *E. coli* (33.4%), *K. pneumoniae* (10.8%), and *E. faecium* (10.7%). Not surprisingly, *Enterobacteriaceae* isolates were the predominant species causing IAIs, accounting for at least 50% of all isolated pathogens.

Our study using data from the CARES program revealed several important findings. First, the combinations of cephalosporins, fluoroquinolones, and  $\beta$ -lactam/ $\beta$ -lactamase inhibitors tested in the CARES exhibited diminished susceptibility against the collected isolates over the study period. Second, the nonfermentative Gram-negative

bacilli were alarmingly resistant to diverse classes of antimicrobial agents. The susceptibilities of *A. baumannii* isolates to carbapenems, third- or fourth-generation cephalosporins, fluoroquinolones, and aminoglycosides were less than ~30%, which presents a key problem for empirical therapeutic choice. Although *A. baumannii* was not a major pathogen for IAIs, the trends of its resistance, especially, to carbapenems should be monitored.<sup>13</sup> Third, amikacin, tigecycline, and carbapenems including imipenem and meropenem were consistently potent against *Enterobacteriaceae* isolates throughout the study period. Thus, tigecycline monotherapy, carbapenem monotherapy, or amikacin-based combination therapy could provide the strongest activity against *Enterobacteriaceae* causing IAIs.<sup>8</sup> Fourth, the overall increase in the isolation of Gram-positive pathogens was accompanied by an increase in the multidrug-resistant phenotypes, making it difficult to choose the appropriate therapy for IAIs.

In our study, ESBL-producing isolates showed high-level resistance to diverse antimicrobial agents. A high prevalence of ESBL-producing isolates in China has been reported in several studies, and the continually diminishing susceptibility to many antimicrobial agents is alarming.<sup>6,14</sup> The SMART study, which monitored the resistance of Gram-negative pathogens causing IAIs, showed that 43.9% of *E. coli* and 30.4% of *K. pneumoniae* isolates were ESBL producers.<sup>3</sup> These ESBL-producing strains exhibited resistance to more antibiotics than non-ESBL-producing strains. Our current study showed that carbapenems and amikacin are the most active antibiotics, which was consistent with our antimicrobial susceptibility results. So far, the recommended antibiotics for the treatment of serious infections caused by ESBL-producing bacteria are carbapenems, particularly for patients with severe sepsis.<sup>15</sup> A previous study showed that the adequacy of initial antibiotic therapy for serious ESBL-infection was associated with mortality.<sup>16</sup>

A steady decrease in the susceptibility to most non-carbapenem antimicrobial agents has been observed over time; however, the carbapenem consumption has increased and maybe the reason for the increasing carbapenem resistance reported among *Enterobacteriaceae* species.<sup>17</sup> Despite increased consumption of carbapenems and the emergence of varieties of carbapenem resistant mechanisms, susceptibility of *Enterobacteriaceae* species to carbapenems was consistently high in our study.

Infections caused by resistant microorganisms increase the risk of mortality, especially because the initial empiric

therapy may be inadequate.<sup>1</sup> Due to the dissimilarity in the nature of the IAI pathogens, appropriate antibiotics for IAIs were studied, leading to differences in antibiotic treatment. Two publications were recommended as guidelines for empirical antibiotic treatment for IAIs.<sup>18,19</sup> To select adequate therapy for IAIs in clinical practice, updated data on the local resistance epidemiology of these pathogens should be available;<sup>1</sup> therefore, surveillance studies are necessary. Many epidemiological surveillance programs and studies worldwide, such as the SMART, China antimicrobial Surveillance Network (<http://www.chinets.com>), and CARES, have provided important information on the pathogens involved in many infections and ongoing resistance to the main classes of antibiotics used in clinical practice. Surveillance studies are key in not only identifying specific pathogens associated with IAIs but also assessing resistance rates and trends in resistance for antimicrobials commonly used to treat IAIs. The combination of resistance rates, trends in resistance over time, and trends in mechanisms of resistance will help physicians, pharmacists, and clinical microbiologists understand the evolution and spread of pathogens.<sup>20</sup>

Despite our important findings, the main problem of the present study is that it is observational in nature, which might result in limitations that preclude accurate comparisons, and thus unknown risk factors might have been unequally distributed between groups.

## Conclusion

Antibiotic resistance among IAI-causing species is a serious threat in China, and close monitoring of antibiotic resistance among pathogens associated with IAIs is crucial for guiding measures to prevent further emergence of resistance and to provide clinicians with the necessary information to appropriately select empirical therapy. Up-to-date national, regional, and global microbial surveillance is needed to provide updated information for the optimal therapy of IAIs.

## Data availability

The data sets supporting the conclusion of this article are included within the article and its [Supplementary materials](#).

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## Author contributions

On behalf of the CARES group, Hui Wang conceived and designed the study. She also checked the data and revised the article. Jiangang Zhang analyzed the data and wrote the paper. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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