Clindamycin susceptibility testing and reporting

Derek Brown
EUCAST Scientific Secretary

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Clindamycin

- Lincosamide agent classified in the macrolide, lincosamide and streptogramin B (MLSB) group

- Inhibits protein synthesis by binding to 23S RNA of the 50S ribosomal subunit

- Used to treat staphylococcal and streptococcal skin and soft tissue infections, particularly in general practice and outpatients
Clindamycin resistance mechanisms in staphylococci and streptococci

- Most resistance to macrolide, lincosamide and streptogramin type B (MLSB) antimicrobial agents is mediated by the \textit{erm} genes (ribosomal methylation) and is induced by erythromycin, clarithromycin and azithromycin, but not by clindamycin (MLSB inducible resistance or dissociated resistance)
- Strains with MLSB constitutive resistance are resistant to clindamycin
- Efflux
- Ribosomal mutation
Clindamycin MIC distribution for *S. aureus*

Clindamycin / *Staphylococcus aureus*
International MIC Distribution - Reference Database 2015-04-05

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L):
- **S**: ≤ 0.002
- **R**: > 0.002

Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L

25955 observations (14 data sources)
Clindamycin MIC distribution for *Streptococcus pyogenes*

**Clindamycin / Streptococcus pyogenes**  
International MIC Distribution - Reference Database 2015-04-05

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

Epidemiological cut-off (ECOFF): 0.25 mg/L  
Wildtype (WT) organisms: ≤ 0.25 mg/L
Detection of inducible clindamycin resistance in staphylococci and streptococci by disk diffusion

- Disk diffusion – the “D test”
- Erythromycin 15 µg and clindamycin 2 µg disks placed 12-20 mm apart (edge to edge) for staphylococci, 12-16 mm apart for streptococci
- “Antagonism” of clindamycin by erythromycin indicates inducible resistance
Detection of inducible clindamycin resistance in staphylococci and streptococci by broth microdilution

- Test clindamycin MIC in presence of fixed concentration of erythromycin
  - Staphylococci 4 mg/L erythromycin
  - Streptococci 1 mg/L erythromycin

- Staphylococci
  - Clindamycin MIC >0.25 mg/L in presence of erythromycin and ≤0.25 mg/L without erythromycin indicates inducible resistance (Swenson et al, JCM, 2007)

- Streptococci
  - Clindamycin MIC >0.5 mg/L in presence of erythromycin and ≤0.5 mg/L without erythromycin indicates inducible resistance (Bowling et al, JCM, 2010)
Detection of inducible clindamycin resistance in staphylococci by automated systems

- **Vitek 2 (Sensitivity 80-95%)**
  - Lavallee et al, JCM 2010. Inducible R detected in 124/134 isolates
  - Buchan et al, DMID 2012. Inducible R detected in 51/56 isolates
  - Gardiner et al, Pathology 2013. Inducible R detected in 191/201 isolates
  - Bobenchik et al, JCM 2014. Inducible R detected in 24/30 isolates

- **Phoenix**
  - Buchan et al, DMID 2012. Inducible R detected in 56/56 isolates

- **Microscan**
  - Ji et al, Korean J Lab Med 2010. Inducible R detected in 58/58 isolates
Detection of inducible clindamycin resistance in streptococci by automated systems

• **Vitek 2** (Sensitivity 36-95%)

• **Phoenix**
  – Buchan et al, DMID 2012. Inducible R detected in 100% of Group B isolates (not clear how many tested)
  – Richter et al, JCM 2007 Inducible R detected in 23/23 of Group B isolates
Reporting inducible clindamycin resistance in staphylococci and streptococci

• Should staphylococci and streptococci with inducible clindamycin resistance be reported resistant or susceptible?

• Inducible strains segregate constitutive clindamycin resistant mutants, which may be selected during treatment, possibly leading to treatment failure
Reporting inducible clindamycin resistance in staphylococci and streptococci

• Guidance on reporting has been inconsistent

Susceptible with warning that resistance may develop during treatment

OR

Resistant with note that less serious infections may still be treatable
EARS-Net External Quality Assessment
*S. aureus* with inducible clindamycin resistance
(MIC 0.12 mg/L, resistance induced by erythromycin)

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Number of participants</th>
<th>Percentage of participants reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>0275 (2011)</td>
<td>775</td>
<td>S: 24.0, I: 1.8, R: 74.2</td>
</tr>
<tr>
<td>1377 (2012)</td>
<td>705</td>
<td>S: 7.5, I: 1.4, R: 91.1</td>
</tr>
</tbody>
</table>
Evidence for clinical significance of inducible resistance to clindamycin in staphylococci and streptococci?

