***Epidemiology and Infection***

**Risk factors for antibiotic resistance development in healthcare settings in China: A systematic review**

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**Supplementary Material**

**Supplementary Table S1.** Detailed overview of the search strategy

|  |  |  |  |
| --- | --- | --- | --- |
| **Database** | **Languages** | **Search Terms** | **# of Hits** |
| PubMed | English | **Drug resistance, antimicrobial**  Drug Resistance, Microbial [MeSH] OR Drug Resistances, Microbial [MeSH] OR Antimicrobial Drug Resistance [MeSH] OR Drug Resistances [MeSH] OR Antibiotic Resistance, Microbial [MeSH] OR Antibiotic Resistance [MeSH] OR Resistance, Antibiotic [MeSH]  **Risk factors**  (Risk Factors [MeSH] OR Factor, Risk [MeSH] OR Factors, Risk [MeSH] OR Risk Factor [MeSH] OR Population at Risk [MeSH] OR Risk, Population at [MeSH] OR Populations at Risk [MeSH] OR Risk, Populations at [MeSH])) | 215 |
| Cochrane Library | 3 |
| CNKI | Chinese | ((Subject: (antibiotic resistance) OR Subject:(bacteria resistant)) AND (Subject:(risk factors) OR Subject:(factors, risk))) | 302 |
| VIP | 48 |
| WanFang | 1411 |
| **Total** | **Total** | **Total** | **1979** |

