Detection of common mobile genetic elements and genotyping of multidrug-resistant Gram-negative bacilli in blood specimens from septicemia patients in southern China

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Background: Integron, ISCR1 and complex class 1 integrons lead bacteria to become resistant to antibiotic regimens. The aim of this study was to detect common mobile genetic elements of multidrug-resistant Gram-negative bacilli and evaluate the genotyping of these bacilli in blood specimens from septicemia patients in southern China.

Methods: A total of 837 Gram-negative bacilli including 578 strains containing Enterobacteriaceae and 259 strains containing non-fermentative bacilli were investigated in blood samples collected from septicemia patients between 2011 and 2014 in southern China. Mobile genetic elements, such as class 1 integrons, the insertion sequence common region 1 (ISCR1), and complex class 1 integrons, were detected from the 837 strains.

Results: Twenty-seven types of gene cassette arrays were found among 837 strains in which 492 (58.8%) class 1 integron-positive isolates and 254 (51.6%) gene cassette-positive isolates were found, including the first description of two types, aacA4-blaADC-1/blaOXA-30-carB3 and aac(6’)-II-\(\text{cat}\)′-B3 and IMP-1-I. Twenty-seven types of gene cassette arrays were found among 837 strains in which 492 (58.8%) class 1 integron-positive isolates and 254 (51.6%) gene cassette-positive isolates were found, including the first description of two types, aacA4-blaADC-1/blaOXA-30-carB3 and aac(6’)-II-\(\text{cat}\)′-B3 and IMP-1-I. In the corresponding species and two gene cassettes, putative helicase and aadA-like, originally detected in integrons. Twelve types of ISCR1-linked resistance gene regions in 196 ISCR1-positive bacilli and seven different types of complex class 1 integron-positive strains were obtained including four distinct complex class 1 integrons that have never been described in any species. Enterobacterial repetitive intergenic consensus (ERIC)-PCR fingerprinting showed that isolates with identical gene profiles were clonally unrelated.

Conclusion: Our results indicated that we should pay more attention to enhance the quality of infection control measures and prevent hospital infection, so as to avoid the outbreak of multidrug-resistant Gram-negative bacilli.

Keywords: septicemia, multidrug-resistant, integron, ISCR1, complex class 1 integrons

Introduction

Septicemia is a serious medical condition where bacteria present in the blood circulatory system provoke an amplified and dysregulated immune response in the individual. A wide range of Gram-negative bacilli, in which the proportion was high, has been described in septicemia patients whose diagnosis of these infections can be confirmed by blood culture. Rapid antibiotic intervention is currently the only way to treat septicemia, which leads more and more bacteria to become resistant to antibiotic regimens, resulting in an urgent health problem worldwide.

Gram-negative bacilli confer high-level resistance to many widely used antibiotics such as β-lactams, tetracycline, aminoglycoside, and even carbapenems which can be encoded by genes that are transferable between bacteria. The rapid dissemination of
Bacterial DNA preparation

Total genomic DNA was extracted from stationary-phase broth cultures that were grown overnight in Luria–Bertani broth with the Ezup Column genomic DNA extraction kit (Sangon Biotech., Shanghai, China) according to the manufacturer’s instructions.

Detection and sequencing of integrons

A multiple PCR was carried out for the detection of integrase genes located at the conserved regions of class 1 integrons, followed by the amplification of the variable region of integrons. To determine the identical arrays of gene cassettes, same-sized amplicons were digested with Rsal and HinfI (Takara Bio., Tokyo, Japan) restriction enzymes, which were dependent on the species. Amplicons showing the same restriction fragment length polymorphism pattern were deemed to be identical, and one representative product of each distinct RFLP was purified and sequenced. The resulting DNA sequences were analyzed with the Basic Local Alignment Search Tool program at the homepage of the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/blast/). All the primers used are summarized in Table S1.

Detection and sequencing of iscr1

All strains were screened for the presence of iscr1 by PCR using the primers, iscr1-F and iscr1-R, designed to amplify orf513 segment of iscr1. Moreover, primers, iscr1-F and sul1-R, were used to amplify the iscr1-linked resistance genes. RFLP and sequencing analysis of the iscr1-linked resistance genes were same as the variable region of integrons.

