

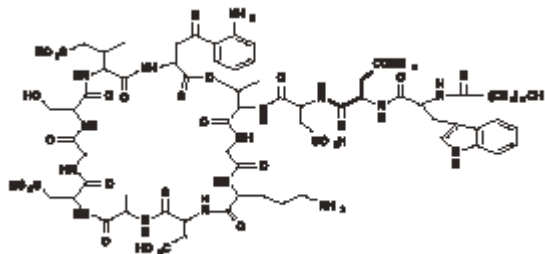
Bon Secours Richmond
Pharmacy and Therapeutics Committee
Daptomycin (Cubicin)
5/2004

Recommendations: MEC approved

- Daptomycin is recommended to be added to formulary as a restricted agent for use in microbiology proven gram-positive skin and skin structure infections resistant to vancomycin and linezolid or that have failed vancomycin/linezolid therapy, or for patients who are allergic or intolerant to vancomycin and linezolid.
- Daptomycin is a third line agent until more clinical data becomes available to reassess its role.
- Infectious disease consult is recommended.

Findings:

- Daptomycin is a cyclic lipopeptide antibiotic for intravenous use with potent bactericidal activity in vitro against most clinically relevant gram-positive organisms (Table 1) and is FDA approved for the treatment of complicated skin and skin structure infections caused by: *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, and vancomycin susceptible *enterococcus faecalis*.
- Daptomycin is not indicated for community-acquired pneumonia. In Phase 3 studies, the death rate and rates of serious cardiorespiratory adverse events were higher in patients with CAP treated with daptomycin than those treated with the other study medications (Rocephin).
- Daptomycin's mechanism of action is believed to be through binding to the bacteria's membrane and causing a rapid depolarization of membrane potential and release of intracellular ions. The loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death. Cell wall disruption does not occur. Daptomycin's action is dependent on physiologic levels of free calcium ions.



Molecular Weight 1620 daltons

- Daptomycin's spectrum of activity is similar to vancomycin, and includes MRSA, and penicillin-resistant *Streptococcus pneumoniae*. Daptomycin, like linezolid is active against VISA, VRSA, and vancomycin-resistant *Enterococcus faecium* and *E. faecalis*.
- Daptomycin is highly protein bound (92%) with an extremely small volume of distribution for an antibiotic (0.096 l/kg). The usual dose of 4 mg/kg achieves a peak of 57.8 mcg/ml and a trough of 7.7 mcg/ml (free level of 0.62 mcg/ml).
- In time-kill analyses comparing daptomycin with vancomycin, linezolid, and quinupristin-dalfopristin against *Staphylococcus* and *Enterococcus* sp, including vancomycin-intermediate and resistant strains, daptomycin had greater bactericidal activity than the other drugs for VRE, with 3 log kill or greater in 8 hours. Killing rates of MRSA, VISA, and MRSE were similar to vancomycin.
- Daptomycin demonstrates concentration-dependent killing (similar to aminoglycosides and fluoroquinolones) and has a significant post antibiotic effect, allowing for once-daily administration. The AUC/MIC ratio is the best predictor of efficacy for daptomycin.
- Daptomycin appears to be minimally affected by a high inoculum, which has a major impact on nafcillin and vancomycin.
- Daptomycin has demonstrated synergy for the following bacteria when combined with the noted antibiotic: VRE rifampin, *E. faecalis* ampicillin, *E. faecium* ampicillin, and ampicillin resistant *E. faecium* with gentamicin.
- Complicated skin and skin structure infections are usually caused by *Staphylococcus aureus* or *epidermidis* or by *Streptococcus pyogenes*.
- Daptomycin retains potency against antibiotic-resistant gram-positive bacteria, including isolates resistant to methicillin, vancomycin, and linezolid.
- Cross-resistance has not been observed with any other class of antibiotic.
- Resistance to daptomycin occurred during clinical trials in 2 patients (< 0.2%) and has been noted during treatment in animal studies.
- Daptomycin is inactive against gram-negative bacteria, which possess an outer membrane that the drug is unable to penetrate.
- Daptomycin has nearly linear pharmacokinetics and is time-independent at doses up to 6 mg/kg administered once daily for 7 days
- T $\frac{1}{2}$ 9 hours and steady state concentrations are achieved by the third daily dose.

- Daptomycin is 92% reversibly bound to human plasma proteins, primarily to serum albumin, in a concentration-independent manner.
- Daptomycin is eliminated by glomerular filtration.
- It is unknown whether daptomycin is a substrate of the CYP450 System, however, it is unlikely to inhibit or induce the metabolism of drugs metabolized by the CYP450 system.
- Dose adjustment is necessary in patients with severe renal insufficiency (CrCl < 30 mL/min)
 - Approximately 15% and 11% of the administered dose is removed by 4 hours of hemodialysis and 48 hours of CAPD, respectively.
- No dose adjustment is needed in patients with mild to moderate hepatic impairment.
- Recommended dosing of Daptomycin: 50% excreted unchanged renally
 - CrCl ≥ 30 mL/min 4 mg/kg every 24 hours
 - CrCl < 30 mL/min 4 mg/kg every 48 hours (including those on hemodialysis and CAPD)
- Daptomycin should be administered by IV infusion over a 30-minute period in 0.9% sodium chloride for 7 to 14 days.
- Study data suggest that skeletal muscle effects (forearm weakness, myalgias, and elevated creatinine kinase levels) seen in the early 90's were more closely related to the dosing interval (2-4 mg/kg q12h) and high trough concentrations than to Cmax or AUC, and therefore once daily dosing is recommended.
- Common side effects include constipation, diarrhea, nausea, vomiting, dyspepsia, dyspnea, elevated serum creatine phosphokinase, arthralgia, myalgia, and muscle cramps.
- Pregnancy category – B
- Susceptibility Testing: Our suppliers do not carry the E-test strip and the disks can only be obtained from the drug rep.

