

Table S1. Correlation of MRSA daptomycin MIC with clinical outcomes in comparative studies

Study	Total # cases with MIC reported*	Infection site	Daptomycin MIC ($\mu\text{g}/\text{mL}$)	Daptomycin dose	Daptomycin cure rate [¶]	Comments
Kullar <i>et al</i> (1)	125	BSI, bone/joint, SSTI/wound, endocarditis, ortho-hardware	$\leq 1 - 4^{\text{ab}}$	>8 mg/kg/day	92.0%	<p>Surgical intervention unknown.</p> <p>Cure rate derived from additional data provided by authors.</p> <p>100% (101/101) of cases with an MIC of ≤ 1 $\mu\text{g}/\text{mL}$, 71% (12/17) cases with an MIC of $2\mu\text{g}/\text{mL}$, and 29% (2/7) with an MIC of $4\mu\text{g}/\text{mL}$ were cured. Outcome of one case was unavailable and not presented.</p>
Fowler <i>et al</i> (2)	120	Uncomplicated and complicated BSI and endocarditis	(See comment) ^a	6mg/kg/day	42.7%	<p>Study included MSSA; data not included in Table 2.</p> <p>37.5% of blood isolates were MRSA of which 44.4% were cured.</p> <p>Overall composite clinical/microbiological cure at 6 weeks was 42.7% (intent-to-treat); however microbiological failure alone was 15.8%.</p> <p>MIC presented for only 7 patients with a rising MIC on daptomycin; 6 were failures (both MSSA and MRSA). MIC rose on therapy from $0.25-0.5^{\text{a}}$ $\mu\text{g}/\text{ml}$ to $2-4^{\text{a}}$ $\mu\text{g}/\text{ml}$ in these 6 failures.</p>

Kullar <i>et al</i> (3)	100	BSI, hardware infection, CLABSI, endocarditis, bone/joint	0.13 - 4 ^a	6-10 mg/kg/day	79%	<p>Unknown what proportion of failures had surgical interventions.</p> <p>6% of patients received rifampicin co-therapy, 6% of patients received gentamicin co-therapy.</p> <p>Microbiological failure was defined as persistent bacteremia ≥ 7 days.</p> <p>75% (75/100) cases with an initial MIC ≤ 1 ug/mL, 50% (1/2) with a peak MIC = 2 ug/mL, and 0% (0/5) with a peak MIC = 4 μg/mL were cured.</p>
Campbell <i>et al</i> (4)	89	BSI, UTI, wound, respiratory, endovascular catheter, hardware	0.25 - 4 ^{bd}	2.6 - 12 mg/kg/day	87%	<p>70% of cases had bacteremia, 70% of cases had permanent/chronic device focus, and 18% had endovascular catheter involvement. Mean dose was 6.9 mg/kg/day.</p>
Murray <i>et al</i> (5)	85	BSI	≤ 1 - 4 ^{bd}	At least 6 mg/kg/day	80%	<p>Prolonged bacteremia noted, but ultimately microbiological and clinical cure. The two isolates with an MIC ≥ 2 had clinical cure and the rise in MIC occurred on daptomycin therapy.</p>
Moore <i>et al</i> (6)	59	BSI, endocarditis, device/graft, genitourinary, wound	≤ 1 ^b	6 mg/kg/day	90%	<p>Surgical intervention or device/graft removal status in failures unknown. 17% had clinical failure. Excluded respiratory infections. 29% had endocarditis, 10% had device/graft infection. Daptomycin dose presented is median initial dose.</p>

Rehm <i>et al</i> (7)	45	BSI, endocarditis, vascular device	0.25-2.0 ^c	6mg/kg/day	44.4%	<p>Not all underwent appropriate surgical intervention and/or intravascular device removal and deep seated infection present in many failures.</p> <p>Baseline MIC 0.25-0.5 µg/ml. 26.7% cases experienced persisting or relapsing bacteremia.</p> <p>All microbiological failures occurred in patients with complicated BSI or endocarditis.</p> <p>Composite clinical endpoint (cure/improvement, bacteremia clearance and/or lack of treatment limiting adverse reactions to daptomycin) presented.</p>
Davis <i>et al</i> (8)	22	SSTI	0.125 - 1 ^c	4mg/kg/day	100.0%	Endpoint defined as clinical cure rather than microbiological cure. All patients cured.
Gomez <i>et al</i> (9)	4	BSI, septic pulmonary emboli, SSTI	0.019 - 1 ^b	6 mg/kg/day	100.0%	Rifampicin co-therapy in all cases. One case died post resolution of infection from non-septic causes. Injectable drug use in 75% of cases.
Miro <i>et al</i> (10)	2	BSI, endocarditis	1 ^a	10mg/kg/day	100%	<p>No surgical valve intervention.</p> <p>Fosfomycin administered with daptomycin. Prior gentamicin, vancomycin and lower dose daptomycin. Severe comorbidities including HIV and cirrhosis.</p>
Levy <i>et al</i> (11)	1	BSI, cardiac ventricular assist device	0.25 - 8 ^b	8 mg/kg/day	0%	Device left in-situ. Concurrent use of rifampicin and gentamicin. Salvage therapy with COXT, linezolid, gentamicin, Q/D and device removal with transplant ultimately successful. Daptomycin MIC increase on therapy.

