EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Clindamycin susceptibility testing and reporting

Derek Brown
EUCAST Scientific Secretary

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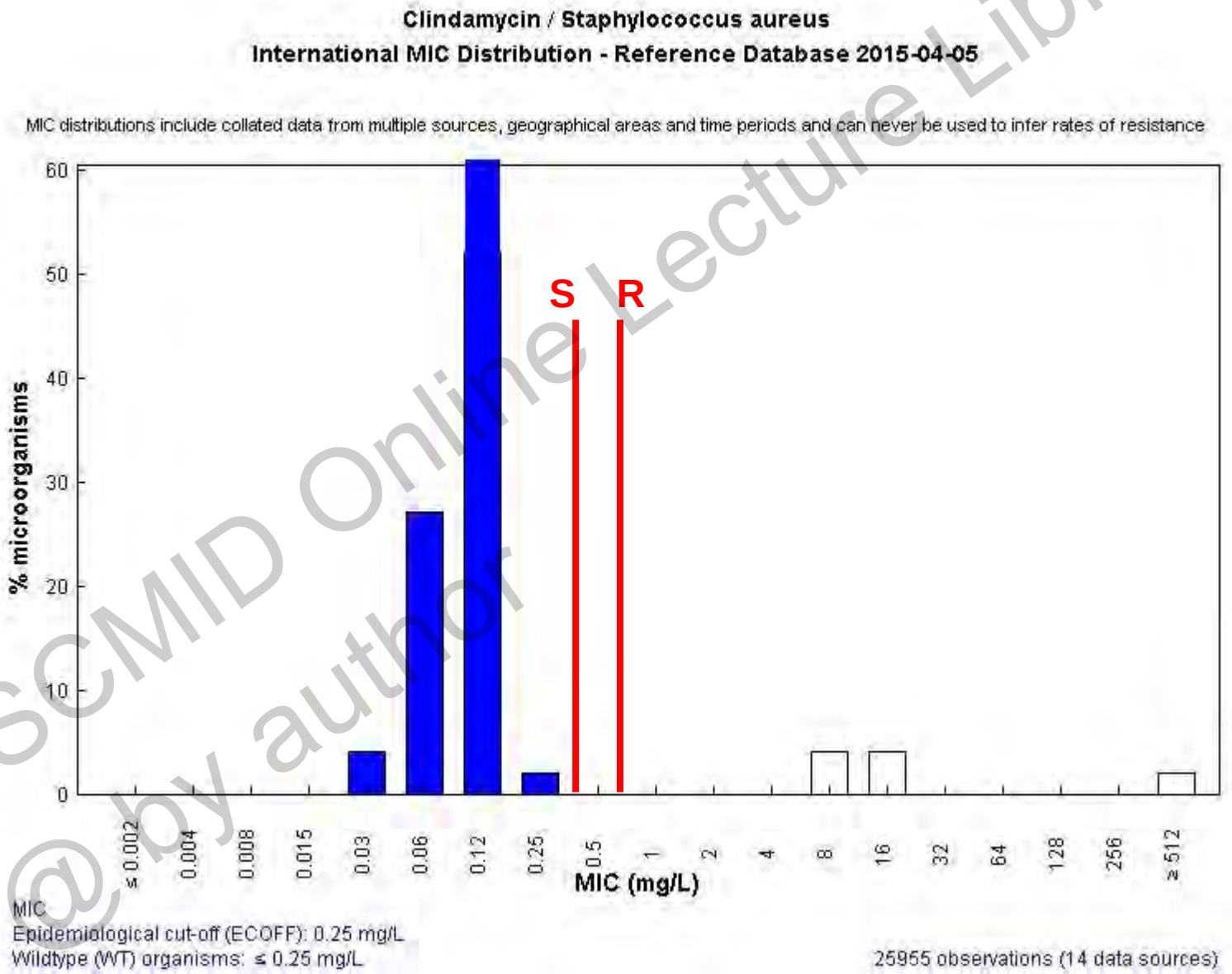
Clindamycin