FDA Approved Indications				
	Daptomycin	Linezolid	Synercid®	Vancomycin
Community Acquired Pneumonia	-	+ (Strep pneumoniae-PCN sensitive, MSSA)	-	+
Noscomial pneumonia	-	+ (MSSA/MRSA, Strep. pneumoniae-PCN sensitive)	-	+
Complicated Skin & Skin Structure	+ (MSSA/MRSA, Strep pyogenes, Strep agalactiae, Strep dysgalactiae subsp equisimilis, Enterococcus faecalis (vancomycin sensitive))	+(MSSA/MRSA, Strep. Agalactiae, pyogenes)	+ (MSSA, Strep. pyogenes)	+
Vancomycin Resistant Enterococcus faecium	-	+	+	-

	Daptomycin	Linezolid	Synercid	Vancomycin
Metabolism		65%	Bile 75%	0%
Fraction excreted unchanged in urine	50%	30%	<5%	100%
Oral Bioavailability	0%	100%	ND/NA	0%
Half-life	8 hours	5.5 Hours	3 hr Quinupristin 1 hr Dalfopristin	8 hours
Renal Failure Adjustment	Yes	No But metabolites accumulate	No	Yes
Hemodialysis	Yes	Administer After Dialysis		No Change

Drug	Dose (mg)	Cost per Dose	Doses per Day	Cost per Day of Therapy
Vancomycin	1000	\$4	1	\$4.36
Daptomycin (Cubicin)	500	\$132	1	\$131.80
Linezolid (Zyvox) Inj	600	\$67	1	\$67.00
Linezolid (Zyvox) Tablet	600	\$51	1	\$50.50
Quniupristin/dalfopristin (Synercid)	600	\$116	3	\$348.60

Table 3 Susceptibility Interpretive Criteria for Daptomycin

Pathogen	Minimal inhibitory concentration ($\mu\text{g/mL}$) ^a			Disk diffusion zone diameter (mm) ^b		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin-resistant)	≤ 1	(c)	(c)	≥ 16	(c)	(c)
<i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , and <i>Streptococcus dysgalactiae</i> subsp <i>equisimilis</i>	≤ 1	(c)	(c)	≥ 16	(c)	(c)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤ 4	(c)	(c)	≥ 11	(c)	(c)

Laboratory Changes

Table 6 Incidence (%) of Creatine Phosphokinase (CPK) Elevations From Baseline While on Therapy in Either Daptomycin or Comparator Treatment Groups in Phase 3 cSSSI Studies

	All Patients		Patients With Normal CPK at Baseline					
	Daptomycin (N=430)		Comparator (N=459)		Daptomycin (N=374)		Comparator (N=392)	
	%	n	%	n	%	n	%	n
No Increase	90.7	390	91.1	418	91.2	341	91.1	357
Maximum Value >1x ULN*	9.3	40	8.9	41	8.8	33	8.9	35
>2x ULN	4.9	21	4.8	22	3.7	14	3.1	12
>4x ULN	1.4	6	1.5	7	1.1	4	1.0	4
>5x ULN	1.4	6	0.4	2	1.1	4	0.0	0
>10x ULN	0.5	2	0.2	1	0.2	1	0.0	0

*ULN (Upper Limit of Normal) is defined as 200 U/L.

Note: Elevations in CPK observed in patients treated with daptomycin or comparator were not clinically or statistically significantly different (P <0.05).

Table 8 Investigator's Primary Diagnosis in the Complicated Skin and Skin Structure Infection Studies (Population: ITT)

Parameters	Study 9801	Study 9901	Pooled
	CUBICIN / Comparator ^a N=264 / N=266	CUBICIN / Comparator ^a N=270 / N=292	CUBICIN/Comparator ^a N=534/N=558
Wound Infection	99 (37.5%) / 116 (43.6%)	102 (37.8%) / 108 (37.0%)	201 (37.6%) / 224 (40.1%)
Major Abscess	55 (20.8%) / 43 (16.2%)	59 (21.9%) / 65 (22.3%)	114 (21.3%) / 108 (19.4%)
Ulcer Infection	71 (26.9%) / 75 (28.2%)	53 (19.6%) / 68 (23.3%)	124 (23.2%) / 143 (25.6%)
Other Infection ^b	39 (14.8%) / 32 (12.0%)	56 (20.7%) / 51 (17.5%)	95 (17.8%) / 83 (14.9%)

a. Vancomycin or semi-synthetic penicillins

b. The majority of cases were subsequently categorized as complicated cellulitis, major abscesses, or traumatic wound infections.

Table 9 Clinical Success Rates by Infecting Pathogen, Primary Comparative Complicated Skin and Skin Structure Infection Studies (Population: Microbiologically Evaluable)

Pathogen	Success Rate	
	CUBICIN n/N (%)	Comparator ^a n/N (%)
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA) ^b	170/198 (85.9)	180/207 (87.0)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) ^b	21/28 (75.0)	25/36 (69.4)
<i>Streptococcus pyogenes</i>	79/84 (94.0)	80/88 (90.9)
<i>Streptococcus agalactiae</i>	23/27 (85.2)	22/29 (75.9)
<i>Streptococcus dysgalactiae</i> subsp <i>equisimilis</i>	8/8 (100)	9/11 (81.8)
<i>Enterococcus faecalis</i> (vancomycin-susceptible only) ^b	27/37 (73.0)	40/53 (75.5)

a. Vancomycin or semi-synthetic penicillins

b. As determined by the central laboratory

Table 1 Mean (SD) Daptomycin Pharmacokinetic Parameters in Healthy Volunteers on Day 7

Dose mg/ kg	C _{max} (µg/ mL)	T _{max} [*] (h)	AUC ₀₋₂₄ (µg·h/ mL)	t _{1/2} (h)	V _d (L/ kg)	CL _T (mL/ h/kg)	CL _R (mL/ h/kg)	Ae ₂₄ %
4 (n=6)	57.8 (3.0)	0.8 (0.5, 1.0)	494 (75)	8.1 (1.0)	0.096 (0.009)	8.3 (1.3)	4.8 (1.3)	53.0 (10.8)
6 (n=6)	98.6 (12)	0.5 (0.5, 1.0)	747 (91)	8.9 (1.3)	0.104 (0.013)	8.1 (1.0)	4.4 (0.3)	47.4 (11.5)
8 (n=6)	133 (13.5)	0.5 (0.5, 1.0)	1130 (117)	9.0 (1.2)	0.092 (0.012)	7.2 (0.8)	3.7 (0.5)	52.1 (5.19)

*Median (minimum, maximum)

C_{max} = Maximum plasma concentration; T_{max} = Time to C_{max}; AUC₀₋₂₄ = Area under concentration-time curve from 0 to 24 hours; t_{1/2} = Terminal elimination half-life; V_d = Apparent volume of distribution; CL_T = Systemic clearance; CL_R = Renal clearance; Ae₂₄ = Percent of dose recovered in urine over 24 hours as unchanged daptomycin following the first dose.

