The Comprehensive Antibiotic Resistance Database

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Motivation:

• Addressing antibiotic resistance requires research at molecular, clinical, population, agricultural, and environmental levels
• Common goals and objectives, but poorly integrated research findings
• Disparate sources of data, survey and experimental approaches, timelines, and research aims

Goal:

• Construction of a Comprehensive Antibiotic Resistance Database
• Development of predictive tools
Challenges:

- Broad diversity of prokaryotic pathogens and strains
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- Broad diversity of prokaryotic pathogens and strains
- Very diverse set of mechanisms and genes
- Plasmid-mediated resistance, transposable elements, horizontal gene transfer

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study


Summary
Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods Enterobacteriaceae isolates were studied from two major centres in India—Chennai (south India), Haryana (north India)—and those referred to the UK’s national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene, blaNDM-1, was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analysed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among Escherichia coli (36) and Klebsiella pneumoniae (11), which were highly resistant to all antibiotics except to tigecycline and colistin. K. pneumoniae isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids: those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

Interpretation The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated international surveillance is needed.

Funding European Union, Wellcome Trust, and Wyeth.

Introduction Bacteria from clinical and non-clinical settings are becoming increasingly resistant to conventional antibiotics. 30 years ago, concern centred on Gram-positive bacteria, particularly meticillin-resistant Staphylococcus aureus and continents. Much of this dissemination is undetected, with resistant clones carried in the normal human flora and only becoming evident when they are the source of endogenous infections. The CTX-M-15 extended-spectrum β-lactamase (ESBL) encoded by blaCTX-M-15, was first reported
Design Decisions:

- Development of a Antibiotic Resistance Ontology
- Initial focus upon molecular data
- Chado as the core organizing principle
- Use of a organismal ontology
- Ontology-centric interface
- Live curation of ontology and data
- Predictive tools
Drupal

1. DATA (NODES, ETC)
2. MODULES
3. BLOCKS & MENUS
4. USER PERMISSIONS
5. TEMPLATE

Chado

CARD modules
Drupal

Live editing of Chado contents

Viroblast

5) TEMPLATE

4) USER PERMISSIONS

3) BLOCKS & MENUS

2) MODULES

1) DATA (NODES, ETC)

Chado

CARD modules

Gbrowse2

Bio:DB:Das:Chado

CARD_GFF_loader

molecular data
The NCBI Taxonomy lacks complexity.
Prokaryote Issues

- The prokaryotic gene model
- Chado and SOFA compliance
- Circular genomes and plasmids
NDM-1 is a metallo-beta-lactamase discovered from a Swedish patient carrying a Klebsiella pneumoniae infection after hospitalization in India.
Data so far:

- 22 prokaryotic genomes, 108 plasmids, 3 transposable elements
- 74.7 Mbp of genome/plasmid sequence
- 67,990 protein-coding genes
- 194 species, subspecies, or strains
- 543 antibiotic resistance ontology (ARO) terms
- 2,560 ARO tagged protein-coding genes
Ontology Centric Website

amino glycoside resistance gene

Definition: Genes conferring resistance to aminoglycoside antibiotics.

Classification:
- is_a_determinant_of_antibiotic_resistance
- confers_resistance_to_aminoglycoside

Includes:
- aminoglycoside_acetyltransferase
- aminoglycoside_nucleotidytransferase
- aminoglycoside_phosphotransferase

Additional resistance information may be available at higher or lower levels of classification.

Taxonomic Distribution of Molecular Data:
- Acinetobacter baumannii 1B057
- Acinetobacter baumannii H2274
- Acinetobacter baumannii A11RR
- Acinetobacter baumannii AYE
- Acinetobacter baumannii SDF
- Staphylococcus aureus
- Campylobacter fetus subsp. fetus
- Campylobacter jejuni
- Brucella melitensis
- Clostridium perfringens
- Enterococcus faecalis
- Enterococcus faecium
- Escherichia coli
- Neisseria meningitidis
- Klebsiella pneumoniae
- Legionella pneumophila
- Mycobacterium fortuitum
- Pseudomonas aeruginosa
- Plasmid R391
- Plasmid R442a
- Plasmid R1466
# Ontology Centric Website

## Acinetobacter baumannii

### Sources
- 6  ➔ circular double stranded DNA chromosome
- 17 ➔ natural plasmid

### Molecular Data
- 21133 ➔ CDS
- 6 ➔ cloned region
- 1 ➔ gap
- 21700 ➔ gene
- 1 ➔ minus 10 signal
- 1 ➔ minus 35 signal
- 21133 ➔ mRNA
- 16 ➔ ncRNA
- 3 ➔ origin of replication
- 1 ➔ PCR product
- 21133 ➔ polypeptide
- 7 ➔ protein binding site
- 705 ➔ pseudogene
- 7 ➔ recombination feature
- 4 ➔ region
- 51 ➔ repeat region
- 1 ➔ ribozyme
- 2 ➔ RNA 6S
- 102 ➔ rRNA
- 415 ➔ tRNA