Detection and sequencing of complex class 1 integron

The strains, whose variable region of integrons and iscr1-linked resistance genes were both positive, were considered carrying complex class 1 integron. Primers were designed at variable region of integrons and iscr1-linked resistance genes. Then, PCR was carried out and sequencing was followed.

Enterobacterial repetitive intergenic consensus (ERIC)-PCR analysis

ERIC sequences, present in many diverse eubacterial species, using genomic sequence information obtained primarily from Escherichia coli and Salmonella typhimurium, can be utilized as efficient primer binding sites in the PCR to produce fingerprints of different bacterial genomes.
ERIC-PCR of bacterial genomes was used to examine the genetic diversity of ESBL-producing *E. coli*, *Klebsiella pneumoniae*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. PCR products were analyzed on 2% agarose gels stained with ethidium bromide. ERIC-PCR fingerprinting was analyzed by visual examination and clustering analysis based on the Dice similarity coefficient and the unweighted pair group method with arithmetic mean (UPGMA) of strains using Quantity One software (Bio-Rad Laboratories Inc., Hercules, CA, USA).

**Results**

**Detection of integrons**

The prevalence of class 1 integron gene varied among different species (Table 1). A total of 492 *intI* gene-positive strains were obtained from 837 bacterial isolates (Table 2; Figure 1), and 254 of the isolates were positive for the variable region and the inserted gene cassette sizes varied in size from 0.6 to 3.0 kb. Gene cassette arrays could be divided into 27 types according to their restriction fragment lengths of the variable region-positive strains.

**Detection of ISCR1**

A total of 349 ISCR1-positive strains were obtained from 837 isolates (Table 1). Among them, regions of ISCR1-linked resistance genes were detected in 196 ISCR1-positive strains (Table 3; Figure 2). The range of detected ISCR1-linked resistance gene regions varied in size from 2.0 kb to 5.0 kb. A total of 12 distinct ISCR1-linked resistance gene arrangements were observed in the 837 isolates.

**Detection of complex class 1 integron**

There are 31 complex class 1 integron-positive strains that were obtained, and among them a total of seven distinct resistance gene arrangements were observed from 837 isolates (Figure 3).

**ERIC-PCR analysis**

ERIC-PCR analysis was performed to determine the genetic relatedness of the 90 *E. coli* and 98 *K. pneumoniae*. ERIC primers generated 1–21 bands, with molecular weights ranging from 0.25 to 5.0 kb. Fingerprinting was analyzed against 81 and 91 genotypes by UPGMA using 80% similarity as a cutoff point. The results of the cluster analysis showed that these isolates were unrelated. Similarly, 44 *A. baumannii* and 40 *P. aeruginosa* also had different genotypes according to the corresponding cluster analysis. ERIC fingerprinting revealed that the isolates were unrelated (Figure 4).

More details about the drug susceptibility of dominating isolates of multidrug-resistant Gram-negative bacilli are summarized in Table S2.

**Discussion**

The current study characterized integrons and their gene cassettes. A high frequency of class 1 integrons was observed.