Table 2 Mean (SD) Daptomycin Population Pharmacokinetic Parameters Following a Single 30-Minute Intravenous Infusion of 4 mg/kg to Infected Patients and Non-Infected Subjects with Varying Degrees of Renal Function

Renal Function	AUC _{0-∞} (μg•h/mL)	t _{1/2} (h)	Vss (L/kg)	CL _r (mL/h/kg)
Normal (CL _{CR} >80 mL/min) (N=165)	417 (155)	9.39 (4.74)	0.13 (0.05)	10.9 (4.0)
Mild Renal Impairment (CL _{CR} 50-80 mL/min) (N=64)	466 (177)	10.75 (8.36)	0.12 (0.05)	9.9 (4.0)
Moderate Renal Impairment (CL _{CR} 30<50 mL/min) (N=24)	560 (258)	14.70 (10.50)	0.15 (0.06)	8.5 (3.4)
Severe Renal Impairment (CL _{CR} <30 mL/min) (N=8)	925 (467)	27.83 (14.85)	0.20 (0.15)	5.9 (3.9)
Hemodialysis and CAPD (N=21)	1244 (374)	29.81 (6.13)	0.15 (0.04)	3.7 (1.9)

Note: CL_{CR} = Creatinine clearance estimated using the Cockcroft-Gault equation with actual body weight.

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Table 1. In Vitro Susceptibility Testing of Several Multidrug-Resistant and -Susceptible Gram-Positive Organisms Against Daptomycin

Organism	No. of Isolates	MIC ₉₀ (µg/ml)	MIC Range (µg/ml)
<i>Enterococcus faecalis</i>			
Vancomycin susceptible ^[19,20,24]	2200	1.0–2.0	0.015–4.0
Vancomycin resistant ^[25,26,28]	231	0.5–4.0	0.25–8.0
<i>Enterococcus faecium</i>			
Vancomycin susceptible ^[20,24]	358	1.0–4.0	0.5–8.0
Vancomycin resistant ^[19,20,22,24,25]	249	1.0–4.0	0.25–4.0
<i>Listeria monocytogenes</i> ^[25]	25	4.0	2.0–8.0
<i>Staphylococcus aureus</i>			
Glycopeptide intermediate ^[21,25,29]	22	4	0.5–16
Methicillin resistant ^[19,20,22–25,27,29,30]	711	0.25–1.0	0.06–2.0
Methicillin susceptible ^[19,20,22–25,27,29,30]	1473	0.5–1.0	0.015–2.0
Vancomycin intermediate ^[20,31]	47	1	0.0625–2.0
Vancomycin resistant ^{[18], a}	2	NA	0.25–1
<i>Staphylococcus coagulase negative</i>			
Methicillin resistant ^[19,23–25]	954	0.5–1.0	0.004–1.0
Methicillin susceptible ^[19,24,25]	728	0.25–2.0	0.03–0.5
<i>Staphylococcus epidermidis</i>			
Methicillin resistant ^[20,25]	65	0.25–0.5	0.12–1.0
Methicillin susceptible ^[20,25]	66	0.25	0.06–1.0
<i>Staphylococcus sp</i>			
<i>S. haemolyticus</i> ^[22,23,25,30]	56	0.25–0.5	0.03–1.0
<i>S. saprophyticus</i> ^[27]	30	0.5	0.25–1.0
<i>Streptococcus sp</i>			
Group G ^[27]	10	0.06	0.015–0.06
<i>S. milleri</i> ^[27]	30	1.0	0.25–1.0
<i>S. pyogenes</i> ^[19,22,25,30]	340	0.06	0.015–0.5
<i>S. viridans</i> ^[19,22,25,30]	126	1.0–2.0	0.016–8.0
<i>S. agalactiae</i> ^[22]	81	0.25	0.12–0.25
Streptococcus pneumoniae ^[22]	50	0.25	0.06–0.25
Penicillin intermediate ^[19,24,25,28]	389	0.25–1.0	0.008–1.0
Penicillin resistant ^[19,24,25,28]	267	0.25–1.0	0.015–1.0
Penicillin susceptible ^[19,24,25,28]	1166	0.25–0.5	0.015–0.5

MIC₉₀ = minimum inhibitory concentration for 90% of strains tested; NA = not applicable.

^aBased on two isolates, Michigan and Pennsylvania.

Table 2. Comparative Inhibitory Activity of Daptomycin, Linezolid, Quinupristin-Dalfopristin and Vancomycin Against Selected Gram-Positive Organisms and Anaerobes

Organism	MIC ₉₀ Range (µg/ml)			
	Daptomycin	Linezolid	Quinupristin-Dalfopristin	Vancomycin
<i>Enterococcus faecalis</i> ^[19,20,22,24,28,30,37-46]				
Vancomycin susceptible	1-2	1-4	8-32	1-4
Vancomycin resistant	0.5-4	2-4	16-32	R
<i>Enterococcus faecium</i> ^[19,20,22,24,28,30,37-43,46,47]				
Vancomycin susceptible	1-4	2-4	0.5-4	1.5-2
Vancomycin resistant	1-4	2-4	0.5-16	R
<i>Staphylococcus aureus</i> ^[4,19,20,22-24,29,31,33,34,37-40,42-44,48-54]				
Methicillin susceptible	0.5-1	2-4	0.25-2	0.5-1
Methicillin resistant	0.25-1	1-4	1-2	0.5-2
Vancomycin intermediate	0.5-1	1-2	0.25	I
Vancomycin resistant ^a	1	2	</= 1	R
<i>Staphylococcus coagulase negative</i> ^[37-40,42,45,48-53]				
Methicillin susceptible	0.25-2	2	0.1-1	1-2
Methicillin resistant	0.5-1	1-2	0.25-1	1-2
<i>Streptococcus pneumoniae</i> ^[19,23,24,28,37-39,47,55-59]				
Penicillin susceptible	0.25-0.5	1.5-2	0.39-1	0.25-0.5
Penicillin intermediate	0.25-1	1	0.5-2	0.25-1
Penicillin resistant	0.25-1	1	0.5-2	0.5-1
Gram-positive anaerobic organisms ^[36]				
<i>Actinomyces</i> group	4	0.5	0.25	1
<i>Clostridium difficile</i>	1	16	16	2
<i>Clostridium perfringens</i>	0.5	2	1	0.5
<i>Lactobacillus</i> sp	16	8	2	32
<i>Peptostreptococcus</i> sp	0.06-1	1-2	1-2	0.25-1
<i>Propionibacterium</i> sp	2	1	0.25	0.5
Anaerobic organisms ^[36]				
<i>Corynebacterium jeikeium</i>	0.25	0.5	0.25	0.5
<i>Corynebacterium</i> sp	1	1	1	0.5

MIC₉₀ = minimum inhibitory concentration for 90% of strains tested; R = resistant; I = intermediate.