**Supplementary Table S2.** OR ranges reported by risk factor domain from 114 papers applying multivariate analyses 1

| Risk factor | | | | OR >1  to ≤2 | OR >2  to ≤3 | OR >3  to ≤4 | OR >4  to ≤5 | OR >5  to ≤6 | OR >6  to ≤7 | OR >7  to ≤8 | OR >8  to ≤9 | OR >9  to ≤10 | OR >10 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sociodemographic factors** | | | |  |  |  |  |  |  |  |  |  |  |
| **Age (n=5)** | | | | 5 (62.5%) | 3 (37.5%) | 1 (12.5%) | 1 (12.5%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (12.5%) | 0 (0) |
| **Sex (n=5)** | | | Male (n=3) | 2 (66.7%) | 1 (33.3%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Female (n=2) | 1 (50.5%) | 1 (50.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Education (n=1)** | | | | 1 (100.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Residence (n=3)** | | | | 1 (33.3%) | 1 (33.3%) | 0 (0) | 1 (33.3%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Annual income (n=3)** | | | | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Patient clinical information** | | | |  |  |  |  |  |  |  |  |  |  |
| **Severity of underlying disease (n=12)** | | | | 5 (41.7%) | 3 (25.0%) | 1  (8.3%) | 2 (16.7%) | 0 (0) | 0 (0) | 1  (8.3%) | 1  (8.3%) | 0 (0) | 0 (0) |
| **Laboratory test results (n=5)** | | | | 2 (40.0%) | 2 (40.0%) | 0 (0) | 0 (0) | 0 (0) | 1 (20.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Underlying diseases (n=38)** | | | NCDs 2 (n=12) | 2 (16.7%) | 1  (8.3%) | 1  (8.3%) | 5 (41.7%) | 0 (0) | 2 (16.7%) | 1  (8.3%) | 0 (0) | 1  (8.3%) | 2 (16.7%) |
|  | | | IDs 2 (n=20) | 2 (10.0%) | 10 (50.0%) | 6 (30.0%) | 5 (25.0%) | 2 (10.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (10.0%) |
|  | | | Other conditions (n=17) | 4 (23.5%) | 4 (23.5%) | 3 (17.6%) | 4 (23.5%) | 0 (0) | 1  (5.9%) | 1  (5.9%) | 0 (0) | 0 (0) | 2 (11.8%) |
| **Bacteria-related risk factors (n=7)** | | | | 2 (28.6%) | 0 (0) | 1  (14.3%) | 3 (42.9%) | 1  (14.3%) | 2 (28.6%) | 1  (14.3%) | 0 (0) | 0 (0) | 2  (28.6%) |
| **Admission in healthcare settings** | | | |  |  |  |  |  |  |  |  |  |  |
| **Hospital stay (n=45)** | | | | 15 (33.3%) | 9 (20.0%) | 9 (20.0%) | 5 (11.1%) | 4  (8.9%) | 3  (6.7%) | 1  (2.2%) | 1  (2.2%) | 1  (2.2%) | 5 (11.1%) |
| Current hospital stay (n=31) | | | | 12 (38.7%) | 4 (12.9%) | 3  (9.7%) | 5 (16.1%) | 4 (12.8%) | 3  (9.7%) | 0 (0) | 0 (0) | 1  (3.2%) | 4 (12.9%) |
|  | General department (n=17) | | | 8 (47.1%) | 2 (11.8%) | 1  (5.9%) | 3 (17.6%) | 2 (11.8%) | 2 (11.8%) | 0 (0) | 0 (0) | 1  (5.9%) | 1  (5.9%) |
|  |  | Length of stay (n=15) | | 8 (53.3%) | 0 (0) | 1  (6.7%) | 2 (13.3%) | 1  (6.7%) | 2 (13.3%) | 0 (0) | 0 (0) | 1  (6.7%) | 0 (0) |
|  | ICU (n=15) | | | 4 (26.7%) | 2 (13.3%) | 2 (13.3%) | 2  (13.3) | 2 (13.3%) | 1  (6.7%) | 0 (0) | 0 (0) | 0 (0) | 3 (20.0%) |
|  |  | Length of stay (n=7) | | 3 (37.5%) | 1 (12.5%) | 0 (0) | 2 (25.0%) | 1 (12.5%) | 1 (12.5%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Previous hospital stay (n=14) | | | | 3 (21.4%) | 5 (35.7%) | 6 (42.9%) | 0 (0) | 0 (0) | 0 (0) | 1  (7.1%) | 1  (7.1%) | 0 (0) | 1  (7.1%) |
|  | General department (n=14) | | | 3 (21.4%) | 4 (28.6%) | 6 (42.9%) | 0 (0) | 0 (0) | 0 (0) | 1  (7.1%) | 1  (7.1%) | 0 (0) | 1  (7.1%) |
|  |  | Length of stay (n=2) | | 2 (100.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
|  | ICU (n=1) | | | 0 (0) | 1 (100.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Invasive procedures (n=48)** | | | Respiratory system (n=25) | 0 (0) | 8 (32.0%) | 7 (28.0%) | 2  (8.0%) | 2  (8.0%) | 0 (0) | 1  (4.0%) | 2  (8.0%) | 0 (0) | 5 (20.0%) |
| Circulatory system (n=5) | 1 (20.0%) | 0 (0) | 2 (40.0%) | 1 (20.0%) | 0 (0) | 0 (0) | 0 (0) | 1 (20.0%) | 2 (40.0%) | 2 (40.0%) |
| Urinary system (n=8) | 0 (0) | 2 (25.0%) | 0 (0) | 0 (0) | 0 (0) | 1 (12.5%) | 2 (25.0%) | 0 (0) | 0 (0) | 0 (0) |
| Digestive system (n=3) | 0 (0) | 0 (0) | 1 (33.3%) | 0 (0) | 0 (0) | 2 (67.7%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Not clear (n=8) | 0 (0) | 1 (12.5%) | 2 (25.0%) | 2 (25.0%) | 2 (25.0%) | 0 (0) | 1 (12.5%) | 0 (0) | 0 (0) | 0 (0) |
| Length of procedure (n=11) | 2 (18.2%) | 0 (0) | 5 (45.5%) | 0 (0) | 0 (0) | 2 (18.2%) | 0 (0) | 1  (9.1%) | 0 (0) | 1  (9.1%) |
| **Surgery (n=3)** | | | | 0 (0) | 1 (33.3%) | 0 (0) | 0 (0) | 0 (0) | 2 (66.7%) | 0 (0) | 0 (0) | 0 (0) | 1 (33.3%) |
| **Drug exposure** | | | |  |  |  |  |  |  |  |  |  |  |
| **Current medication (n=33)** | | | | 10 (30.3%) | 9 (27.3%) | 9 (27.3%) | 6 (18.2%) | 0 (0) | 4 (12.2%) | 0 (0) | 1 (3.0%) | 0 (0) | 9 (27.3%) |
| Antibiotic exposure (n=32) | | | Monotherapy (n=20) | 5 (25.0%) | 3 (15.0%) | 5 (25.0%) | 4 (20.0%) | 0 (0) | 2 (10.0%) | 0 (0) | 1 (5.0%) | 0 (0) | 5 (25.0%) |
| Longer duration (n=12) | 3 (25.0%) | 3 (25.0%) | 3 (25.0%) | 1  (8.3%) | 0 (0) | `1  (8.3%) | 0 (0) | 0 (0) | 0 (0) | 3 (25.0%) |
| Combination therapy (n=7) | 3 (42.9%) | 2 (28.6%) | 0 (0) | 1 (14.3%) | 0 (0) | 1 (14.3%) | 0 (0) | 0 (0) | 0 (0) | 1 (14.3%) |
| Other drug exposure (n=2) | | | | 0 (0) | 1 (50.0%) | 1 (50.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Prior medication** 3 **(n=57)** | | | | 11 (19.3%) | 14 (24.6%) | 9 (15.8%) | 9 (15.8%) | 9 (15.8%) | 7 (12.3%) | 2  (3.5%) | 5  (8.8%) | 3  (5.3%) | 15 (26.3%) |
| Antibiotic exposure 4 (n=57) | | | Monotherapy (n=51) | 8 (15.7%) | 9 (17.7%) | 7 (13.7%) | 8 (15.7%) | 8 (15.7%) | 8 (15.7%) | 2  (3.9%) | 5  (9.8%) | 3  (5.9%) | 14 (27.5%) |
| Longer duration (n=5) | 2 (40.0%) | 1 (20.0%) | 0 (0) | 2 (40.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Combination therapy (n=10) | 1 (10.0%) | 2 (20.0%) | 1 (10.0%) | 4 (40.0%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (20.0%) |

