Haemophilus influenzae

Benzylpenicillin 1 unit as screen for beta-lactam resistance
**Haemophilus influenzae**

MIC and zone diameter correlates

- The following histograms present inhibition zone diameter distributions from EUCAST antimicrobial susceptibility testing. In most, the different colours of the bars indicate different MIC values. In some, the colours of the bars indicate a resistance gene or a resistance mechanism.

- The distributions include data for wild-type isolates and for isolates with acquired resistance mechanisms. A large number of isolates with MIC values close to the edge of the wild-type distribution and/or close to EUCAST clinical breakpoints were intentionally included. These distributions can not be used to infer resistance rates or the performance of the tests with routine isolates.

- For some agents, isolates were tested on more than one occasion, including parallel tests with disks and media from several manufacturers. When this is the case, data are presented as both the “number of isolates tested” and the “total number of MIC-zone diameter correlates”, including replicate tests and parallel tests with disks and media from different sources.
**Haemophilus influenzae**

Materials and methods

- Antimicrobial susceptibility testing was performed on a collection of *Haemophilus influenzae*, including many isolates with beta-lactam resistance. Disk diffusion was performed on MH-F media according to EUCAST methodology and MIC determination was performed with the ISO broth microdilution method using MH-F broth.

- The following graphs present inhibition zone distributions for benzylpenicillin 1 unit with MIC values for clinically important beta-lactam agents or resistance mechanisms as coloured bars. A nitrocefin-based disk test was used to analyse β-lactamase production and PCR was used to detect PBP mutations.

- The distributions in this presentation are the result of a collaboration between EUCAST, JMI Laboratories (USA) and Laboratory Specialists Inc. (USA).

- This presentation is based on EUCAST Clinical Breakpoint Tables v. 9.0.
## Changes from previous version (4.1)

<table>
<thead>
<tr>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Information added on the use of benzylpenicillin 1 unit as screen for beta-lactam resistance.</td>
</tr>
<tr>
<td>• Flow chart updated.</td>
</tr>
<tr>
<td>• Amoxicillin and amoxicillin-clavulanic acid breakpoints also valid for oral administration.</td>
</tr>
<tr>
<td>• New distributions for benzylpenicillin 1 unit vs. piperacillin-tazobactam MIC.</td>
</tr>
<tr>
<td>• MIC breakpoints changed for cefpodoxime.</td>
</tr>
<tr>
<td>• Graph for benzylpenicillin 1 unit vs. doripenem removed due to removed breakpoints.</td>
</tr>
</tbody>
</table>
**Haemophilus influenzae**
Screen for beta-lactam resistance

- The benzylpenicillin 1 unit disk screen test shall be used to exclude beta-lactam resistance mechanisms.

- The screening breakpoint for benzylpenicillin 1 unit is S $\geq 12$ mm.

- When the screen is negative, all beta-lactam agents for which clinical breakpoints are available, including those with a “Note”, can be reported susceptible without further testing.

- When the screen is positive, see flow chart for interpretation.
Haemophilus influenzae
Screen for beta-lactam resistance

Disk diffusion test with benzylpenicillin 1 unit disk
Always perform in parallel with testing of other beta-lactam agents

Zone diameter ≥12 mm
Excludes all beta-lactam resistance mechanisms

- Report susceptible (S) to any beta-lactam agents for which clinical breakpoints are available, including those with “Note”.

Zone diameter <12 mm
Beta-lactamase and/or PBP3 mutations

- Ampicillin, amoxicillin and piperacillin (without beta-lactamase inhibitor)
  - Beta-lactamase positive
    - Report resistant (R)
  - Beta-lactamase negative
    - Report susceptibility according to the clinical breakpoints for the agent in question.

- Other beta-lactam agents except cefepime, cefpodoxime and imipenem*

*For cefepime, cefpodoxime and imipenem, if resistant by both screen and agent disk diffusion test, report resistant. If resistant by screen test and susceptible by agent disk diffusion test, determine the MIC of the agent and interpret according to breakpoints.
Explanation of graphs:

Zone diameter distribution with MIC values or resistance mechanisms as coloured bars.