^aBased on two isolates in Michigan and Pennsylvania.

Table 3. Adverse Events in a Large, Randomized, Phase III Clinical Trial Evaluating Daptomycin versus Vancomycin or a Semisynthetic Penicillin in Complicated Skin and Soft Tissue Infection^[99,104]

Adverse Event	Daptomycin (n=534)	Comparator (n=558)
Constipation	6.2	6.8
Nausea	5.8	9.5
Injection site reaction	5.8	7.7
Headache	5.4	5.4
Diarrhea	5.2	4.3
Insomnia	4.5	5.4
Rash	4.3	3.8
Vomiting	3.2	3.8
Abnormal liver function tests	3.0	1.6
Pruritus	2.8	3.8
Elevated creatine kinase	2.8	1.8
Fungal infections	2.6	3.2
Hypotension	2.4	1.4
Urinary tract infections	2.4	0.5
Renal failure	2.2	2.7
Dizziness	2.2	2.0
Anemia	2.1	2.3
Dyspnea	2.1	1.6
Fever	1.9	2.5
Limb pain	1.9	2.0
Hypertension	1.1	2.0
Dyspepsia	0.9	2.5
Arthralgias	0.9	2.2

Data are percentages.

Daptomycin: Another novel agent for treating infections due to drug-resistant gram-positive pathogens.

Carpenter CF, Chambers HF.

Division of Infectious Diseases, William Beaumont Hospital, Royal Oak, Michigan, USA.

Clin Infect Dis. 2004 Apr 1;38(7):994-1000. Epub 2004 Mar 11.

Daptomycin is a novel cyclic lipopeptide antibiotic that provides rapid bactericidal activity against gram-positive pathogens in vitro, including methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus*, vancomycin-resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae*, and ampicillin- and vancomycin-resistant enterococci. The United States Food and Drug Administration recently approved daptomycin for treatment of complicated skin and skin-structure infections. Its efficacy in the treatment of more-serious infections (e.g., staphylococcal bacteremia) is under investigation. As an intravenous agent that is administered once per day, it offers a convenient regimen for therapy that is continued after discharge, with a side effect profile that appears minimal and manageable. Spontaneous acquisition of resistance in vitro is rare, and hopefully this characteristic will extrapolate into the clinical setting. A study looking at patients with skin or soft-tissue infections revealed cure or improvement in 29 (96.6%) of 30 evaluable patients who were treated with daptomycin, compared with 37 (94.9%) of 39 evaluable patients who were treated with conventional therapy. Another study showed that patients tended to have a shorter duration of intravenous therapy with daptomycin than with the comparator. An animal study conducted suggested that the skeletal myopathy correlated more closely with frequency of dosing than with C_{max} or the AUC, suggesting an association with high trough concentrations which supported the switch to once daily dosing. The rapid bactericidal activity, low potential for resistance, and promising safety profile associated with this agent will make it a useful addition to our growing armamentarium of antibiotics active against gram-positive pathogens.

Table 2. Summary of in vitro activity of daptomycin against gram-positive pathogens, by study.

Variable	Study					
	Critchley et al. [10]	Critchley et al. [11]	Wise et al. [9] ^a	Fuchs et al. [8] ^a	Rybak et al. [12]	Chang et al. [13], Bozdogan and Applebaum [14] ^b
No. of isolates	6973	5948	328	844	203	2
<i>Staphylococcus aureus</i>						
Oxacillin-susceptible	0.25	0.5	0.5	1	0.13	...
Oxacillin-resistant	0.5	0.5	0.5	1	0.13	...
Vancomycin-intermediate	0.5–1 ^c	...
Vancomycin-resistant	0.5–1
Coagulase-negative staphylococci	0.5	0.5	0.5	0.5–1	0.25–0.5	...
<i>Enterococcus faecium</i>						
Any	2	...	4	...
Vancomycin-susceptible	4	4	...	2
Vancomycin-resistant	4	4	...	2
<i>Enterococcus faecalis</i>						
Any	2	...	1	...
Vancomycin-susceptible	2	2	...	1
Vancomycin-resistant	2	2	...	1
Other enterococci	4	4
<i>Streptococcus pneumoniae</i>						
Any	0.25
Penicillin-susceptible	0.12	0.25	...	0.12
Penicillin-intermediate/resistant	0.12–0.25	0.25	...	0.25
<i>Streptococcus pyogenes</i>	0.06	0.06
<i>Streptococcus agalactiae</i>	0.25	0.25	...	0.25
Viridans streptococci	1	1

NOTE. Data are MIC₅₀ of daptomycin in µg/mL, unless otherwise indicated.

^a Data is only listed for Ca²⁺ concentration of 50 µg/mL.

^b Each study involved 1 isolate. Data is MIC₅₀ range for the Michigan isolate (MIC₅₀ 1.0 µg/mL) described in Chang et al. [13] and the Pennsylvania isolate (MIC₅₀ 0.5 µg/mL) described in Bozdogan and Applebaum [14].

^c Data is MIC₅₀ range for 3 isolates; see also Howe et al. [15].

1. **Comparative In vitro activities of daptomycin and vancomycin against resistant gram-positive pathogens.**

Snydman DR, Jacobus NV, McDermott LA, Lonks JR, Boyce JM.

New England Medical Center, Boston, Massachusetts 02111, USA.

Antimicrob Agents Chemother. 2000 Dec;44(12):3447-50.