• In vitro studies

• Animal models

• Clinical outcome data
In vitro studies (S. aureus)

• Constitutive resistant mutants can be selected from inducible resistant isolates by culture in the presence of clindamycin

Constitutive resistance developed in 2-4 passages in clindamycin

McGehee et al. AAC 1968: 13; 392-7 (4/4 isolates)
Panagea et al. JAC 1999: 44; 581-2 (5/5 isolates)

Resistance develops readily in \( \textit{erm}(C) \) isolates
\( 1.7 \times 10^{-6} - 4.4 \times 10^{-8} \). Less frequent in \( \textit{erm}(A) \)

Daurel et al. JCM 2008: 46; 546-55
In vitro studies (S. aureus)

- Time-kill studies indicate initial killing but rapid regrowth

Laplante et al. AAC 2008: 52; 2156-62
Animal models of infection with MLSBi S. aureus
Neutropenic mouse thigh model Laplante et al. AAC 2008: 52; 2156-62

- Low inoculum ($10^5$)
  Clindamycin reduced CFU by 0.45 and 1.3 logs for two isolates at 72h.
  Constitutive resistant mutants detected at 72h.

- high inoculum ($10^7$)
  Clindamycin showed bacteriostatic activity at 24h and growth of 0.39 and 1.28 logs for two isolates at 72h.
  Constitutive resistant mutants detected at 24h.
Animal models of infection with MLSBi streptococci

Neutropenic mouse thigh model Lewis et al. AAC 2014: 58; 1327-31

- With inoculum $10^7$ Clindamycin reduced CFU over 12h for two isolates (one Group A and one Group B) but then regrowth to similar level to constitutive resistant isolates by 72h.
Issues in assessing clinical data on significance of MLSB1i resistance

- No controlled trials
- Anecdotal cases of failures more likely to be reported than successes
- Initial treatment often with a β-lactam agent or vancomycin
- Non-severe cases may have spontaneous favourable outcome
- With treatment of non-severe cases in general practice or as outpatients there is usually no follow up unless treatment fails
- Contribution of treatment when there is surgical intervention is unclear
Clinical data on outcome of infection with MLSBi S. aureus

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Outcome</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGehee et al. AAC 1968:13;392</td>
<td>3</td>
<td>2 failed, 1 success</td>
<td>2 S pre-treatment, 3 R post-treatment, Not tested for MLSBi</td>
</tr>
<tr>
<td>Drinkovic et al. JAC 2001:48;315</td>
<td>3</td>
<td>1 failed, 2 success</td>
<td>1 MLSBc</td>
</tr>
<tr>
<td>Frank. Ped Inf Dis J 2002:21;530</td>
<td>10</td>
<td>2 failed</td>
<td>1 MLSBc</td>
</tr>
<tr>
<td>Rao. JAC 2000:45;715</td>
<td>3</td>
<td>1 failed, 2 success</td>
<td>1 MLSBc</td>
</tr>
<tr>
<td>Watanakunacorn. Am J Med 1976:60;419</td>
<td>1</td>
<td>1 failed</td>
<td>1 S pre-treatment, 1 R post-treatment, Not tested for MLSBi</td>
</tr>
<tr>
<td>Siberry et al. Clin Inf Dis 2003:37;1257</td>
<td>1</td>
<td>1 failed</td>
<td>1 MLSBc</td>
</tr>
</tbody>
</table>
Clinical data on outcome of infection with MLSBi streptococci

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Outcome</th>
<th>Post therapy susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. AAC 2014:58;1327</td>
<td>8 with Gp B</td>
<td>8 failed</td>
<td></td>
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Inducible clindamycin resistance in staphylococci and streptococci

- There is a significant risk of failure of therapy in treatment of more severe infections

- There is not strong evidence relating to treatment of less serious infections
Current recommendations for reporting inducible clindamycin resistance

- EUCAST v 5.0 (2015)
  If MLSBi detected, then report as resistant. Consider adding this comment to the report:
  "Clindamycin may still be used for short-term therapy of less serious skin and soft tissue infections as constitutive resistance is unlikely to develop during such therapy".

- Recently agreed to add comment for streptococci
  "The clinical importance of inducible clindamycin resistance in combination treatment of severe S. pyogenes infections is not known".