مرور نظام‌مند استفاده از Colistin در درمان عفونت‌های گرم منفی

Mohammad J. Nasiri, PhD, MPH
Assistant professor
Shahid Beheshti University of Medical Sciences

November 2021
E-Mail: mj.nasiri@hotmail.com
Overview

✓ Global action plan on antimicrobial resistance
✓ Carbapenem-resistant gram-negative bacteria
✓ Colistin-resistant gram-negative bacteria
✓ Tigecycline-resistant gram-negative bacteria
✓ How to manage and detect drug resistant gram-negative bacteria
Antimicrobial resistance threatens the very core of modern medicine.

More than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result (CDC, 2019).

May 2015 World Health Organization (WHO) adopted a global action plan on antimicrobial resistance.
✓ to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;

✓ to strengthen the knowledge and evidence base through surveillance and research;

✓ to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;

✓ to optimize the use of antimicrobial medicines in human and animal health; and

✓ to increase investment in new medicines, diagnostic tools, vaccines and other interventions.
WHO priority list of antibiotic-resistant bacteria (2016):

- Carbapenem-resistant Acinetobacter baumannii and Pseudomonas aeruginosa
- Carbapenem-resistant and third-generation cephalosporin-resistant Enterobacteriaceae
WHO Action plan: Evidence-based research

Prevalence of Drug-resistant *Pseudomonas aeruginosa* in Iran: A Meta-analysis

A total of 34 reports available from different areas of Iran were included in the current study up to 2015.

Our meta-analyses showed that >40% of *P. aeruginosa* were resistant to imipenem.

The most common resistance was seen against ceftazidime (66.9%), followed by ciprofloxacin (52.9%) and cefepime (52.3%).
WHO Action plan: Evidence-based research; *P. aeruginosa*

Prevalence of Drug-resistant *Pseudomonas aeruginosa* in Iran: A Meta-analysis
WHO Action plan,
Evidence-based research; *P. aeruginosa*

---

**Antipseudomonal β-Lactams Resistance in Iran**

Mohammad Mahdi Rabiei,1 Keivan Asadi,1 Shervin Shokouhi,1,2 Mohammad Javad Nasiri,3 and Ilad Alavi Darazam1,2

**Table 1: The percentage of antimicrobial resistance.**

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Percent of articles reporting high resistance rate (&gt;50%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>42.4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>48.3</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>53.2</td>
</tr>
<tr>
<td>Cefepime</td>
<td>72</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>61</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>54.5</td>
</tr>
</tbody>
</table>

**High resistance frequency means more than 50%.
Prevalence of Drug-resistant *Klebsiella pneumoniae* in Iran: A Review Article
WHO Action plan:
Evidence-based research; *K. pneumoniae*
WHO Action plan:
Evidence-based research; *K. pneumoniae*

---

**Authors** | **ES (95% CI)** | **% Weight**
---|---|---
Bahramian | 0.10 (0.06, 0.17) | 3.07
Zare | 0.22 (0.10, 0.42) | 2.63
Kiaei | 0.21 (0.16, 0.28) | 3.11
Jafari | 0.10 (0.08, 0.12) | 3.19
Vaez | 0.04 (0.01, 0.12) | 2.99
Badamchi | 0.30 (0.22, 0.40) | 3.04
Ghasemnejad | 0.56 (0.46, 0.66) | 3.04
Tabrizi | 0.09 (0.04, 0.20) | 2.92
Gheitani | 0.73 (0.66, 0.79) | 3.12
Koraei | 0.24 (0.16, 0.35) | 3.01
Moghadampour | 0.64 (0.53, 0.73) | 3.01
Khodadadian | 0.26 (0.22, 0.30) | 3.17
Armin | 0.08 (0.05, 0.14) | 3.10
Shoja | 0.06 (0.04, 0.11) | 3.11
Hosseinzadeh | 0.14 (0.10, 0.19) | 3.13
Shokri1 | 0.68 (0.59, 0.75) | 3.07
Firoozeh1 | 0.27 (0.21, 0.33) | 3.12
Shahcheraghi1 | 0.12 (0.06, 0.22) | 2.97
Navidinia | 0.12 (0.07, 0.20) | 3.05
Sedighi | 0.08 (0.04, 0.15) | 3.05
Firoozeh2 | 0.27 (0.21, 0.33) | 3.12
Eftekhar | 0.09 (0.04, 0.20) | 2.93
Fazeli | 0.44 (0.35, 0.53) | 3.06
Zeighami | 0.08 (0.05, 0.14) | 3.10
Rajabnia | 0.30 (0.19, 0.44) | 2.91
Roodbari | 0.25 (0.20, 0.30) | 3.15
Farajzadeh | 0.19 (0.13, 0.26) | 3.09
Japoni-Nejad | 0.12 (0.07, 0.20) | 3.05
Kamali | 0.05 (0.02, 0.13) | 2.97
Nobari | 0.14 (0.10, 0.20) | 3.12
Rastegar-Lari | 0.66 (0.47, 0.80) | 2.73
Shokri2 | 0.87 (0.77, 0.93) | 3.00
Shahcheraghi2 | 0.16 (0.08, 0.29) | 2.88
**Overall** (I^2 = 96.60%, p = 0.00) | 0.24 (0.18, 0.31) | 100.00