The objective of this study was to compare the antibacterial activity of daptomycin to that of vancomycin against recently isolated resistant gram-positive cocci and to demonstrate its bactericidal effect against VRE and MRSA. In vitro activity of daptomycin against 224 current gram-positive clinical isolates including vancomycin-resistant *Enterococcus faecium* (VREF), methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus* spp. (MRSS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP) was evaluated. Time-kill studies were performed with antibiotic concentration equivalent to 1x, 4x, and 8x the MIC. Bactericidal activity was defined as a 99.9% reduction in the numbers of CFU per milliliter compared to the numbers of CFU per milliliter for the initial inoculum. Daptomycin was two- to fourfold more active than vancomycin against the staphylococcal isolates, *S. pyogenes*, and *E. faecalis*. The MICs at which 90% of isolates are inhibited for daptomycin and vancomycin, respectively, were as follows: MRSA, 1 and 2 microg/ml; MRSS, 1 and 4 µg/ml; PRSP (penicillin resistant *Strep. pneumoniae*), 1 and 0.5 µg/ml; and VREF, 2 and >64 µg/ml. Daptomycin was bactericidal against 82% of 17 VREF isolates. Daptomycin showed activity superior to that of vancomycin against MRSA, MRSS, and VREF. The antibacterial activity of daptomycin was strongly dependent on the calcium concentration of the medium. Increasing the concentration of calcium in the medium enhanced the antibacterial activity of daptomycin. Daptomycin was active against all gram-positive cocci tested, confirming its role as an alternative agent for the treatment of infections with resistant gram-positive bacteria.

TABLE 1. Susceptibilities of gram-positive isolates to daptomycin and vancomycin

Species (no. of isolates tested)	MIC (µg/ml)					
	Daptomycin			Vancomycin		
	50%	90%	Range	50%	90%	Range
MRSA (54)	1	1	0.5-1	2	2	1-2
MSSA (27)	0.25	1	0.06-1	0.5	1	0.5-2
MRSS (29)	0.5	1	0.25-2	2	4	2-4
<i>S. pneumoniae</i> (penicillin susceptible; MIC, ≤0.06 µg/ml) (16)	0.03	0.125	0.015-0.5	0.125	0.25	0.125-0.25
<i>S. pneumoniae</i> (penicillin intermediate; MIC, 0.12 to 1.0 µg/ml) (21)	0.25	1	0.008-1.0	0.25	0.5	0.008-1.0
<i>S. pneumoniae</i> (penicillin resistant; MIC, ≥2 µg/ml) (24)	0.5	1	0.015-1.0	0.25	0.5	0.125-0.5
<i>S. pyogenes</i> (10)	0.015	0.125	0.008-0.5	0.25	0.5	0.25-1
<i>E. faecalis</i> (vancomycin susceptible) (20)	1	1	0.25-2	1	2	0.5-2
VREF (23)	1	2	0.5-2	>64	>64	>64

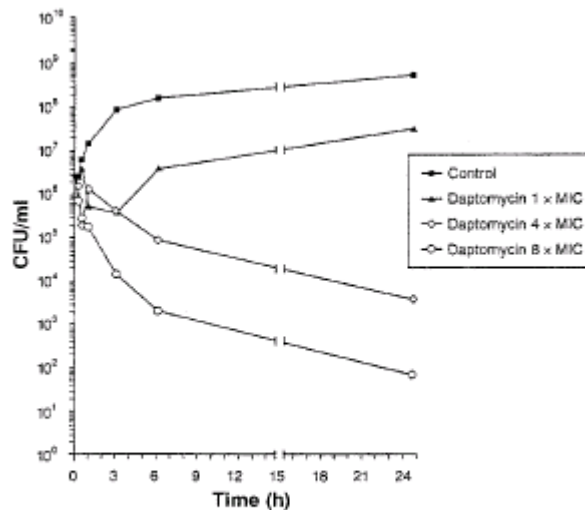


FIG. 1. Effect of daptomycin concentration on in vitro time-kill kinetics for *E. faecium* SSL 110 (VRE) in MH II broth (25 µg of Ca²⁺/ml).

2. **In vitro activities of Daptomycin, Linezolid, and Quinupristin-Dalfopristin against a challenge panel of Staphylococci and Enterococci, including vancomycin-intermediate staphylococcus aureus and vancomycin-resistant Enterococcus faecium.**

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We assessed the in vitro activities of daptomycin, linezolid, and quinupristin-dalfopristin (QD) against a contemporary challenge panel of 88 staphylococcal and 90 enterococcal isolates. The staphylococci selected included vancomycin-intermediate *Staphylococcus aureus* (VISA), methicillin-resistant *S. aureus*, and coagulase negative staphylococci. Enterococcal isolates included vancomycin-resistant *Enterococcus faecium* (VREF) containing either vanA, vanB1, or vanD. The MICs of daptomycin, linezolid, and QD were determined using commercial broth microdilution panels. All three VISA isolates were susceptible to daptomycin, linezolid, and QD. QD was the most active agent against staphylococcal isolates (MIC₅₀ < or = 0.5 µg/ml and MIC₉₀ = 1 µg/ml), including those with decreased susceptibility to vancomycin. One MRSA isolate was nonsusceptible to linezolid (MIC = 8 µg/mL), intermediate to QD (MIC = 2 µg/mL), and susceptible to both daptomycin and vancomycin. QD was also the most active agent against VREF (MIC₉₀ < or = 0.5 µg/ml). No differences were seen for susceptibility of vanA, vanB1, and vanD VREF strains for daptomycin, linezolid, or QD. Daptomycin was the most effective against *E. faecalis*. On the basis of manufacturer-suggested interpretive criteria, 92% of isolates were susceptible (MIC₉₀ = 4 µg/ml). All isolates tested were susceptible to at least one antimicrobial agent for which interpretive criteria have been defined. Population analysis of three *S. aureus* isolates for which the daptomycin MICs were 8 µg/ml showed a pattern of homogeneous resistance.

TABLE 1. ACTIVITY OF DAPTOMYCIN, LINEZOLID, QUINUPRISTIN-DALFOPRISTIN (QD), AND VANCOMYCIN AGAINST GRAM-POSITIVE BACTERIA

Bacteria (number tested)	Antimicrobial agent	MIC (µg/ml)		
		50%	90%	Range
DSV ^a <i>Staphylococcus aureus</i> (19) ^b	Daptomycin	2	8	1-8
	Linezolid	2	4	1-8
	QD	≤0.5	≤0.5	≤0.5-2
	Vancomycin	4	8	4-8
VS ^c <i>Staphylococcus aureus</i> (38)	Daptomycin	0.5	1	0.12-4
	Linezolid	2	4	1-4
	QD	≤0.5	≤0.5	≤0.5-1
	Vancomycin	1	2	≤0.5-2
DSV Coagulase-negative staphylococci (17) ^d	Daptomycin	1	4	0.25-4
	Linezolid	2	2	1-2
	QD	≤0.5	≤0.5	≤0.5-1
	Vancomycin	4	4	4-8
VS Coagulase-negative staphylococci (14)	Daptomycin	0.5	1	0.25-2
	Linezolid	2	2	1-4
	QD	≤0.5	1	≤0.5-1
	Vancomycin	2	2	1-2
VR ^e <i>Enterococcus faecium</i> (63)	Daptomycin	4	8	2-8
	Linezolid	2	4	2-4
	QD	≤0.5	≤0.5	≤0.5-1
	Vancomycin	≥128	≥128	≥128
Enterococci, other ^f (27)	Daptomycin	2	8	0.5-8
	Linezolid	4	4	2-4
	QD	2	16	≤0.5-32
	Vancomycin	8	≥128	1-≥128

^aDSV, Decreased susceptibility to vancomycin.