Mariani <i>et al</i> (12)	1	Bone with prosthetic joint	0.5 - 8 ^a	650 mg/day	0%	Long delay to removal of infected hardware. Patient died. MIC of 8 µg/mL seen on bone cultures only. Daptomycin MIC increase on therapy.
Tascini <i>et al</i> (13)	1	BSI, cardiac device, endocarditis	2 ^a	6 mg/kg/day	100%	Pacemaker explanted.
Wahby <i>et al</i> (14)	1	BSI, meningitis, peritoneal fluid	<0.5 ^c	6mg/kg/q48 hr (renally adjusted)	0%	Febrile neutropenia and peritoneal dialysis dependent. CSF analysis showed undetectable daptomycin concentrations. Salvage therapy with rifampicin, linezolid and vancomycin (intraperitoneal) successful.
Ho <i>et al</i> (15)	1	Endocarditis, BSI	2 ^b	6mg/kg/day	0%	Did not undergo valve replacement during daptomycin failure. Ceftaroline salvage therapy and subsequent mitral valve replacement with cure.
Kelesidis <i>et al</i> (16)	1	BSI, spinal osteomyelitis, meningitis and neurological shunt	≤0.5 ^a	Unknown	100.0%	Shunts removed. Linezolid and rifampicin co-therapy. MIC available on blood isolate only.
Twele <i>et al</i> (17)	1	BSI, right sided endocarditis	0.125 - 1..5 ^d	6 -12 mg/kg/day	0% (see comment)	No surgical intervention for endocarditis. MIC increased on daptomycin therapy. Salvage therapy with linezolid and gentamicin cleared bacteremia but progression of vegetation size noted.

Boyle-Vavra <i>et al</i> (18)	1	BSI, possible septic arthritis	$\leq 0.25 - 2^b$	6 mg/kg/day	0.0%	Nil surgical intervention beyond shoulder aspirate. MIC increase after daptomycin commenced. Dosing was based on ideal rather than actual body weight. Clearance of bacteremia with vancomycin therapy.
Tascini <i>et al</i> (19)	1	CLABSI, biliary	1^c	8 mg/kg/day	100.0%	Vascular catheter removed. Failed teicoplanin. Biliary VRE co-infection.
Hussain <i>et al</i> (20)	1	BSI, peripheral vascular catheter	0.19^b	10mg/kg/day	100.0%	Neonate.
Sheridan <i>et al</i> (21)	1	BSI, endophthalmitis, pericarditis, cardiac device	0.5^b	10 mg/kg q48 hr	100.0%	Cardiac device and vascular catheters removed. Prior vancomycin and linezolid. Death 3 weeks after resolution of infection with nil apparent signs of sepsis.
Lee <i>et al</i> (22)	1	BSI, bone, joint, vascular catheter related	$0.38 - 4^b$	12 mg/kg/day	0.0%	Vascular catheter removed but nil surgical intervention of infected joint. Advanced malignancy. MIC increased on therapy. Failed linezolid therapy.
Ritchie <i>et al</i> (23)	1	Chronic prosthetic joint	0.38^b	6 mg/kg/day	100.0%	Wash-out of joint occurred. HIV and sickle cell anaemia. Fusidic acid co-therapy.
Vernadakis <i>et al</i> (24)	1	CLABSI, endocarditis	0.5^b	6 mg/kg/day	100.0%	Valve replacement and central line removed. Failed vancomycin and linezolid. Infection occurred post liver transplant for cirrhosis.

Tenover <i>et al</i> (25)	1	BSI, cardiac device	≤0.5 - 4 ^a	6 mg/kg/48 hr	0.0%	Long delay till removal of infected hardware. Daptomycin MIC increase on therapy. Daptomycin dosing renally adjusted. Salvage therapy of Q/D, linezolid and COXT ultimately successful.
Cunha <i>et al</i> (26)	1	BSI, prosthetic valve endocarditis	1-2 ^a	6 - 12 mg/kg/48 hr	0.0%	No surgical intervention. Rifampicin co-therapy. Patient died.
Kuo <i>et al</i> (27)	1	CLABSI, endocarditis	0.5 - 2 ^a	350mg/day	0.0%	Vascular catheter removed, re-inserted and removed again. No surgical intervention for endocarditis. Daptomycin MIC increased on therapy. Patient died. Candidemia co-infection. Dosing renally adjusted.
Cunha <i>et al</i> (26)	1	BSI	0.25 ^a	12 mg/kg/day	0.0%	Failed linezolid salvage. Patient died.
Liu <i>et al</i> (28)	1	BSI, infected cardiac device, endocarditis and septic pulmonary emboli with abscesses	0.25 ^a	300mg/day	0.0%	Cardiac device removed. Rifampicin co-therapy. Salvage therapy with fusidate and linezolid successful. Dose renally adjusted.
Kuo <i>et al</i> (27)	1	BSI, mycotic aneurysm	0.5 - 2 ^a	250mg q48 hr	0.0%	Surgical repair of aneurysm. Dose renally adjusted. Daptomycin MIC increased on glycopeptide therapy before daptomycin therapy was commenced.