- 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

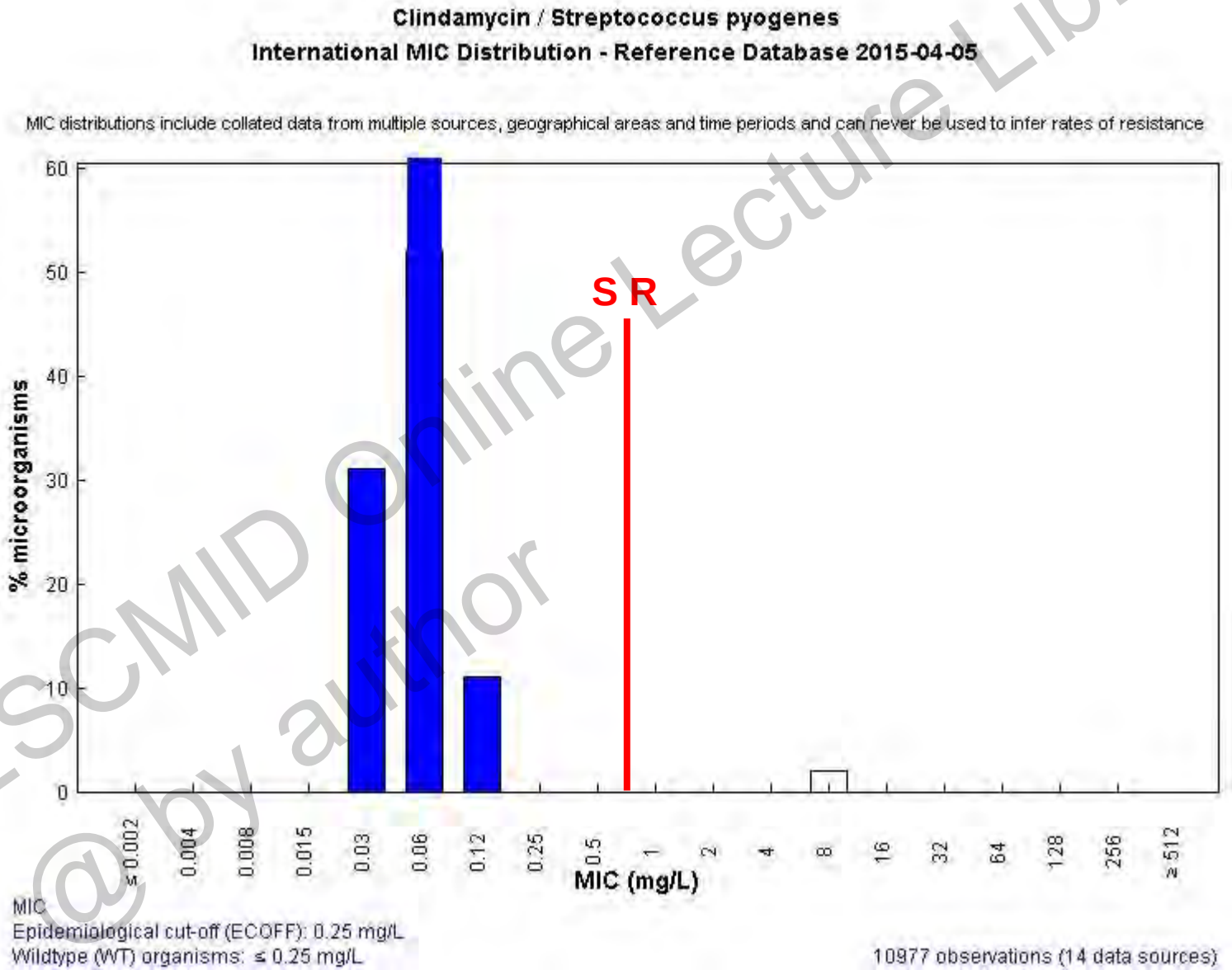
Clindamycin resistance mechanisms in staphylococci and streptococci

- Most resistance to macrolide, lincosamide and streptogramin type B (MLSB) antimicrobial agents is mediated by the *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*