^bIncludes three *S. aureus* with vancomycin MIC = 8 µg/ml.

^cVS, Vancomycin-susceptible.

^dIncludes one CoNS with vancomycin MIC = 8 µg/ml.

^eIncludes *E. faecalis*, *E. casseliflavus*, *E. gallinarum*, and vancomycin-intermediate *E. faecium*.

^fVR, Vancomycin-resistant.

3. **Comparative efficacy of daptomycin and vancomycin in the therapy of experimental foreign body infection due to *Staphylococcus aureus*.**

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J Antimicrob Chemother. 2003 Jul;52(1):89-95. Epub 2003 May.

The therapeutic activity of once-daily daptomycin was compared with that of twice-a-day vancomycin in a rat model of subcutaneously implanted tissue cages chronically infected with strain Rev1, a spontaneous methicillin-susceptible revertant of the methicillin-resistant *Staphylococcus aureus* strain MRGR3, showing equivalent virulence to its parent. The MIC and MBC of daptomycin (in Mueller-Hinton broth supplemented with 50 mg/L Ca²⁺) or vancomycin for strain Rev1 were 1-2 and 2-4 or 1 and 2 mg/L, respectively. In vitro elimination of strain Rev1 in the presence of 50% tissue cage fluid was more rapid with daptomycin 4 mg/L compared with vancomycin. After 2 weeks of infection, viable counts of strain Rev1 averaged 6.49 log₁₀ cfu/mL of tissue cage fluid (n = 87). Intraperitoneal administration of daptomycin 30 mg/kg once daily, or vancomycin 50 mg/kg twice daily, produced antibiotic levels continuously above MBC. After 7 days of therapy with daptomycin or vancomycin, mean ± S.E.M. counts of Rev1 decreased (P < 0.05) by 1.11 ± 0.25 (n = 28) or 0.80 ± 0.31 (n = 35) log₁₀ cfu/mL, respectively, compared with cages of untreated animals, but were not significantly different from each other. *In daptomycin-treated rats, three cages yielded subpopulations with reduced susceptibility to daptomycin.* In conclusion, a low dose regimen of daptomycin was at least equivalent to vancomycin against chronic foreign body infections due to *S. aureus*. Drug dosage should be adapted to obtain inflammatory fluid levels of daptomycin minimizing emergence of resistant subpopulations.

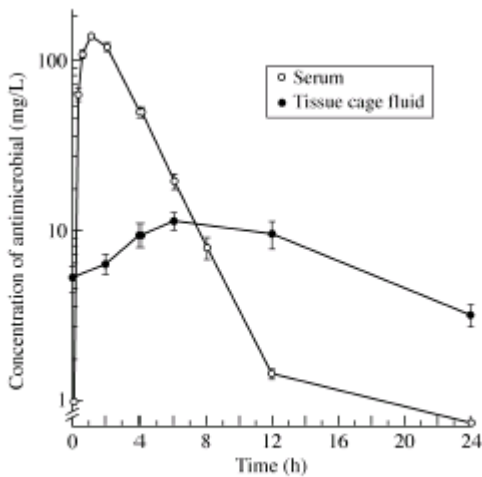


Figure 1. Pharmacokinetic levels of daptomycin in plasma, and tissue cage fluids of rats on day 4 of therapy with 30 mg/kg once-daily dosing.

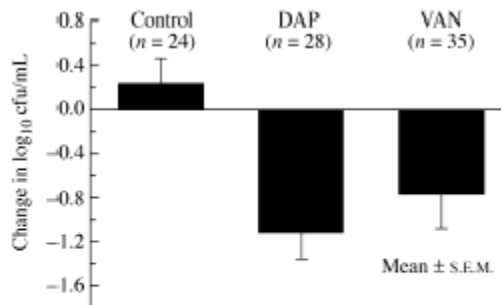


Figure 2. Decrease in viable counts of *S. aureus* Rev1 in tissue cage fluids of rats treated with the different regimens for 7 days. DAP, rats treated with daptomycin 30 mg/kg once a day; VAN, rats treated with vancomycin 50 mg/kg twice a day. n, number of evaluated cages in each group.

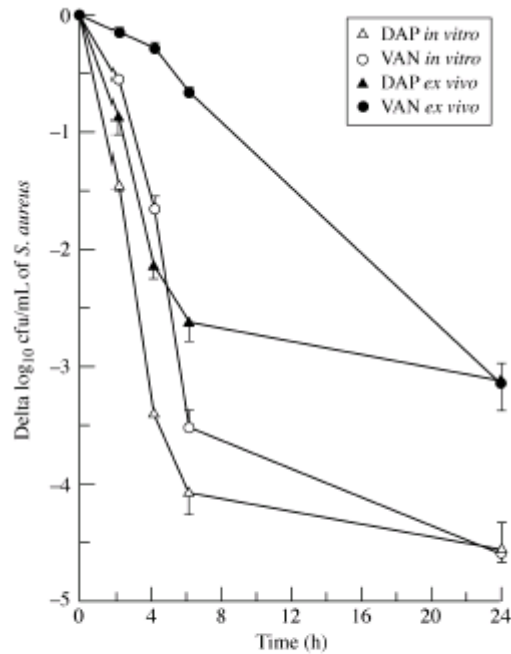


Figure 3. Comparison of daptomycin bactericidal activity on *S. aureus* Rev1, either grown in MHB as stationary phase cultures (*in vitro*), or recovered from pooled, chronically infected tissue cages (*ex vivo*). Incubation with either daptomycin (DAP; 4 mg/L) or vancomycin (VAN; 4 mg/L) was carried out in a 1:1 mixture of MHB and sterile tissue cages fluids pooled from 20 different uninfected cages implanted in rats.