### Definition:

### External Data:

### Classification:

- **is_a Bacteria**

#### Includes:
- Acinetobacter baumannii 1656-2
- Acinetobacter baumannii AB0057
- Acinetobacter baumannii AB056
- Acinetobacter baumannii AB058
- Acinetobacter baumannii AB059
- Acinetobacter baumannii AB307-0294
- Acinetobacter baumannii AB500
- Acinetobacter baumannii ACICU
- Acinetobacter baumannii ATCC 17978
- Acinetobacter baumannii ATCC 19606
- Acinetobacter baumannii AYE
- Acinetobacter baumannii MDR-ZJ06
- Acinetobacter baumannii SDF
- Acinetobacter baumannii WBA9388
- Acinetobacter baumannii WBL7215
- Acinetobacter baumannii WBL7355

*additional resistance information may be available at higher or lower levels of classification*

[Visualize Ontology Subtree [new window]]

### Taxonomic Distribution of Molecular Data:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>279</td>
<td>Acinetobacter baumannii 1656-2</td>
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<tr>
<td>15416</td>
<td>Acinetobacter baumannii AB0057</td>
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<tr>
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<tr>
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<tr>
<td>13658</td>
<td>Acinetobacter baumannii ATCC 17978</td>
</tr>
<tr>
<td>48</td>
<td>Acinetobacter baumannii ATCC 19606</td>
</tr>
<tr>
<td>15112</td>
<td>Acinetobacter baumannii AYE</td>
</tr>
<tr>
<td>12681</td>
<td>Acinetobacter baumannii SDF</td>
</tr>
</tbody>
</table>
## Ontology Centric Website

### Definition:
A plasmid that occurs naturally.

### External Data:
- **ls_a_plasmid**
- **ls_a_extrachromosomal_mobile_genetic_element**

### Classification:
- Includes:
  - **natural_transposable_element**

*additional resistance information may be available at higher or lower levels of classification*

Visualize Ontology Subtree [new window]

### Taxonomic Distribution of Molecular Data:
- **4 Acinetobacter baumannii**
- **1 Acinetobacter baumannii A00507**
- **2 Acinetobacter baumannii ACICU**
- **2 Acinetobacter baumannii ATCC 17978**
- **1 Acinetobacter baumannii ATCC 19606**
- **4 Acinetobacter baumannii AYE**
- **3 Acinetobacter baumannii SDF**
- **1 Enterococcus faecalis**
- **3 Escherichia coli**
- **1 Escherichia coli O157:H7 str. Sakai**
- **2 Klebsiella pneumoniae**
- **1 Salmonella enterica subspp. enterica serovar Typhi**
- **68 Staphylococcus aureus**
  - **1 Staphylococcus aureus subspp. aureus COL**
  - **2 Staphylococcus aureus subspp. aureus ED98**
  - **1 Staphylococcus aureus subspp. aureus IH1**
  - **1 Staphylococcus aureus subspp. aureus IH9**
  - **1 Staphylococcus aureus subspp. aureus MSSA476**
  - **1 Staphylococcus aureus subspp. aureus Mu50**
  - **1 Staphylococcus aureus subspp. aureus N315**
  - **1 Staphylococcus aureus subspp. aureus RT388**
  - **3 Staphylococcus aureus subspp. aureus USA300 FRH3757**
  - **2 Staphylococcus aureus subspp. aureus USA300 TCH1516**
  - **1 Staphylococcus aureus subspp. aureus USA300 TCH959**

### Antibiotic Resistance
Clicking on numbers will list only those sequences precisely tagged for the term listed.
- **7 aminoglycoside**
- **14 aminoglycoside acetyltransferase (AAC)**

### Publications
More from PubMed...
Feature Page

**blaCTXM-1 protein.**
Encoded by gene blaCTXM-1.

**Related Features**
- X92506.gene (gene)
- X92506.gene.t01 (mRNA)

**Antibiotic Resistance**
(based on curations)
- CTX-M beta-lactamase
gene detected by antibiotic resistance screening microarray

**Sequence Ontology**
polypeptide

**Organism**
Escherichia coli

**Gene Ontology**
(based on curated, automated annotation)

**E.coli bla(CTX-M-1) gene (CARD: X92506)**

![Image of DNA sequence](image)

Coordinates: 1 - 876 (+ strand), Length: 876 bp (291 aa). Click on the image to view sequence in GBrowse, a tool for working with molecular sequences.

**Bioinformatics**
CARD: X92506.gene.p01
PMID: 8834013

**Experimental Data**

**>X92506.gene.p01**

HVEKSLAQFTLMAATAVVLLLSVPLYQAQTVQRLAELEQRGCSGRLQVALINTADDQIYTRADERFAMCSRSTSKNVAAYVLEKSERSDEFHELWQBEI
KREDLVY4TFIAXKHVQGQTHSLAELSSAATLTSIDRWHNKLISHVQPSAVTFAPAQLGDETFTLDMTEPLNTAIIPGDPDTTSPRAMAQTLKMLTLGK
ALGSGQRAQLTVVKKGGVNTGAASIQALPSAVVQGETGSAYGTTNCDIAVNPKEKDAPIVLVYTFTPQPKAESX3YLSAAKIV7NGL

**Publications:**
Lists as Power Tools
Resistance Gene Identifier
Resistance Gene Identifier
Future work:

- Ontology development
- Custom HMMs
- SNP models
- Data curation
- Minimum inhibitory concentration (MIC)
- Prevalence
- Metagenomics
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