### Table 1  Number of common mobile genetic elements in multidrug-resistant Gram-negative bacilli

| Bacterial species | No. of isolates | No. of *intI* gene-positive isolates (%) | No. of gene cassette-positive isolates (%) | No. of isolates containing ISCR1 (%) | No. of isolates containing ISCR1-linked genes (%) |
|-------------------|-----------------|-----------------------------------------|------------------------------------------|-------------------------------------|-----------------------------------------------|
| *Escherichia coli*| 182             | 168 (92.3)                              | 82 (48.8)                                | 53 (29.1)                           | 31 (38.5)                                    |
| *Klebsiella pneumoniae* | 204        | 144 (70.6)                              | 70 (48.6)                                | 133 (65.2)                          | 86 (64.7)                                   |
| *Klebsiella oxytoca* | 18             | 7 (38.9)                                | 3 (42.9)                                 | 5 (27.8)                            | 1 (20.0)                                    |
| *Enterobacter cloacae* | 63            | 21 (33.3)                               | 5 (23.8)                                 | 36 (57.1)                           | 18 (50.0)                                   |
| *Enterobacter aerogenes* | 52          | 17 (32.7)                               | 6 (35.3)                                 | 23 (44.2)                           | 11 (47.8)                                   |
| *Proteus mirabilis*  | 14             | 6 (42.9)                                | 3 (50.0)                                 | 2 (14.3)                            | 1 (50.0)                                    |
| *Serratia marcescens* | 12             | 5 (41.7)                                | 2 (40.0)                                 | 1 (8.3)                             | 1 (100.0)                                   |
| *Salmonella typhi*   | 15             | 5 (33.3)                                | 2 (40.0)                                 | 0                                  | –                                            |
| *Morganella morganii*| 5              | 1 (20.0)                                | 1 (100)                                  | 0                                  | –                                            |
| *Citrobacter freundii* | 13           | 2 (15.4)                                | 2 (100)                                  | 3 (23.1)                           | 1 (33.3)                                    |
| *Acinetobacter baumannii* | 89         | 60 (67.4)                               | 48 (80.0)                                | 54 (60.7)                           | 32 (39.3)                                   |
| *Acinetobacter spp.* | 15             | 5 (33.3)                                | 2 (40.0)                                 | 2 (13.3)                            | 1 (50.0)                                    |
| *Pseudomonas aeruginosa* | 82           | 35 (42.7)                               | 17 (48.6)                                | 34 (41.5)                           | 12 (35.3)                                   |
| *Pseudomonas putida*  | 12             | 3 (25.0)                                | 2 (66.7)                                 | 3 (25.0)                            | 1 (33.3)                                    |
| *Burkholderia cepacia* | 19            | 4 (21.1)                                | 3 (75.0)                                 | 0                                  | –                                            |
| *Achromobacter spp.*  | 8              | 4 (50.0)                                | 2 (50.0)                                 | 0                                  | –                                            |
| *Stenotrophomonas maltophilia* | 34      | 5 (14.7)                                | 4 (80.0)                                 | 0                                  | –                                            |

**Notes:** *Number of *intI* gene-positive isolates/total no. of isolates. *Number of gene cassette-positive isolates/no. of *intI* gene-positive isolates. *Number of isolates containing ISCR1/total no. of isolates. *Number of isolates containing ISCR1-linked gene/no. of isolates containing ISCR1.

**Abbreviation:** ISCR1, insertion sequence common region 1.
among multidrug-resistant Gram-negative bacteria, which corroborates well with a previous report.\textsuperscript{14,15} According to these results, most isolates carrying \textit{intI1} genes contained gene cassettes. However, a few isolates among the \textit{intI1}-positive strains did not contain gene cassettes. The main reasons may be the following: defects or mutations at the 3′-CS; gene cassette array in novel complex or unusual class 1 integrons; or the variable region was too long to be amplified. Of 27 different gene cassettes detected from 837 isolates, the most common type of gene cassettes included aminoglycoside resistance (\textit{aadA11}, \textit{aadA22}, \textit{aadA5}, \textit{aadA24}, \textit{aadA-like}, \textit{aadB}, \textit{aac(6′)-II}, \textit{aacA4}, and \textit{aphA15}), followed by \textit{β}-lactamase (\textit{bla}\textsubscript{OXA-10}, \textit{bla}\textsubscript{OXA-21}, \textit{bla}\textsubscript{PSE-1} and \textit{bla}\textsubscript{VIM-1}), trimethoprim resistance (\textit{dfrA1}, \textit{dfrA14}, \textit{dfrA17}, and \textit{dfr6}), and chloramphenicol resistance (\textit{cat}, \textit{catB2}, \textit{catB3}, and \textit{catB-like}). Two gene cassettes (putative helicase and \textit{aadA-like}) were first detected in integrons, indicating that integrons can efficiently capture and integrate genes. To the best of our knowledge, the resistance gene arrangement, \textit{aac6-aadA13-cmlA8-aadA1}, was reported for the first time in all bacteria, indicating that the resistance gene arrangement may disseminate between different bacteria and produce new gene arrangement.

