

Supplementary Materials

Table S1. Studies related to daptomycin and gentamicin combination therapy.

Author (Year)	Isolates Tested	Methods	Dose	Findings
<i>in vitro</i> combination studies				
Snydman <i>et al.</i> , (2005) [1]	20 MSSA (DAP-S) 20 MRSA (DAP-S)	Checkerboard (fractional inhibitory concentration index)	DAP 0.01–8 µg/mL (0.0625–4× MIC) Gen 0.01–4096 µg/mL (0.0625–4× MIC)	DAP + Gen synergy observed for 1 MRSA strain. No synergistic inhibition of bacterial growth was observed among other isolates.
Tsuji <i>et al.</i> , (2006) [2]	1 GISA (DAP-S) 1 hGISA (DAP-S)	Time-kill E-test	DAP 0.25 µg/mL (0.5× MIC) Gen 1 µg/mL (0.5× MIC)	DAP + Gen and DAP alone were indifferent in Time-kill assays but showed additive effects using E-test
Credito <i>et al.</i> , (2007) [3]	8 MSSA (DAP-S) 24 MRSA (DAP-S) 3 VISA (DAP-R) 3 VRSA (DAP-S)	Time-kill	DAP 0.125–0.5 µg/mL for isolates with DAP-S (0.25–0.5× MIC) DAP 0.5–4 µg/mL for isolates with DAP-R (0.25–0.5× MIC)	DAP + Gen showed synergy in killing 4 MSSA, 17 MRSA, 2VISA and 2 VRSA. Additive effects were observed among other isolates.
Baltch <i>et al.</i> , (2007) [4]	1 MRSA (DAP-S)	Extracellular and Intracellular killing of staphylococci in human monocytes culture	DAP 0.5 µg/mL (1× MIC) Gen 1µg/mL (0.5× MIC)	DAP + Gen showed synergy for killing staphylococci inside human monocytes and staphylococci in broth.
Baltch <i>et al.</i> , (2008) [5]	2 Pairs of SCV and parental isolates (All DAP-S)	Extracellular and Intracellular killing of staphylococci in human monocytes culture	DAP 0.5–1 µg/mL (1× MIC) Gen 1–8 µg/mL (0.5× MIC)	DAP + Gen showed synergy for killing intracellular parental isolates and 1 SCV. For extracellular killing, DAP alone efficiently killed 1 SCV and the parental isolates.
Miro <i>et al.</i> , (2009) [6]	3 MRSA (DAP-S)	Time-kill	DAP 0.25–1 µg/mL (0.5–2× MIC) Gen 0.5–2 µg/mL	DAP + Gen showed synergy against all strains compared to monotherapy.
Entenza <i>et al.</i> , (2010) [7]	4 MRSA (DAP-S) 2 GISA (1 DAP-S, 1 DAP-R)	Progressive DAP resistance selection followed by MIC test	2-fold stepwise increasing DAP Gen 0.0625–32µg/mL (0.25× MIC)	Addition of Gen did not prevent DAP-R among all the tested isolates.

Table S1. Cont.

Author (Year)	Isolates Tested	Methods	Dose	Findings
<i>in vitro</i> pharmacodynamic models				
LaPlante <i>et al.</i> , (2004) [8]	1 MSSA (DAP-S) 1 MRSA (DAP-S)	Simulated endocardial vegetation	DAP 6 mg/kg/day Gen 1.3 mg/kg/day	DAP + Gen increased bactericidal rates in the first 24 h and eradicated staphylococci as efficient as DAP monotherapy after 72 h
Tsuji <i>et al.</i> , (2006) [2]	1 MSSA (DAP-S) 1 MRSA (DAP-S)	Simulated endocardial vegetation	DAP 6 or 8 mg/kg 3 dose of Gen 1 mg/kg or 1 dose of Gen 5 mg/kg	Gen enhanced bactericidal activity of DAP in all combinations.
DeRyke <i>et al.</i> , (2006) [9]	1 MRSA (DAP-S) 1 CA-MRSA (DAP-S) 1 MSSA (DAP-S)	Serum bactericidal titers (Serum from volunteers with DAP alone or DAP + Gen)	DAP 6 mg/kg Gen 1 mg/kg	Addition of Gen did not enhance serum bactericidal titers against staphylococci compared to DAP monotherapy.
Rose <i>et al.</i> , (2008) [10]	3 DAP-S 4 DAP-R	Simulated endocardial vegetation	DAP 6 mg/kg/day (DAP6) DAP 10 mg/kg/day (DAP10) Gen 5 mg/kg/day	2 DAP-S isolates were eradicated by DAP6 alone or DAP6 + Gen. 1 DAP-S isolate was only eradicated by DAP6 + Gen. For DAP-R isolates, only 1 isolate was eradicated by DAP6 + Gen. 2 isolates were eradicated by DAP10 alone or DAP10 + Gen.
LaPlante <i>et al.</i> , (2009) [11]	2 MRSA (DAP-S)	Simulated endocardial vegetation	DAP 6 mg/kg/day Gen 1.3 mg/kg/day	DAP monotherapy has better <i>in vitro</i> activity than DAP + Gen within the first 24 h.
Animal model				
Miró <i>et al.</i> , (2009) [6]	1 MRSA (DAP-S)	Rabbit infective endocarditis	DAP 6 mg/kg Gen 1 mg/kg	DAP + Gen eradicated staphylococci as efficient as DAP monotherapy.