**Benzylpenicillin 1 unit vs. Ceftaroline MIC**

*H. influenzae*, 105 isolates

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>No of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Zone diameter breakpoint

Resistant by EUCAST MIC breakpoints

Susceptible by EUCAST MIC breakpoints
Benzylpenicillin 1 unit vs. β-lactam resistance mechanism

*H. influenzae*, 137 clinical isolates

Breakpoints

Benzylpenicillin zone diameter (screen)  S≥12 mm
Benzylpenicillin 1 unit vs. Ampicillin MIC
H. influenzae, 167 isolates (212 correlates)

(3 data sources)

Breakpoints
Ampicillin MIC  S≤1, R>1 mg/L  
Benzylpenicillin zone diameter (screen)  S≥12 mm

ECOFF  1 mg/L
Benzylpenicillin 1 unit vs. Ampicillin-sulbactam MIC

*H. influenzae*, 145 isolates

(1 data source)

- MICs with fixed concentration of sulbactam at 4 mg/L.

**Breakpoints**

<table>
<thead>
<tr>
<th>Ampicillin-sulbactam MIC</th>
<th>S≤1, R&gt;1 mg/L</th>
<th>ECOFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
<td>1 mg/L</td>
</tr>
</tbody>
</table>
Benzylpenicillin 1 unit vs. Amoxicillin MIC

*H. influenzae*, 173 isolates (226 correlates)

(3 data sources)

### Breakpoints

<table>
<thead>
<tr>
<th>Amoxicillin MIC (iv and oral)</th>
<th>S≤2, R&gt;2 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
</tr>
</tbody>
</table>

**ECOFF**

- **MIC (mg/L)**
  - ≥128
  - 64
  - 32
  - 16
  - 8
  - 4
  - 2
  - 1
  - 0.5
  - ≤0.25
Benzylpenicillin 1 unit vs. Amoxicillin-clavulanic acid MIC

_H. influenzae_, 114 isolates

(2 data sources)

MICs with fixed concentration of clavulanic acid at 2 mg/L.

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>No of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥16</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
</tr>
<tr>
<td>≤0.125</td>
<td>0</td>
</tr>
</tbody>
</table>

Breakpoints

- **Amoxicillin-clavulanic acid MIC (iv and oral)**: S≤2, R>2 mg/L
- **Benzylpenicillin zone diameter (screen)**: S≥12 mm
- **ECOFF**: 2 mg/L
Benzylpenicillin 1 unit vs. Piperacillin-tazobactam MIC

*H. influenzae*, 146 isolates

(1 data source)

**Breakpoints**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Breakpoint</th>
<th>ECOFF (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam MIC</td>
<td>S≤0.25, R&gt;0.25 mg/L</td>
<td>0.06 mg/L</td>
</tr>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
<td></td>
</tr>
</tbody>
</table>
Benzylpenicillin 1 unit vs. Cefepime MIC

*H. influenzae*, 189 isolates

(2 data sources)

**Breakpoints**

<table>
<thead>
<tr>
<th>Cefepime MIC</th>
<th>S≤0.25, R&gt;0.25 mg/L</th>
<th>ECOFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
<td>0.25 mg/L</td>
</tr>
</tbody>
</table>
Benzylpenicillin 1 unit vs. Cefixime MIC

*H. influenzae*, 147 isolates

(1 data source)

**Breakpoints**

<table>
<thead>
<tr>
<th>Cefixime MIC</th>
<th>S ≤ 0.125, R &gt; 0.125 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S ≥ 12 mm</td>
</tr>
</tbody>
</table>

**ECOFF** 0.125 mg/L
Benzylpenicillin 1 unit vs. Cefotaxime MIC
*H. influenzae*, 161 isolates (193 correlates)

(3 data sources)

**Breakpoints**

<table>
<thead>
<tr>
<th>Cefotaxime MIC</th>
<th>Benzylpenicillin zone diameter (screen)</th>
<th>ECOFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>S≤0.125, R&gt;0.125 mg/L</td>
<td>S≥12 mm</td>
<td>0.06 mg/L</td>
</tr>
</tbody>
</table>
Benzylpenicillin 1 unit vs. Cefpodoxime MIC

*H. influenzae*, 146 isolates

(1 data source)

**Breakpoints**

<table>
<thead>
<tr>
<th>Cefpodoxime MIC</th>
<th>S\leq0.25, R&gt;0.25 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S\geq12 mm</td>
</tr>
<tr>
<td>0.25 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

**Diagram Description**

- The graph shows the inhibition zone diameter (mm) for Benzylpenicillin 1 unit vs. Cefpodoxime MIC for *H. influenzae*, 146 isolates.
- The x-axis represents the inhibition zone diameter in millimeters, ranging from 6 to 40 mm.
- The y-axis represents the number of observations.
- Different colors and shades indicate the MIC (mg/L) ranges:
  - 0.03
  - 0.06
  - 0.125
  - 0.25
  - 1
  - 2
  - 4
  - 8
  - \geq16

**Legend**

- No of observations: 0, 1, 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40.