According to the results, of the 837 strains, 196 isolates contained \textit{ISCR1}-linked resistance genes among \textit{ISCR1-positive} strains. Eleven genes (\textit{qnrA1}, \textit{qnrB2}, \textit{qnrB6}, \textit{bla}\textsubscript{DHA-1′}, \textit{ampR}, \textit{bla}_{\textsubscript{PER-1}}, \textit{insB}, \textit{sapA-like}, \textit{GST}, \textit{ABC} transporter, and short-chain dehydrogenase/reductase) were detected in 12 distinct \textit{ISCR1}-linked resistance gene arrays.

A total of seven distinct complex class 1 integron gene arrangements with a different gene cassette variable region composed of the 5′-CS and the 3′-CS. Enterobacteriaceae strains carrying complex class 1 integrons are becoming more

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**Table 2** Characterization of class 1 integron in multidrug-resistant Gram-negative bacilli

| Bacterial species (N) | Gene cassette array | No. of isolates (%) \* |
|-----------------------|---------------------|------------------------|
| \textit{Escherichia coli} (82) | dfrA27; dfrA17-aadA5 | 4 (4.9) |
| dfrB-aadA2 | 4 (4.9) |
| dfrA12-orfF-aadA2 | 1 (1.2) |
| dfrA17-aadA5 | 62 (75.6) |
| aacA4-cmlA1 | 2 (2.4) |
| dfrA5 | 4 (4.9) |
| dfrA1-orfC | 3 (3.7) |

**Table 3** Characterization of \textit{ISCR1}-linked gene in multidrug-resistant Gram-negative bacilli

| Bacterial species (N) | \textit{ISCR1}-linked gene | No. of isolates (%) \* |
|-----------------------|---------------------------|------------------------|
| \textit{Escherichia coli} (31) | \textit{bla}\textsubscript{CTX-M+}+ \textit{insB} | 31 (100.0) |
| \textit{Klebsiella pneumoniae} (86) | qnrA1+ \textit{ampR} | 66 (76.7) |
| \textit{aacA6+ arr-3} | 11 (12.8) |
| \textit{dfrA12+ aadA2} | 9 (10.5) |
| \textit{Klebsiella oxytoca} (1) | \textit{aacA6+ arr-3} | 1 (100.0) |
| \textit{Enterobacter cloacae} (18) | \textit{blac}_{\textsubscript{CTX-M+}}+ \textit{insB} | 18 (100.0) |
| \textit{Acinetobacter baumannii} (32) | arr-3+ dfrA16+ aadA2 | 4 (1.25) |
| \textit{aacB}+ \textit{bla}_{\textsubscript{PER-1}} | 11 (34.4) |
| \textit{DHA-1′}+ \textit{ampR} | 4 (12.5) |
| \textit{blac}_{\textsubscript{PER-1′}}+ \textit{GST}+ \textit{ABC} | 12 (37.5) |
| \textit{dfrA10} | 1 (3.1) |
| \textit{Acinetobacter spp.} (1) | \textit{sapA-like+ qnrB2} | 1 (100.0) |
| \textit{Pseudomonas aeruginosa} (12) | \textit{aacA6+ arr-3} | 10 (83.3) |
| \textit{reductase+ qnrB6} | 2 (16.7) |
| \textit{Pseudomonas putida} (1) | \textit{DHA-1′}+ \textit{ampR} | 1 (100.0) |

\*Note: Number of gene cassette-positive isolates/no. of \textit{intI1} gene-positive isolates.

Abbreviation: \textit{ISCR1}, insertion sequence common region 1.
Figure 1 Twenty-seven distinct class 1 integron resistance gene arrangements.

Notes: Integrase is represented by orange boxes. qacEΔ1/sul1 is represented by gray boxes.
common. In this study, two distinct complex class 1 integrons (C and G type) that have never been described before.