4. **Pharmacodynamics of daptomycin in a murine thigh model of *Staphylococcus aureus* infection.**
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 Antimicrob Agents Chemother. 2001 Mar;45(3):845-51.

Daptomycin is a lipopeptide antibiotic with activity against gram-positive bacteria, including *Staphylococcus aureus*. We used a murine neutropenic thigh model of *S. aureus* infection to define the pharmacokinetics and complete dose-range activity of daptomycin in infected mice. In Mueller-Hinton broth, the MICs for three *S. aureus* isolates were 0.1 to 0.2 µg/ml. In mouse serum, the MICs were 1.0 µg/ml. The protein binding of daptomycin was 90 to 92.5% in mouse serum. Single-dose intraperitoneal (i.p.) pharmacokinetic studies with infected mice showed a linear relationship between dose versus the maximum concentration of drug in serum and dose versus the area under the concentration-time curve (AUC). The serum half-life of daptomycin in infected mice was approximately 1.8 h. In single-dose, dose-ranging studies using mice, daptomycin showed a dose-response effect described by an inhibitory sigmoid E_{max} (maximum effect) curve ($r = 0.974$; $P \ll 0.001$). The density of *S. aureus* in untreated controls was 8.26 log₁₀ CFU/g, and the E_{max} was 3.97 log₁₀ CFU/g. The 50% effective dose (ED₅₀) was 3.7 mg/kg of body weight i.p. and the stasis dose was 7.1 mg/kg. Dose fractionation studies at schedules of Q6h, Q12h, and Q24h, for total 24-h ED₃₀, ED₆₀, and ED₈₀ doses of 2.5, 5.6, and 15 mg/kg i.p., showed no difference in effect at each total 24-h dose level by schedule, indicating that the AUC/MIC ratio is the dynamically linked variable.

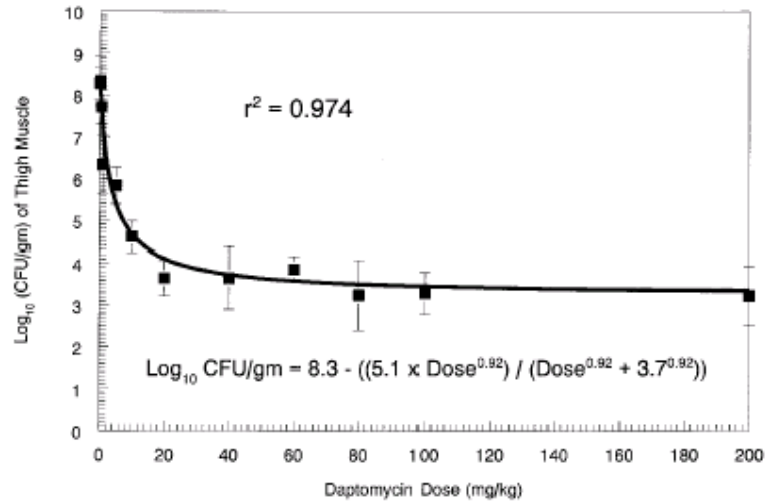


FIG. 3. First dose-ranging study demonstrating the dose-response relationship between the dose of daptomycin administered to infected mice and the *S. aureus* density in thigh muscles (mean \pm 1 SD). Daptomycin was given i.p. as a single dose 2 h after neutropenic mice were inoculated i.m. with 10^5 CFU of *S. aureus* in each posterior thigh muscle. Quantitative cultures of thigh muscles were done 24 h after drug administration. There were seven to eight mice in each group.

TABLE 2. Calculated pharmacodynamic variables for three total dosages of daptomycin administered in one, two, or four equally divided doses over 24 h

Total dose (mg/kg/24 h)	Regimen ^a	C_{max}/MIC^b	AUC/MIC ratio	Time > MIC/24 h
2.5	2.5 mg/kg (1 dose)	8.28	20.06	5.0
	1.25 mg/kg q12h (2 doses)	4.14	21.28	9.1
	0.625 mg/kg q6h (4 doses)	2.07	23.72	17.2
5.6	5.6 mg/kg (1 dose)	18.54	43.41	6.08
	2.8 mg/kg q12h (2 doses)	9.27	44.63	10.17
	1.4 mg/kg q6h (4 doses)	4.63	47.08	18.34
15.0	15.0 mg/kg (1 dose)	49.65	114.24	9.44
	7.5 mg/kg q12h (2 doses)	24.83	115.46	13.52
	3.75 mg/kg q6h (4 doses)	12.41	117.90	21.34

^a The first dose was administered 2 h after infection.

^b The MIC for *S. aureus* ATCC 29213 was 1.0 μ g/ml in 100% mouse serum by the NCCLS macrobroth dilution method.

TABLE 3. *S. aureus* densities in thigh muscles of mice that were treated with various total doses of daptomycin, administered in one, two, or four divided doses

Total dosage (mg/kg)	<i>S. aureus</i> densities (\log_{10} CFU/g \pm 1 SD) with:			P value ^a
	1 dose	2 divided doses ^b	4 divided doses ^c	
2.5	6.54 \pm 0.98	6.83 \pm 0.88	6.61 \pm 0.93	0.64
5.6	5.12 \pm 0.66	4.96 \pm 0.59	5.02 \pm 0.52	0.73
15.0	3.73 \pm 0.48	3.82 \pm 0.55	3.68 \pm 0.43	0.59

^a By analysis of variance. A P value of < 0.05 was considered statistically significantly different.

^b One-half of the single dose was administered at 0 h and then 12 h later.

^c One-fourth of the single dose was administered at 0 h and then 6, 12, and 18 h later.

5. **Efficacy of daptomycin in experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*.**

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Antimicrob Agents Chemother. 2003 May;47(5):1714-8.

