

# Antistaphylococcal Activity of NXL 103 (linopristine-flopristine) Compared to Other Agents

F1-365

P. MCGHEE<sup>1</sup>, J. LOWTHER<sup>2</sup>, A. BRYSKIER<sup>2</sup> and P.C. APPELBAUM<sup>1</sup>,

<sup>1</sup> Hershey Med. Ctr., Hershey, PA - <sup>2</sup> Novexel SA, Romainville, France



## ABSTRACT REVISED

**Background:** MRSA are therapeutic problems all over the world and life-threatening infections caused by community-acquired MRSA strains are increasingly found. MRSA strains not susceptible to glycopeptides have appeared in many locations. NXL103 is an oral streptogramin with activity against gram-positive and -negative aerobic and anaerobic strains. We describe anti-MRSA activity of NXL103 in comparison to vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, clarithromycin, clindamycin and quinupristine/dalfopristine.

**Methods:** 200 MRSA isolates were tested: of these 127 were community-acquired, isolated from sites throughout the US, and 40 were hospital-acquired. Strains also comprised 3 hetero-vanco intermediate (hVISA), 25 VISA and 5 vanco-resistant (VRSA). Both hVISA, 5 VISA and 1 VRSA were isolated in Hershey. Agar dilution MICs, (CLSI), was used with added Ca for daptomycin, 24 h incubation for vancomycin, and fresh tigecycline drug substance for each run. Each strain was tested for inducible clindamycin susceptibility by the D test.

**Results:** Twenty-eight strains showed inducible clindamycin R (8 community-, 11 hospital-acquired, 9 vancomycin non-S). MIC<sub>50</sub> and MIC<sub>90</sub>s (µg/ml) were:

Drug	Community-acquired			Hospital-acquired			hVISA+VISA+VRSA		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
NXL103	0.125-0.5	0.25	0.25	0.125-0.5	0.25	0.5	0.06-2	0.5	1
Vancomycin	0.5-1	1	1	0.5-2	1	1	1->128	4	32
Teicoplanin	0.25-2	1	1	0.25-1	0.5	1	1->32	8	16
Linezolid	2-4	4	4	1-4	4	4	1-4	2	4
Daptomycin	0.5-1	0.5	1	0.5-1	1	1	1-4	2	4
Tigecycline	0.25-0.25	0.25	0.25	0.125-0.5	0.25	0.5	0.06-1	0.25	0.5
Azithromycin	>8->8	>8	>8	1->8	>8	>8	1->8	>8	>8
Clarithromycin	>8->8	>8	>8	0.25->8	>8	>8	0.25->8	>8	>8
Clindamycin	0.125-0.25	0.25	0.25	0.125->16	0.25	>16	0.06->16	>16	>16
Quinu/Dalfo	0.25-1	0.5	0.5	0.25-1	0.25	1	0.125-2	0.5	1

NXL103 has excellent activity against all strains regardless of phenotype with MICs ranging from 0.125-0.5 µg/ml and MIC<sub>50</sub> and MIC<sub>90</sub>s of 0.25 and 0.25-0.5 µg/ml, in vanco-S strains against vancomycin non-S strains NXL103 had MICs of 0.06-2 µg/ml, with MIC<sub>50</sub> and MIC<sub>90</sub>s of 0.5 and 1 µg/ml. All strains were susceptible to linezolid, quinupristine/dalfopristine, and tigecycline and all except 21 strains (all VISA) (MICs 2-4 µg/ml) were daptomycin susceptible. All community-acquired and the majority of other strains were macrolide resistant.

**Conclusion:** Linopristine-flopristine (NXL103) exhibited a good in vitro activity against all MRSA, with an MIC range of 0.06-2 µg/ml. Clinical trials against MRSA infections are warranted.

## INTRODUCTION

For many years methicillin resistant *Staphylococcus aureus* (MRSA) infections have been encountered only in the hospital (nosocomial). However among MRSA the landscape has changed in the last decade with worrisome emergence of community-acquired strains (cMRSA) many of which produce Panton-Valentine leukocidin (PVL) and cause serious and life-threatening infections. Most community and nosocomial MRSA are also fluoroquinolone-resistant, and nosocomially-acquired MRSA strains are often multiresistant (7, 10, 13, 14).