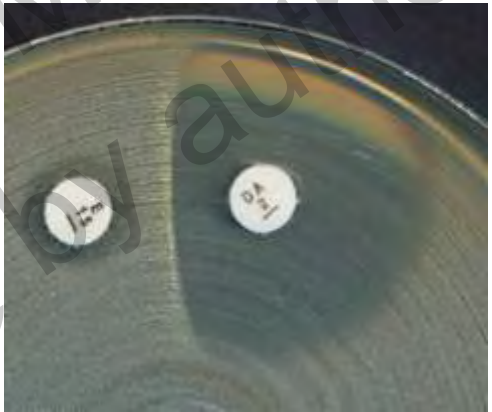


Clindamycin MIC distribution for Streptococcus pyogenes



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%)
  - Tang et al, JCM 2004. Inducible R detected in 17/18 of Group B isolates
  - Tazi et al, JAC 2007. Inducible R detected in 9/25 of Group B isolates

- 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)

Specimen	Number of participants	Percentage of participants reporting		
		S	I	R
0275 (2011)	775	24.0	1.8	74.2
1377 (2012)	705	7.5	1.4	91.1

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)

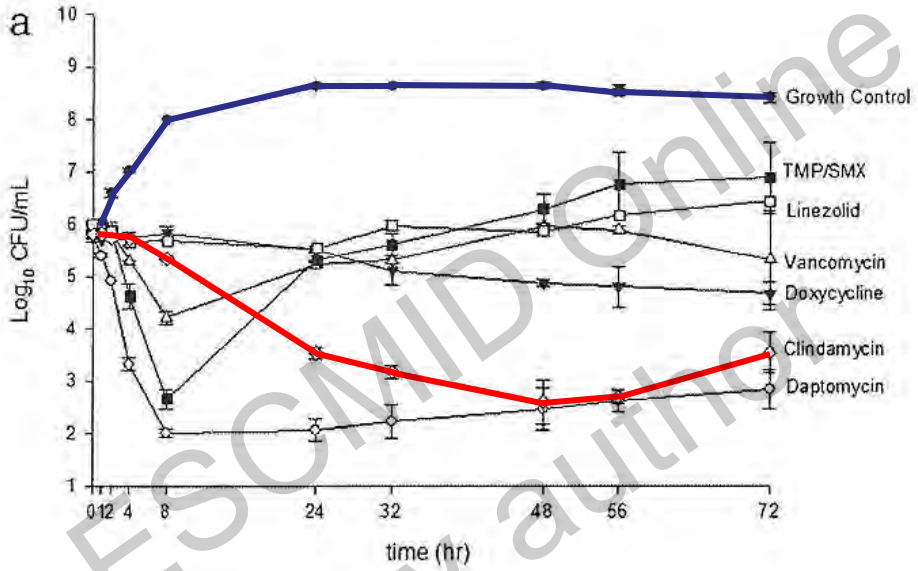
Resistance develops readily in *erm*(C) isolates
1.7×10^{-6} - 4.4×10^{-8}. Less frequent in *erm*(A)

Daurel et al. JCM 2008: 46; 546-55

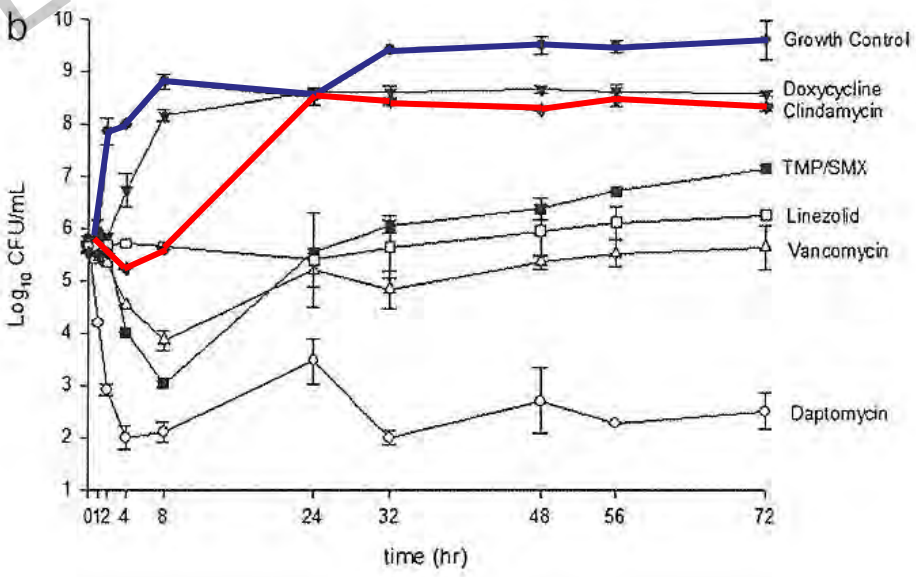
In vitro studies (*S. aureus*)