DAP: daptomycin; Gen: gentamicin; DAP-S: daptomycin-susceptible; DAP-R: daptomycin-resistant; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; MIC: minimum inhibitory concentration; GISA: glycopeptides-intermediate *Staphylococcus aureus*; hGISA: heterogeneous glycopeptides-intermediate *Staphylococcus aureus*; VISA: vancomycin-intermediate *Staphylococcus aureus*; VRSA: vancomycin-resistant *Staphylococcus aureus*; SCV: small-colony variant.

Table S2. Mutations identified between isogenic *S. aureus* strain pairs used in this study [12,13].

Gene	Protein	Function	^a Mutation		Reference
			Type	Change	
1. A6224/A6226					
<i>dltA</i>	D-alanine-poly(phosphoribitol) ligase, subunit 1	Cell wall/outer membrane metabolism	^b SNP	Ser38Arg	
<i>yycI</i>	Regulatory protein, WalKR operon	Cell wall/outer membrane metabolism	Deletion	Frameshift	
<i>atl</i>	Bifunctional autolysin	Cell wall/outer membrane metabolism	SNP	Ser752Ser	
<i>arlS</i>	Histidine-kinase	Signal transduction	Insertion	Frameshift	
<i>mraW</i>	S-adenosyl-methyltransferase	Amino acid metabolism/transport	Deletion	Frameshift	
<i>pcrA</i>	ATP-dependent helicase	DNA replication and repair	SNP	Glu455Glu	
<i>tilS</i>	tRNA(ile)-lysidine synthetase	Nucleic acid metabolism/transport	SNP	Met128Ile	[13]
SA0587	PsaA adhesion homologue	Inorganic ion transport/metabolism	Deletion	Frameshift	
SA1528	Universal stress protein	Stress response	SNP	Leu105Leu	
SA0837	2-siopropylmalate synthase	Amino acid metabolism/transport	Insertion	Frameshift	
SA1778	Hypothetical protein	Unknown	Deletion	Frameshift	
SA0349	Hypothetical protein	Unknown	SNP	Pro474Ser	
SA0668	Hypothetical protein	Unknown	SNP	Val41Ile	
2. A9719/A9744					
<i>mprF</i>	Lysylphosphatidylglycerol synthetase	Oxacillin resistance related protein	SNP	Ser337Leu	
<i>cls2</i>	Cardiolipin synthetase	Phosphatidylcholine-hydrolysing phospholipase D	SNP	Ala23Val	
<i>atl</i>	N-acetylmuramoyl-L-alanine amidase	Bi-funtional autolysin involved in cell envelope biogenesis	Insertion	Frameshift	[12]
<i>agrC</i>	Accessory gene regulator C	Sensor histidine kinase	Insertion	Frameshift	
<i>stp1</i>	Protein phosphatase 2C domain-containing protein	Serine/threonine specific protein phosphatase	SNP	Met99Ile	
SA1264	Conserved hypothetical protein	Unknown function	SNP	Gly47Glu	
3. A8819/A8817					
<i>mprF</i>	Lysylphosphatidylglycerol synthetase	Oxacillin resistance related protein	SNP	Thr345Ile	
<i>cls2</i>	Cardiolipin synthetase	Phosphatidylcholine-hydrolysing phospholipase	SNP	Phe60Ser	
<i>leuS</i>	Leucyl-tRNA synthetase	Incorporation of leucine into tRNA	SNP	Asn468Asp	[12]
<i>mnaA</i>	UDP-N-acetylglucosamine 2-epimerase	Sialic acid synthesis	SNP	Arg302Ser	
<i>ispA</i>	Geranyltranstransferase	Polyketide biosynthesis	Deletion	Frameshift	

Table S2. Cont.

Gene	Protein	Function	^a Mutation		Reference
			Type	Change	
4. A9635/A9639					
<i>vraG</i>	ABC transporter permease	ABC transporter, defense	SNP	Ala580Val	[13]
<i>rsbW</i>	Ser-protein kinase, anti- σ β factor	Transcriptional regulation	Deletion	88Ser/89Phe	
<i>rpsU</i>	Ribosomal protein S21	Translation	Deletion	Frameshift	
<i>ilvC</i>	Ketol-acid reductoisomerase	Amino acid metabolism/transport	Deletion	30Gln/31Gly	

^a Nucleotide and amino acid mutations are those identified in the daptomycin-exposed strains compared to their isogenic parent strains; ^b SNP—Single nucleotide polymorphism.

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