In this study, we compared the efficacy of daptomycin with that of vancomycin, each with or without rifampin, in a model of experimental aortic valve endocarditis due to MRSA. The infecting strain (MRSA strain 32) was susceptible to daptomycin (MIC = 1 micro g/ml), vancomycin (MIC = 0.5 micro g/ml), and rifampin (MIC = 0.5 micro g/ml). Daptomycin was administered at 25 or 40 mg/kg q24h (q24h) by subcutaneous injection in an attempt to simulate human doses of 4 and 6 mg/kg q24h, respectively. Vancomycin was given at 150 mg/kg q24h by continuous intravenous infusion. Rifampin was given at 25 mg/kg by intramuscular injection q24h. Treatment was started 6 hours postinoculation and continued for 4.5 days. Outcome was assessed by counting the residual viable bacteria in vegetations. The mean peak daptomycin levels in serum at 2 hours after subcutaneous administration of 25 and 40 mg/kg were 64 and 91 µg/ml, respectively. Daptomycin was undetectable in serum at 24 hours. The total exposure was comparable to that achieved clinically in humans receiving the drug. Bacterial counts (mean log₁₀ number of CFU per gram ± the standard deviation) in untreated controls reached 10.6 ± 0.8. In treated rats, bacterial counts were as follows: vancomycin, 7.1 ± 2.5; daptomycin at 25 mg/kg, 5.5 ± 1.7; daptomycin at 40 mg/kg, 4.2 ± 1.5. The difference between daptomycin at 40 mg/kg and vancomycin at 150 mg/kg was statistically significant (P = 0.004). In the study of combination therapy, vegetation bacterial counts were as follows: daptomycin at 40 mg/kg, 4.6 ± 1.6; rifampin, 3.6 ± 1.3; vancomycin plus rifampin, 3.3 ± 1.1; daptomycin plus rifampin, 2.9 ± 0.8. The difference between daptomycin and daptomycin plus rifampin was statistically significant (P = 0.006). Daptomycin monotherapy administered to rats at 40 mg/kg was shown to be superior to vancomycin monotherapy, as determined by a statistically significant decrease in the bacterial density of aortic valve vegetations after 5 days of therapy. This study also provides evidence that the bactericidal activity of daptomycin is augmented by the addition of rifampin. Both daptomycin and vancomycin performed better in combination with rifampin, than either agent alone. These results support the continued evaluation of daptomycin for serious MRSA infections, including infective endocarditis.

TABLE 1. Pharmacokinetics of daptomycin and rifampin in the rat

Antibiotic	Dose (mg/kg) route	Species	C _{max} ^c	T _{max} ^d (h)	AUC ₀₋₂₄ ^e	t _{1/2} ^f
Daptomycin	25, s.c.	Rat	63.6	2	278.4	1.6
Daptomycin	40, s.c.	Rat	90.9	2	605.4	2.9
Daptomycin	4, i.v. ^a	Human ^b	57.8	0.5	493.5	8.2
Daptomycin	6, i.v. ^a	Human	98.6	0.5	747.4	8.9
Rifampin	25, i.m.	Rat	15.6	2	258.8	9.5

^a Administered as a 30-min-infusion.

^b The following data come from a single- and multiple-dose proportionality study with healthy human subjects. The values shown are the mean values at steady state (day 7 of q-24 h administration).

^c C_{max}: maximum drug concentration in serum.

^d T_{max}: time required to reach C_{max}.

^e AUC₀₋₂₄: area under the concentration-time curve from 0 to 24 h.

^f t_{1/2}: half-life.

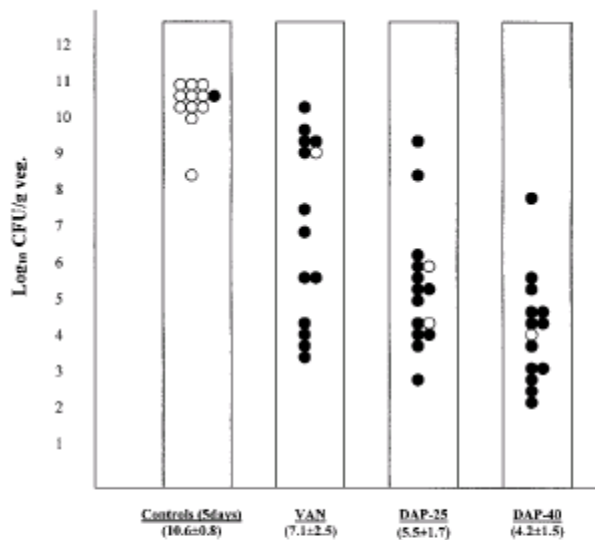


FIG. 1. Vegetation (veg.) bacterial densities after monotherapy for 5 days with vancomycin (VAN; $n = 14$), daptomycin at 25 mg/kg (DAP-25; $n = 15$), or daptomycin at 40 mg/kg (DAP-40; $n = 14$) and in control animals sacrificed at 5 days ($n = 12$). Each datum point represents one rat. The mean \log_{10} number of CFU per gram \pm the SD for each group is noted at the bottom of each column. $P < 0.05$ for controls versus all treatment groups and for vancomycin versus daptomycin at 40 mg/kg. Surviving animals at 5 days are shown as solid circles, while animals that were sacrificed or that died before 5 days are shown as open circles.

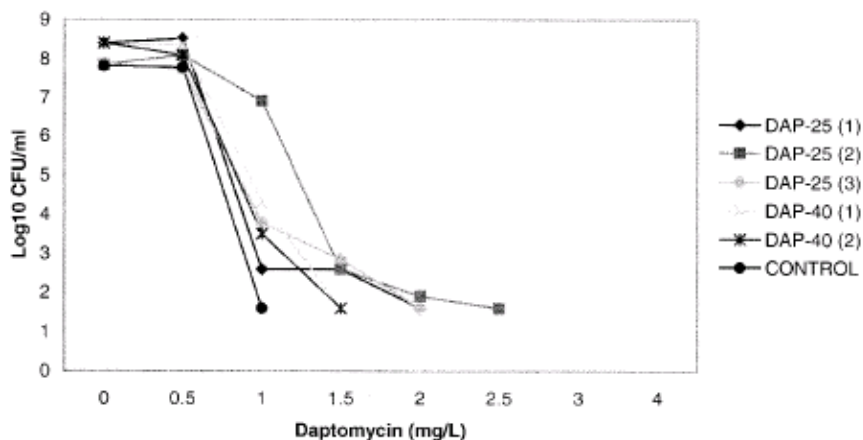


FIG. 3. Population analysis of surviving colonies from daptomycin-treated animals. Individual colonies were isolated and analyzed as described in Materials and Methods. Shown in the graph are three representative clones isolated from three individual animals treated with daptomycin at 25 mg/kg (DAP-25), two colonies from two individual animals treated with daptomycin at 40 mg/kg (DAP-40), and one colony from an untreated animal (CONTROL).