WHO Action plan:
Evidence-based research; *K. pneumoniae*

![Image](image_url)

**Table 3. Mechanisms of Carbapenem Resistance in *Klebsiella pneumoniae***

<table>
<thead>
<tr>
<th>Genes responsible for carbapenem resistance</th>
<th>Number of studies</th>
<th>Number of carbapenem-resistant <em>K. pneumoniae</em></th>
<th>Number of genes responsible for carbapenem resistance, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>bla</em>&lt;sub&gt;OXA-48&lt;/sub&gt;</td>
<td>9</td>
<td>484</td>
<td>228 (47.1)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
<td>17</td>
<td>684</td>
<td>206 (30.1)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;GES&lt;/sub&gt;</td>
<td>7</td>
<td>366</td>
<td>102 (27.8)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;KPC&lt;/sub&gt;</td>
<td>15</td>
<td>815</td>
<td>99 (12.1)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;VIM&lt;/sub&gt;</td>
<td>14</td>
<td>880</td>
<td>94 (10.6)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;IMP&lt;/sub&gt;</td>
<td>9</td>
<td>523</td>
<td>24 (4.5)</td>
</tr>
</tbody>
</table>

Prevalence and Mechanisms of Carbapenem Resistance in *Klebsiella pneumoniae* and *Escherichia coli*: A Systematic Review and Meta-Analysis of Cross-Sectional Studies from Iran

Mohammad Javad Nasiri, Mehdi Miresaidi, Seyyed Mohammad Javad Mousavi, Mania Arshadi, Fatemeh Fardzadeh, Behnaz Dehghani, Sara Davoudabadi, Samin Zamani, Bahareh Hajikhan, Hossein Goudarzi, Mehdi Goudarzi, Zahra Sadat Seghatoleslami, Hossein Dabiri, and Payam Tabarsi
WHO Action plan: Evidence-based research; *E. coli*

**WHO Action plan:**
Evidence-based research; *E. coli*

### Table 4. Mechanisms of Carbapenem Resistance in Escherichia coli

<table>
<thead>
<tr>
<th>Genes responsible for carbapenem resistance</th>
<th>Number of studies</th>
<th>Number of carbapenem-resistant E. coli</th>
<th>Number of genes responsible for carbapenem resistance, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>bla</em>&lt;sub&gt;OXA-48&lt;/sub&gt;</td>
<td>2</td>
<td>78</td>
<td>29 (37.1)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;NDM&lt;/sub&gt;</td>
<td>4</td>
<td>114</td>
<td>25 (21.9)</td>
</tr>
<tr>
<td><em>bla</em>&lt;sub&gt;IMP&lt;/sub&gt;</td>
<td>3</td>
<td>83</td>
<td>8 (9.6)</td>
</tr>
</tbody>
</table>

Prevalence and Mechanisms of Carbapenem Resistance in *Acinetobacter baumannii*: A Comprehensive Systematic Review of Cross-Sectional Studies from Iran

Mohammad Javad Nasiri, Samin Zamani, Fatemeh Fardoosnej, Mania Arshadi, Reza Bigverdi, Bahareh Haijkhani, Hossein Goudarzi, Payam Tabarsi, Hossein Dabiri, and Mohammad Mehdi Feizabadi
WHO Action plan: Evidence-based research; A. baumannii

WHO Action plan:
Evidence-based research; A. baumannii

NOTE: Weights are from random effects analysis.
WHO Action plan: Evidence-based research; *A. baumannii*

### Table 2. Mechanisms of Carbapenem Resistance in Clinical Isolates of *Acinetobacter baumannii*

<table>
<thead>
<tr>
<th>Genes responsible for carbapenem resistance</th>
<th>Number of studies</th>
<th>Number of carbapenem-resistant <em>A. baumannii</em></th>
<th>Number of genes responsible for carbapenem resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$bla_{OXA-23}$</td>
<td>44</td>
<td>4,493</td>
<td>2,489 (55.3)</td>
</tr>
<tr>
<td>$bla_{OXA-24}$ like ($bla_{OXA-24}$, $bla_{OXA-40}$)</td>
<td>31</td>
<td>14,656</td>
<td>1,847 (41.4%)</td>
</tr>
<tr>
<td>$bla_{OXA-58}$</td>
<td>9</td>
<td>930</td>
<td>46 (5.2)</td>
</tr>
</tbody>
</table>