## INTRODUCTION (cont'd)

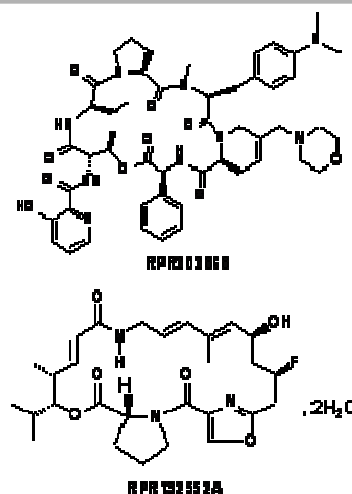
Since the report of vancomycin intermediate *S. aureus* clinical isolates (VISA) in Japan, these organisms have been reported all over the world. The Clinical Laboratory Standards Institute (CLSI, formerly NCCLS) had recently lowered the vancomycin susceptibility breakpoint from ≤4.0 µg/ml to ≤2.0 µg/ml (5). This will surely lead to a much wider appreciation of the clinical distribution of these isolates (4,8,15). In 2002, the first report of vancomycin-resistant *S. aureus* (VRSA) harboring *vanA* gene occurred: to date, eight VRSA strains have been reported, 6 in Michigan (1,4,15, M. Rybak, personal communication).

It seems that the widespread use of vancomycin in the community and hospital settings produces the selective pressure for VISA and VRSA strains: in most cases, prior vancomycin use has been found in individual patients.

It was recently shown that MICs of daptomycin in VISA (but not VRSA) strains increased. There is therefore a need for additional alternate antistaphylococcal agents with unique mechanisms of action.

NXL103 (formerly XRP 2868 – linopristine-flopristine) is an inhibitor of protein synthesis belonging to the streptogramin family.

## CHEMICAL STRUCTURES



## MATERIAL AND METHODS

The two hundred recent MRSA isolates comprised 127 community and 40 hospital acquired organisms. Strains were isolated from throughout the US.

Of the 200 strains, 127 were obtained from The Jones Group, (Liberty City, IA) 3 Hershey hVISA strains, 25 VISA, and 5 VRSA organisms. Some of the latter two groups were obtained from NARSA through Eurofins Laboratories, (Herndon, Va).

Vancomycin non-susceptible strains were identified by overnight as well as macro Etest methodology and hVISA were confirmed by population analysis.

## MATERIAL AND METHODS (cont'd)

Ten coagulase-negative staphylococci (not speciated) were also tested, including two linezolid resistant strains (MIC 16-64 µg/ml) isolated within the past six months at Hershey Medical Center and 2 vancomycin intermediate strains obtained from NARSA.

For MIC testing, CLSI agar dilution methodology was used (2,5) using cation-adjusted Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md) and final inocula of 10<sup>4</sup> cfu/ml. Added calcium was used for daptomycin testing and fresh tigecycline drug substance was used with each run. Vancomycin susceptibility plates were incubated for a full 24 h. Standard quality control strains were included in each run. Additionally, each strain was tested for inducible clindamycin susceptibility by means of the D test.

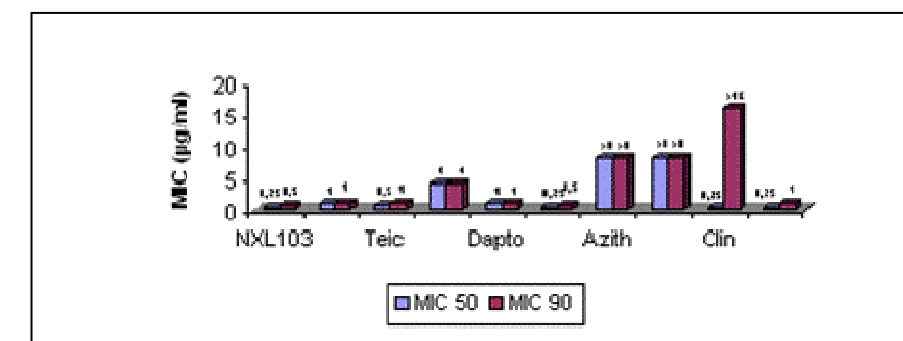
## RESULTS

MICs are listed in Table 1. NXL103 (linopristine-flopristine) had a good anti-staphylococcal activity with an MIC range (µg/ml) of 0.125-0.5, and MIC<sub>50</sub> and MIC<sub>90</sub> values (µg/ml) of 0.25 µg/ml, against all strains regardless of the resistance phenotype (Figure 1).