**Conclusion**
The study detected the molecular characteristics of Gram-negative bacilli in blood specimens from septicemia patients in southern China. Among 837 strains, two novel gene cassette arrays were found in 254 class 1 integron-positive isolates and seven different complex class 1 integron-positive strains were obtained in which two were not previously reported. The study of Gram-negative bacilli in blood specimens from hospitalized patients aids in the understanding of the propagation of Gram-negative bacilli, and effective infection control measures are urgently required to control
Figure 4.ERIC-PCR profile of (A) 90 ESBL-producing Escherichia coli, (B) 98 ESBL-producing Klebsiella pneumoniae, (C) 44 carbapenem-resistant Acinetobacter baumannii and (D) 40 carbapenem-resistant Pseudomonas aeruginosa.

Abbreviation: ERIC, enterobacterial repetitive intergenic consensus.

the transmission of Gram-negative bacilli in health care facilities in the country.

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Disclosure
The authors report no conflicts of interest in this work.
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## Supplementary materials

### Table S1 Primers used in this study

| Target                                   | Primer          | Sequence (5′-3′)                  | Reference |
|-------------------------------------------|-----------------|-----------------------------------|-----------|
| intI gene                                 | intI1-F         | GCATCTCGGTGTTTCTGG                | 1         |
|                                            | intI1-R         | GGTGTGCGGCGCTGCGTTG              |           |
| Resistance genes associated with class 1 integrons | 5′-CS          | GGCATCCAAGCAGAAG                  | 2         |
|                                            | 3′-CS           | AAGCAGACTGACCTGACGTA             |           |
| ISCR1                                     | ISCR1-F         | ATGGTTTACTGCCGTTGTT              | 3         |
|                                            | ISCR1-R         | CTAGGCTGACGTAGC                  |           |
| ISCR1-linked resistance genes             | ISCR1-F         | ATGGTCCATGCGGCTGTT               | 4         |
|                                            | sul1-R          | AGCCCGATACTAACCAGGCGCT           | 5         |
| 3′CS-ISCR1                                | Pc-F            | TATGGCTGAGCGCGACTG               |           |
|                                            | Pc-R            | CATTGAGGGAGTCGTGG                |           |
| aadA5-bla<sub>PeR-1</sub>                 | P1-F            | ACTGGTCTCAGTTGCGTCTTA            |           |
|                                            | P1-R            | ATGGGTCCGAGTCATTGAC              |           |
| bla<sub>PeR-2</sub> - dfrA10               | P2-F            | TGGTGCCTGATGGACG                 | This study|
|                                            | P2-R            | CTGATACGGAATGCTGCT               |           |
| aadA5-qnrA1                               | P4-F            | CGTGCTTTGCTGCTCTG                |           |
|                                            | P4-R            | TCTATGCGTACGTGAGTTGAG            | 5         |
| aadA2-bla<sub>PeR-3</sub>                 | P5-F            | CGTGCTTTGCTGCTG                 |           |
|                                            | P5-R            | GATTCGACGATGGTTGAGGTC            |           |
| dfrA25-sapa-like                          | P6-F            | ACGBCCGCGTGGTGAAGG               |           |
|                                            | P6-R            | TGGGAGGTCACTGAGA                 |           |
| bla<sub>OXa-10</sub>-sapa-like            | P7-F            | TTCAAAAGATCGCCAGAAG              | This study|
|                                            | P7-R            | CCGTAAACCGCAACC                  |           |
| ERIC-PCR                                  |                 |                                   |           |