The remarkable therapeutic choices for carbapenem-resistant infections are colistin and tigecycline
Global prevalence of colistin resistance in clinical isolates of Acinetobacter baumannii: A systematic review and meta-analysis

Ali Pormohammad a, Kobra Mehdinejadi b, Pourya Gholizadeh c, Mohammad Javad Nasiri d, Naser Mohtavinejad e, Masoud Dadashi f, Samira Karimaei g, Hossein Safari h, Taher Azimi i

Colistin resistance in multidrug-resistant Acinetobacter baumannii: A systematic review and meta-analysis

Kamyab Makhdoomi Sharabiani i, Masoud Dadashi j,k, Narjess Bostanghadiri l, Mania Arshadi m, Mohammad Dashti Khavidaki n, Zahra Golzari o, Mohammad Sadegh Gholami p, Asma Hamzeyee q, Sina Shool r, Bita Mesgarpour s, Bahareh Hajikhani t, and Mohammad Javad Nasiri u
Colistin resistance in *A. baumannii, cont’*

Records identified through databases  
PubMed: 1234  
Embase: 2965  
Web of science: 1976

Records after duplicates removed (n=3843)

Title and abstract of records screened (n=3843)

Excluded irrelevant (n=2449)

Full-text articles assessed for eligibility (n=1394)

Excluded irrelevant (n=)
Reason for exclusion:
- Article not available
- Missing data, inconclusive or inexplicit data (invisible percentage, MIC50, combined bacteria stats, vague statements instead of numbers)
- Study population all COL-R
- Clinical study results were GNB not AB

Studies included (n=576)
Colistin resistance in *A. baumannii*, cont’

Table 1. The prevalence of colistin resistant in MDR isolates of *A. baumannii*

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of study</th>
<th>Prevalence of CRAB (95% CI)</th>
<th>n/N</th>
<th>Heterogeneity test, I² (%)</th>
<th>Heterogeneity test, P value</th>
<th>Egger’s test, t</th>
<th>Egger’s test, P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effects</td>
<td>576</td>
<td>3.1 (2.7-3.5)</td>
<td>3370/85825</td>
<td>80.301</td>
<td>&lt;.001</td>
<td>13.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Researches before 2006</td>
<td>53</td>
<td>1.9 (1.2-2.9)</td>
<td>325/9108</td>
<td>86.229</td>
<td>&lt;.001</td>
<td>10.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Researches between 2006-2011</td>
<td>205</td>
<td>2.4 (1.9-2.9)</td>
<td>685/32156</td>
<td>78.431</td>
<td>&lt;.001</td>
<td>7.624</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Researches After 2011</td>
<td>318</td>
<td>3.9 (3.3-4.5)</td>
<td>2360/44561</td>
<td>86.224</td>
<td>&lt;.001</td>
<td>8.197</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; n: Number of events (CRAB isolates); N: The total number of *A. baumannii*. 
### Colistin resistance in *A. baumannii*, cont’

<table>
<thead>
<tr>
<th>AB</th>
<th>Country</th>
<th>Resistance (CFU/mL)</th>
<th>Resistance (CFU/mL)</th>
<th>Resistance (CFU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Greece</td>
<td>31</td>
<td>1450/18451</td>
<td>5.2 (3.2-8.4)</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>43</td>
<td>201/3305</td>
<td>3.9 (2.4-6.3)</td>
</tr>
<tr>
<td></td>
<td>Iran</td>
<td>92</td>
<td>440/9944</td>
<td>3.8 (2.9-5.1)</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>26</td>
<td>35/2460</td>
<td>2.5 (1.9-3.4)</td>
</tr>
<tr>
<td></td>
<td>Japan</td>
<td>3</td>
<td>4/75</td>
<td>7.3 (3.1-16.3)</td>
</tr>
<tr>
<td></td>
<td>Jordan</td>
<td>4</td>
<td>2/322</td>
<td>1.3 (0.5-1.6)</td>
</tr>
<tr>
<td></td>
<td>Korea</td>
<td>21</td>
<td>140/1562</td>
<td>6.2 (3.5-10.7)</td>
</tr>
<tr>
<td></td>
<td>Lebanon</td>
<td>7</td>
<td>1/366</td>
<td>1.7 (0.6-4.5)</td>
</tr>
</tbody>
</table>
Colistin resistance in *P. aeruginosa*

Detection of New Delhi Metallo-β-lactamase-1 among *Pseudomonas aeruginosa* isolated from adult and Pediatric patients in Iranian hospitals


According to the results of the MIC test, the rate of Colistin resistance was 12 (17.1%), which was observed in 1 (1.4%) of children (Table 3).
Moreover, according to MIC results, a much lower level of resistance to colistin was observed at 31.7 % (19) in this study (Table 2).
Colistin resistance in *E. coli*