- Time-kill studies indicate initial killing but rapid regrowth

Laplante et al. AAC 2008: 52; 2156-62



Susceptible

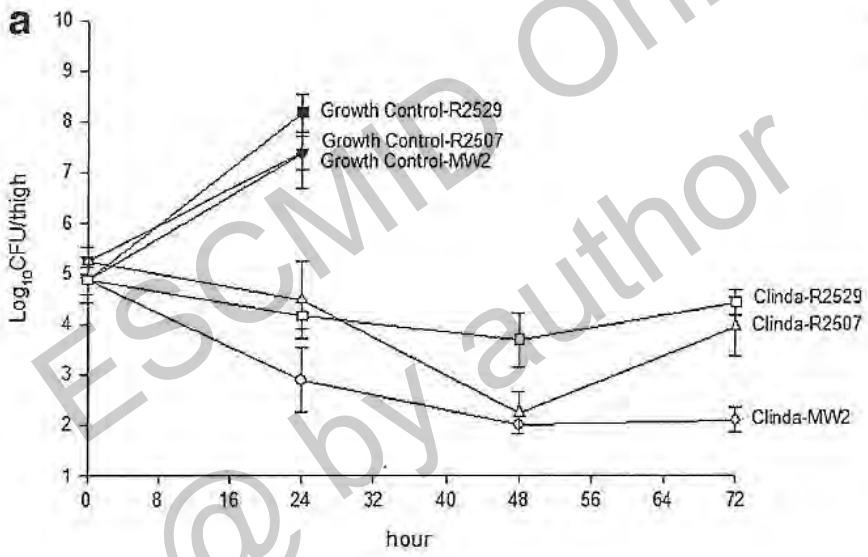


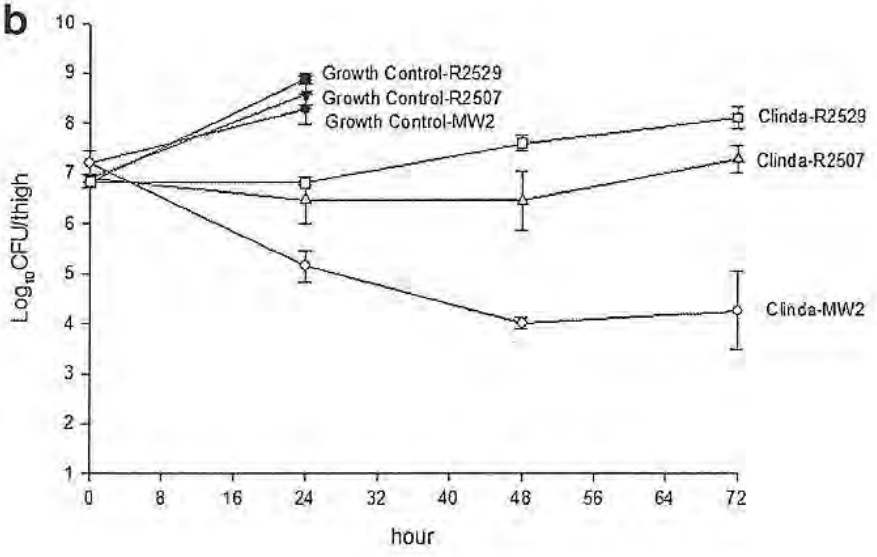
MLSB inducible

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 and1.3 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.