**Additional Note**

- No specific locations are provided for the Breakpoints and ECOFF values within the diagram.
**Benzylpenicillin 1 unit vs. Ceftaroline MIC**

*H. influenzae, 105 isolates*

(1 data source)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>No of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.002</td>
<td>6</td>
</tr>
<tr>
<td>≤0.008</td>
<td>2</td>
</tr>
<tr>
<td>≤0.016</td>
<td>1</td>
</tr>
<tr>
<td>≤0.03</td>
<td>4</td>
</tr>
<tr>
<td>≤0.06</td>
<td>2</td>
</tr>
<tr>
<td>≤0.125</td>
<td>1</td>
</tr>
<tr>
<td>≤0.25</td>
<td>1</td>
</tr>
<tr>
<td>≤0.5</td>
<td>1</td>
</tr>
<tr>
<td>≤1</td>
<td>1</td>
</tr>
<tr>
<td>≤2</td>
<td>1</td>
</tr>
<tr>
<td>≤4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Breakpoints**

- **Ceftaroline MIC**: S≤0.03, R>0.03 mg/L
- **Benzylpenicillin zone diameter (screen)**: S≥12 mm
- **ECOFF**: 0.03 mg/L
Benzylpenicillin 1 unit vs. Ceftibuten MIC

*H. influenzae*, 147 isolates

(1 data source)

**Breakpoints**

- **Ceftibuten MIC**
  - S≤1, R>1 mg/L
  - ECOFF: 0.5 mg/L

- **Benzylpenicillin zone diameter (screen)**
  - S≥12 mm
Benzylpenicillin 1 unit vs. Ceftriaxone MIC

*H. influenzae*, 174 isolates

(2 data sources)

**Breakpoints**

- **Ceftriaxone MIC**
  - S≤0.125, R>0.125 mg/L
  - ECOFF: 0.06 mg/L

- **Benzylpenicillin zone diameter (screen)**
  - S≥12 mm
Benzylpenicillin 1 unit vs. Cefuroxime MIC

*H. influenzae*, 188 isolates

(2 data sources)

**Breakpoints**

<table>
<thead>
<tr>
<th>Breakpoint</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime (iv) MIC</td>
<td>S≤1, R&gt;2 mg/L</td>
</tr>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
</tr>
</tbody>
</table>

**ECOFF**

- 2 mg/L
Benzylpenicillin 1 unit vs. Ertapenem MIC
*H. influenzae*, 124 isolates

(1 data source)

**Breakpoints**
- **Ertapenem MIC**
  - $S \leq 0.5$, $R > 0.5$ mg/L
- **Benzylpenicillin zone diameter (screen)**
  - $S \geq 12$ mm
Benzylpenicillin 1 unit vs. Imipenem MIC

*H. influenzae*, 116 isolates

(2 data sources)

**Breakpoints**

<table>
<thead>
<tr>
<th>Imipenem MIC</th>
<th>S≤2, R&gt;2 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin zone diameter (screen)</td>
<td>S≥12 mm</td>
</tr>
</tbody>
</table>

**MIC (mg/L)**

- 8
- 4
- 2
- 1
- 0.5
- 0.25
- 0.125
- ≤0.06

**ECOFF**

2 mg/L
Benzylpenicillin 1 unit vs. Meropenem MIC
*H. influenzae*, 200 isolates (298 correlates)

(4 data sources)

**Breakpoints**
- **Meropenem (non-meningitis) MIC**
  - $S \leq 2$, $R > 2$ mg/L
- **Benzylpenicillin zone diameter (screen)**
  - $S \geq 12$ mm

**ECOFF**
- 0.25 mg/L