1 Risk factors are reported as mentioned in the papers (n=number of papers). Because some papers reported multiple ORs for multiple factors within each domain, the individual rows add up to more than 100%.

2 Abbreviations: Non-communicable diseases, NCD; infectious diseases, IDs.

3 Prior medication refers to the medication history of the investigated patients within the past three months, such as prescriptions from clinical workers before they transferred from another hospital or clinical department, or self-medication by patients.

4 Papers only referred to antibiotic exposure (not to any other type of medication).

**Supplementary Table S3.** Information on Clinical Assessments Found to be Significant Risk Factors in Patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Risk Factors** | **Reported Terms 1** | **Reference Number 2** | **Range of Values 3** |
| Abnormal laboratory test results | Blood glucose (mmol/L) | 44 | 9 ± 7 |
| Hemoglobin (g/L) | 44 | 104 ± 26 |
| Serum albumin (g/L) | 165 | 25.28 ± 5.37 |
| TB sputum smear | 9, 95 | Positive test result |
| Bacteria-related risk factors for additional ABR infection | M. Tb resistance test 4 | 95, 148 | Test result as resistance |
| Produce ESBL | 29, 112, 115, 153 |
| Virulence genes *esp* | 139 |
| Physical functional scoring systems | APACHE II score | 83, 106, 131 | > 20 |
| Encephalopathy Grades | 5, 8 | II-IV level |
| mMRC dyspnea scores | 47 | 2.8 ± 1.2 |
| Modified Reiff HRCT score | 47 | 12.8 ± 5.0 |
| NYHA Classification | 161 | III or IV level |
| SOFA score | 175 | > 5 |
| Wagner Classification | 163 | III to V level |
| Pitt Bacteremia score | 55, 60 | > 3 |

1 Physical functional scoring systems refers to clinical assessments: Acute Physiology and Chronic Health Evaluation Ⅱ score (APACHE Ⅱ) [1]; Hepatic encephalopathy Grade [2]; modified score of Medical Research Council (mMRC) Dyspnea Scale [3]; modified Reiff score of High-resolution Computed Tomography (HRCT) [4]; New York Heart Association (NYHA) Classification [5]; Pitt Bacteremia score [6]; Wagner classification [7]; Sepsis-related Organ Failure Assessment (SOFA) scores [8].