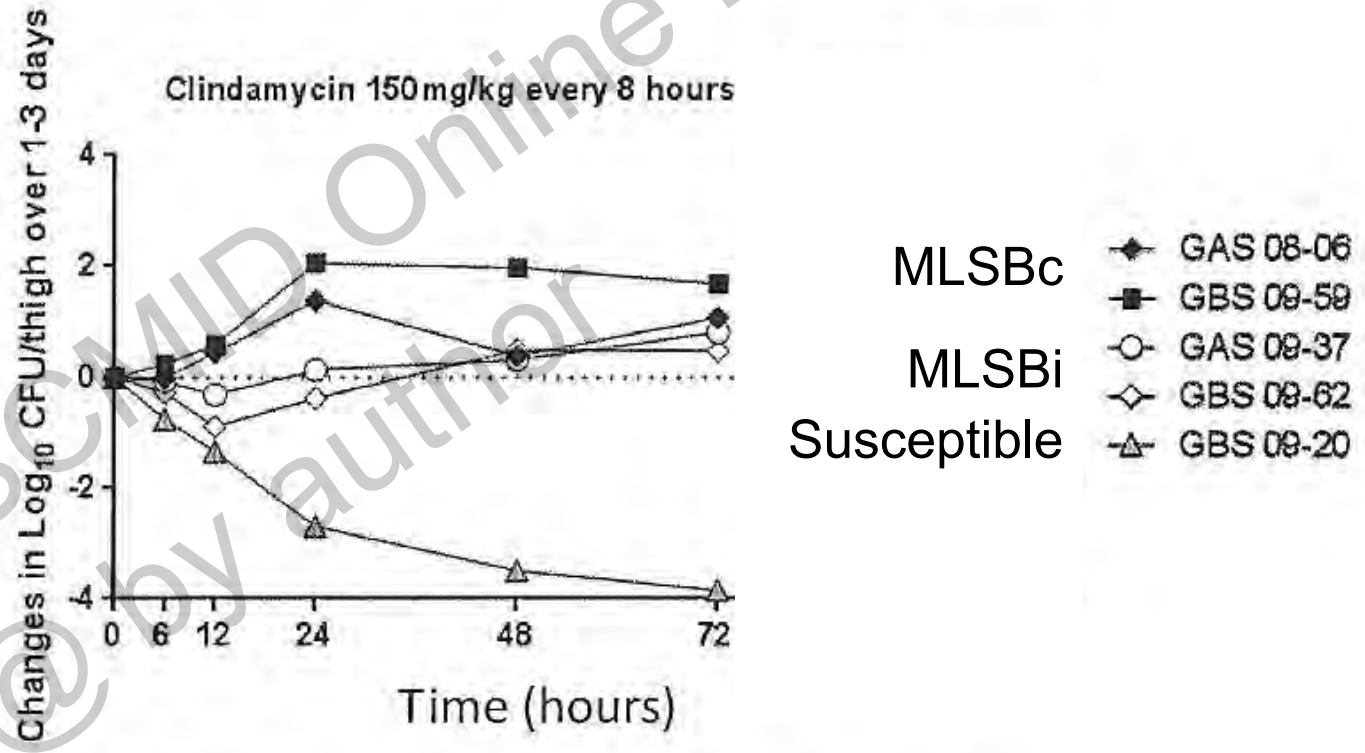




Animal models of infection with MLSBi streptococci

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 MLSBi 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*

Reference	No. of patients	Outcome	Susceptibility
McGehee et al. AAC 1968:13;392	3	2 failed 1 success	2 S pre-treatment 3 R post-treatment Not tested for MLSBi
Drinkovic et al. JAC 2001:48:315	3	1 failed 2 success	1 MLSBc
Frank. Ped Inf Dis J 2002:21;530	10	2 failed	1 MLSBc
Rao. JAC 2000:45;715	3	1 failed 2 success	1 MLSBc
Watanakunacorn. Am J Med 1976:60;419	1	1 failed	1 S pre-treatment 1 R post-treatment Not tested for MLSBi
Siberry et al. Clin Inf Dis 2003:37;1257	1	1 failed	1 MLSBc

Clinical data on outcome of infection with MLSBi streptococci

Reference	No. of patients	Outcome	Post therapy susceptibility
Lewis et al. AAC 2014:58;1327	8 with Gp B	8 failed	

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".