Table 1 - Comparative in vitro activity of NXL103 against MRSA

Drug	Community-acquired			Hospital-acquired			hVISA+VISA+VRSA		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
NXL103	0.125-0.5	0.25	0.25	0.125-0.5	0.25	0.5	0.06-2	0.5	1
Vancomycin	0.5-1	1	1	0.5-2	1	1	1->128	4	32
Teicoplanin	0.25-2	1	1	0.25-1	0.5	1	1->32	8	16
Linezolid	2-4	4	4	1-4	4	4	1-4	2	4
Daptomycin	0.5-1	0.5	1	0.5-1	1	1	1-4	2	4
Tigecycline	0.25-0.25	0.25	0.25	0.125-0.5	0.25	0.5	0.06-1	0.25	0.5
Azithromycin	>8->8	>8	>8	1->8	>8	>8	1->8	>8	>8
Clarithromycin	>8->8	>8	>8	0.25->8	>8	>8	0.25->8	>8	>8
Clindamycin	0.125-0.25	0.25	0.25	0.125->16	0.25	>16	0.06->16	>16	>16
Quinu/Dalfo	0.25-1	0.5	0.5	0.25-1	0.25	1	0.125-2	0.5	1

Figure 1 - Comparative Anti-staphylococcal activity of NXL103 against 40 recent US clinical isolates consisting of hospital acquired strains



All strains were susceptible to linezolid and tigecycline and all except 21 strains (all VISA) had non-susceptible daptomycin MICs ranging from 2 to 4 µg/ml. Previous reports (8, 9) have confirmed higher daptomycin MICs against VISA strains and the propensity of daptomycin therapy to select for such resistance phenotypes. Fluoroquinolone resistance was only found amongst hospital acquired and vancomycin non-susceptible strains.

Twenty-eight strains showed inducible clindamycin resistance (8 community-, 11 hospital-acquired, 9 vancomycin non-susceptible (Table 2):

	inducible	susceptible	resistance
cMRSA	8	119	0
hVISA, VISA, VMRSA	9	4	19
hosp MRSA	11	14	16

Amongst the 10 coagulase-negative staphylococci (data not shown but on file with Novexel), NXL103 had an MIC range between 0.125-0.5 µg/ml (Mode MIC 0.25 µg/ml). All strains were susceptible to tigecycline and all except the two vancomycin intermediate strains were daptomycin susceptible. Fluoroquinolone resistance occurred in most of the 10 strains.

## CONCLUSION

**NXL103 (linopristine-flopristine) exhibits a good antistaphylococcal activity regardless vancomycin resistance phenotype. Clinical trials are warranted to evaluate whatever linopristine-flopristine should be included in the armamentarium of antistaphylococcal drugs.**

## REFERENCES

- Bartley, J. 2002. Epidemiol. 23: 480.
- Bogdanovich, T. et al. Antimicrob. Agents Chemother. 49:3325-3333.
- Boyle-Vavra, S. et al. 2000. Antimicrob. Agents Chemother. 44:272-277.
- Centers for Disease Control and Prevention. 2004. Morb. Mortal. Wkly. Rep. 53:322-323.
- Clinical and Laboratory Standards Institute 2006. Approved standard M7-A7, Seventh Edition. Clinical and Laboratory Standards Institute, Wayne PA.
- Eliopoulos, G.M. et al. 2005. Antimicrob. Agents Chemother. 49:3034-3039.
- Fergie, J.E., and K. Purcell. 2001. Pediatr. Infect. Dis. J. 20:860-863.
- Julian, K., et al. 2007. Antimicrob. Agents Chemother. 51:3445-3448.
- Kaatz, G.W., et al. 2006. International Journal of Antimicrobial Agents. 28:280-287.
- Kazakova, S.V., 2005. N. Engl. J. Med. 352: 468-475.
- Morbidity and Mortality Weekly Report. 1999. Morb. Mortal. Wkly. Rep. 48: 707-710.
- Naimi, T.S., et al. 2003. JAMA 290:2976-2984.
- Pankuch, G.A., et al. 2003. Antimicrob. Agents Chemother. 47: 3270-3274.
- Tenover, F.C., et al. 1998. J. Clin. Microbiol. 36: 1020-1027.
- Tenover, F.C., et al. 2004. Antimicrob. Agents Chemother. 48: 275-280.