Molecular characteristics of antibiotic-resistant *Escherichia coli* and *Klebsiella pneumoniae* strains isolated from hospitalized patients in Tehran, Iran

Javad Yasbolaghi Sharahi¹, Ali Hashemi¹✉, Abdollah Ardebili²,³ and Sara Davoudabadi¹

**Results:** Notably, 16 (9.7%) isolates showed resistance to colistin.
Colistin resistance

- Colistin resistance is caused by:
  - Decreases in the net negative charge of the outer membrane,
  - Loss of lipid A
  - Efflux pumps
  - Plasmid-encoded mcr genes (plasmid-mediated)
Tigecycline

- Tigecycline: The Only FDA Approved Analog of Glycycline which is a Derivative of Tetracycline.
- Tigecycline is Broad Spectrum Antibiotic
- It is Bacteriostatic in Antibiotic’s Classification (i.e. It Inhibit and Stop the Growth Of Bacteria)
- FDA
  Approved for the Treatment of Skin Infections: 2005
  Approved for the Treatment of Intra-abdominal Infections: 2005
  Approved for the Treatment of Community Acquired Pneumonia: 2009
Tigecycline

Tigecyclines Mode Of Action

- Tigecycline, a glycycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit.

- Tigecycline is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux.
Tigecycline: mechanisms of resistance

Overexpression of efflux pumps in the was the main mechanisms of resistance.
**Tigecycline: in-vitro study**

**Table 1** Antibiotic resistance patterns of 165 isolates of *K. pneumoniae* and *E. coli*

<table>
<thead>
<tr>
<th>Species (no (%) of isolates)</th>
<th>Antibiotic resistance patterns</th>
<th>TGC</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em> (113)</td>
<td>Susceptible</td>
<td>104 (92%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>6 (5.3%)</td>
</tr>
<tr>
<td></td>
<td>Resistant</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> (52)</td>
<td>Susceptible</td>
<td>32 (61.5%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>14 (26.9%)</td>
</tr>
<tr>
<td></td>
<td>Resistant</td>
<td>6 (11.5%)</td>
</tr>
</tbody>
</table>
Clinical Studies on Complicated Skin Infections

Randomized, Double-blind, Active-controlled, Multinational, Multicenter Studies

- These studies compared TigecyclineL (100 mg i/v initial dose followed by 50 mg every 12 hours) with Vancomycin (1 g i/v every 12 hours)/aztreonam (2 g intravenous every 12 hours) for 5 to 14 days

- No. of Patients: 1116
- Patients Cured with Tigecycline were 566 and with combination are 550
- Duration: 14 days
- Nausea vomiting cause with Tigecycline / with combination elevated hepatic aminotransferase
- Conclusion: Tigecycline is safe mono therapy then combination

[Link to Google Scholar]
Clinical Studies on Complicated Intra-Abdominal Infections
Randomized, Double-blind, Active-controlled, Multinational, Multicenter Studies

- These studies compared Tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg intravenous every 6 hours)

- Patients with complicated diagnoses including appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies

- Complicated intra-abdominal infections (cIAI) remain challenging to treat because of their polymicrobial etiology including multi-drug resistant bacteria. The efficacy and safety of tigecycline, an expanded broad-spectrum glycyclcline antibiotic, was compared with imipenem/cilastatin (IMI/CIS) in patients with cIAI.

- This study demonstrates that tigecycline is as efficacious as imipenem/cilastatin in the treatment of patients with cIAI.

Clinical Studies on Community Acquired Bacterial Pneumonia

Randomized, Double-blind, Active-controlled, Multinational, Multicenter Studies

• These studies compared

  Tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) with levofloxacin (500 mg intravenous every 12 or 24 Hours)

• No. of Patients : 428

• Patients who received at least one dose of study drug, 79% had CAP of mild-moderate severity according to their Fine score.

• Clinical cure rates for the CE population were 88.9% for Tigecycline and 85.3% for levofloxacin.

https://www.ncbi.nlm.nih.gov/pubmed/27754764
How to detect colistin and tigecycline resistance

- The minimum inhibitory concentrations (MICs) should be determined by broth microdilution method on Cation-Adjusted Mueller Hinton broth (Merck, Germany), and the results were analyzed according to the CLSI guidelines.

- *E. coli* ATCC 25922 should be used as a quality control strain for MIC results.

- Sequencing of plasmid-mediated genes (mcr-1, mcr-2, mcr-3, and mcr-4), and chromosomally-mediated genes of the LPS (mgrB, pmrA, pmrB, phoP, and phoQ)
Conclusions

- The emergence and spread of multi-drug-resistant bacteria will further limit the treatment options.

- Performing CLSI recommended drug susceptibility testing for all cases to provide effective treatment, and continuous monitoring of drug resistance are recommended for prevention and control of drug-resistant isolates.
Thank you for your attention