**Abbreviation:** eRIC, enterobacterial repetitive intergenic consensus.

### Table S2 Susceptibility (SIR) pattern of dominating isolates of multidrug-resistant Gram-negative bacilli

| Antibiotic                  | Susceptibility SIR (%) | Escherichia coli (n=182) | Klebsiella pneumoniae (n=204) |
|-----------------------------|------------------------|--------------------------|------------------------------|
|                             |                        | ESBL producing (n=90)    | ESBL nonproducing (n=92)     | ESBL producing (n=98) | ESBL nonproducing (n=106) |
| Amikacin                    | 11.1                   | 0.0                      | 88.9                        | 3.3               | 0.0                        | 96.7                        | 6.6                        | 0.0                        | 93.4                        |
| Amoxicillin/clavulanic      | 43.3                   | 23.3                     | 66.7                        | 6.5               | 30.4                       | 94.6                        | 54.3                       | 20.4                       | 92.5                        |
| Ampicillin                  | 100.0                  | 0.0                      | 0.0                         | 65.2              | 0.0                        | 34.8                        | 0.0                        | 0.0                        | 0.0                         |
| Ampicillin/sulbactam        | 60.0                   | 25.6                     | 14.4                        | 15.2              | 30.4                       | 94.6                        | 54.3                       | 20.4                       | 92.5                        |
| Aztreonam                   | 76.7                   | 13.3                     | 10.0                        | 5.4               | 0.0                        | 94.6                        | 66.3                       | 13.3                       | 90.7                        |
| Cefazolin                   | 100.0                  | 0.0                      | 0.0                         | 27.2              | 0.0                        | 72.8                        | 100.0                     | 0.0                        | 100.0                      |
| Cefepime                    | 63.3                   | 13.3                     | 23.3                        | 5.4               | 0.0                        | 94.6                        | 57.1                       | 9.2                        | 33.7                       | 2.8                        | 97.2                        |
| Cefoperazone/sulbactam      | 11.1                   | 33.3                     | 55.6                        | 6.2               | 0.0                        | 93.8                        | 26.5                       | 20.4                       | 53.1                       | 5.7                        | 94.3                        |
| Cefotaxime                  | 100.0                  | 0.0                      | 0.0                         | 3.3               | 2.2                        | 94.6                        | 76.5                       | 0.0                        | 23.5                       | 6.6                        | 93.4                        |
| Cefazidime                  | 60.0                   | 6.7                      | 33.3                        | 6.3               | 0.0                        | 93.5                        | 60.2                       | 3.9                        | 96.1                       | 7.8                        | 92.5                        |
| Ciprofloxacin               | 73.3                   | 6.7                      | 20.0                        | 25.0              | 0.0                        | 75.0                        | 33.7                       | 6.1                        | 60.2                       | 11.3                       | 88.7                        |
| Gentamicin                  | 61.1                   | 0.0                      | 38.9                        | 30.4              | 0.0                        | 69.6                        | 53.1                       | 0.0                        | 46.9                       | 15.1                       | 84.9                        |
| Imipenem                    | 0.0                    | 1.1                      | 98.9                        | 0.0               | 0.0                        | 100.0                       | 2.0                        | 0.0                        | 98.0                       | 0.0                        | 100.0                      |
| Levofloxacin                | 73.3                   | 6.7                      | 20.0                        | 19.6              | 0.0                        | 80.4                        | 26.5                       | 0.0                        | 73.5                       | 6.6                        | 93.4                        |
| Meropenem                   | 0.0                    | 0.0                      | 100.0                       | 0.0               | 0.0                        | 100.0                       | 1.0                        | 0.0                        | 99.0                       | 0.0                        | 100.0                      |
| Piperacillin                | 100.0                  | 0.0                      | 0.0                         | 59.8              | 0.0                        | 40.2                        | 96.9                       | 0.0                        | 3.1                        | 19.8                       | 13.2                       | 67.0                        |
| Piperacillin/tazobactam     | 6.7                    | 0.0                      | 93.3                        | 0.0               | 0.0                        | 100.0                       | 20.4                       | 6.1                        | 73.5                       | 0.0                        | 100.0                      |
| Tetracycline                | 73.3                   | 6.7                      | 20.0                        | 59.8              | 0.0                        | 40.2                        | 53.1                       | 0.0                        | 46.9                       | 13.2                       | 6.6                        | 80.2                        |
| Trimethoprim/sulfamethoxazole| 70.0                  | NA                       | 30.0                        | 50.0              | NA                         | 50.0                        | 62.2                       | NA                         | 37.8                       | 22.6                       | NA                         | 77.4                        |

**Abbreviations:** R, resistance; I, indeterminate; S, sensitive; NA, not available.
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