2 Reference numbers in this table are correspondent to the reference numbers in Supplementary Word 2.

3 Results reported as mean ± standard deviations or scoring levels of patients diagnosed as antibiotic-resistant bacterial infections.

4 *M. Tb* refers to *Mycobacterium tuberculosis*.

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**Supplementary List 1.** A List of included papers published in English and Chinese

**Included papers published in English [1-60]:**

(1) **Cao B, et al.** Risk factors and clinical outcomes of nosocomial multi-drug resistant *Pseudomonas aeruginosa* infections. *Journal of Hospital Infection* 2004; **57**(2): 112-118.

(2) **Ye Y, et al.** *Enterobacter* bacteremia: Clinical features, risk factors for multiresistance and mortality in a Chinese University Hospital. *Infection* 2006; **34**(5): 252-257.

(3) **Huang Y, Zhuang S, Du M.** Risk factors of nosocomial infection with extended-spectrum beta-lactamase-producing bacteria in a neonatal intensive care unit in China. *Infection* 2007; **35**(5): 339-345.

(4) **Cao B, et al.** First report of clinical and epidemiological characterisation of vancomycin-resistant *enterococci* from mainland China. *International journal of antimicrobial agents* 2008; **32**(3): 279-281.

(5) **Shi S, et al.** Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. *Transplant Infectious Disease* 2009; **11**(5): 405-412.

(6) **Xu P, et al.** Prevalence of fluoroquinolone resistance among Tuberculosis patients in Shanghai, China. *Antimicrobial Agents and Chemotherapy* 2009; **53**(7): 3170-3172.

(7) **Zhang J, et al.** Carbapenem resistance mechanism and risk factors of *Pseudomonas aeruginosa* clinical isolates from a University Hospital in Xi'an, China. *Microbial drug resistance (Larchmont, NY)* 2009; **15**(1): 41-45.

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(9) **Yang X, et al.** Risk factors for drug resistance in pulmonary tuberculosis inpatients. *Journal of Evidence-Based Medicine* 2010; **3**(3): 162-167.

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(14) **Liu Q, et al.** Rates and risk factors for drug resistance tuberculosis in Northeastern China. *BMC Public Health* 2013; **13:1171.**(doi): 7.

(15) **Ji X, et al.** Clinical characteristics and risk factors of diabetic foot ulcer with multidrug-resistant organism infection. *The International Journal of Lower Extremity Wounds* 2014; **13**(1): 64-71.

(16) **Li D, et al.** Risk factors for hospital-acquired bloodstream infections caused by extended-spectrum beta-lactamase *Klebsiella pneumoniae* among cancer patients. *Irish Journal of Medical Science* 2014; **183**(3): 463-469.

(17) **Pang Y, et al.** Diagnostic dilemma: treatment outcomes of tuberculosis patients with inconsistent rifampicin susceptibility. *International Journal of Tuberculosis and Lung Disease* 2014; **18**(3): 357-362.

(18) **Peng Y, et al.** Multidrug-resistant *Pseudomonas aeruginosa* infections pose growing threat to health care-associated infection control in the hospitals of Southern China: a case-control surveillance study. *American Journal of Infection Control* 2014; **42**(12): 1308-1311.

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(20) **Wang K, et al.** Factors contributing to the high prevalence of multidrug-resistant tuberculosis among previously treated patients: a case-control study from China. *Microbial drug resistance (Larchmont, NY)* 2014; **20**(4): 294-300.

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(46) **Tan D, et al.** Identification of Risk Factors of Multidrug-Resistant Tuberculosis by using Classification Tree Method. *American Journal of Tropical Medicine and Hygiene* 2017; **97**(6): 1720-1725.

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**Supplementary Figure S1.** Study Quality: Risk of Bias Assessment According to MINORS