Lee <i>et al</i> (29)	1	Meningitis, BSI, infected dialysis graft	1 ^b	6mg/kg/48 hr	100.0%	Graft removed. Background of chronic kidney disease and lupus. Renally adjusted dosing.
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^aReference broth microdilution, ^bEtest, ^cmethod not described, ^dautomated method

MRSA = methicillin-resistant *S.aureus*, COXT = co-trimoxazole, Q/D = quinupristin-dalfopristin, BSI = bloodstream infection, UTI = urinary tract infection, MIC = minimum inhibitory concentration (mg/L), CLABSI = central line associated central line, SSTI = skin and soft tissue infection

*Subjects only included where MIC and correlating clinical outcome could be derived from published study findings, [¶]cure defined as clearance of bacteraemia or other cultures unless otherwise stated

Table S2. Correlation of VRE daptomycin MIC with clinical outcomes in comparative studies

Study	Total # cases with MIC reported*	Organism (infection site)	Daptomycin MIC (µg/ml)	Daptomycin dose (IV unless stated)	Daptomycin cure rate [¶]	Comments
Gallagher <i>et al</i> (30)	14	<i>E. faecium</i> <i>E. faecalis</i> <i>E. raffinosus</i> (BSI)	<1 - 4 ^{bd}	3.7 – 6.7 mg/kg/day	57%	<p>Death in all microbiological failures. 2 cases had MIC < 1µg/mL, of which 50% cured. 2 cases had MIC = 2 µg/mL, of which 0% cured. 10 cases had MIC = 4 µg/mL, of which 70% cured.</p> <p>Doses < 6 mg/kg/day associated with treatment failure.</p> <p>All failures occurred with <i>E. faecium</i> isolates</p>
King <i>et al</i> (31)	46	<i>E. faecium</i> <i>E. faecalis</i> (BSI, CLABSI)	0.5 - 4 ^b	5.35 – 8.2 mg/kg/day	78.2%	<p>Vascular catheter present in majority. Vascular catheter removed in under 40% of cases in total, and not removed in any failures. Excluded cases with MIC > 4 µg/mL or use of other VRE active agents.</p> <p>Higher daptomycin dosing (eg, >6 mg/kg/day) was not associated with cure.</p> <p>All failures occurred with <i>E. faecium</i> isolates</p>

Arias <i>et al</i> (32)	1	<i>E. faecium</i> (BSI, endocarditis, vascular graft)	2-4 ^a	6-8 mg/kg/day	(see comment)	No surgical intervention. Initial isolate had MIC = 4 µg/mL by BMD (6 µg/mL by Etest) and failed daptomycin. Subsequent VRE isolate had an MIC = 2 µg/mL (3µg/mL by Etest) and responded to ampicillin, gentamicin and 8mg/kg/day daptomycin.
Long <i>et al</i> (33)	1	<i>E. faecium</i> (BSI)	> 8-32 ^a	6mg/kg/day	0%	Febrile neutropenia post induction chemotherapy for AML. Linezolid salvage therapy resulted in cure. Possible late onset relapse 2 months later during stem cell transplantation.
Beneri <i>et al</i> (34)	1	<i>E. faecium</i> (CLABSI, cardiac shunt infection)	1.0 ^b	6mg/kg/day	100%	All vascular catheters removed and replaced but cardiac shunt left in-situ. Original dose 4mg/kg/q48hrs (renally adjusted). Gentamicin and doxycycline co-therapy.
Schutt <i>et al</i> (35)	1	<i>E. faecium</i> (BSI, prosthetic valve endocarditis)	3 - 4 ^a	6-8 mg/kg/day	100%	No surgical intervention. 6mg/kg/day daptomycin (with gentamicin combination) failed. 2nd line salvage regimen of 8mg/kg/day daptomycin plus tigecycline resulted in cure.
Huen <i>et al</i> (36)	1	<i>E. faecium</i> (dialysis associated peritonitis)	4 ^c	20mg/L (intra- peritoneal)	100%	Peritoneal catheter not removed. Intraperitoneal gentamicin co-therapy used.

Akins <i>et al</i> (37)	1	<i>E. faecium</i> (CLABSI, endocarditis)	2 ^a	6-8 mg/kg/day	(see comment)	No surgical intervention and unknown if vascular catheter removed. Severely immunosuppressed. Cleared blood culture initially, but subsequently died from respiratory failure.
Schwartz <i>et al</i> (38)	1	<i>E. faecium</i> (BSI, endocarditis)	2 ^c	6-8 mg/kg/day	0%	No surgical intervention. Failed Q/D salvage therapy.
Kelesidis <i>et al</i> (39)	1	<i>E. faecium</i> (post-operative intrabdominal abscess, urine)	2 - >256 ^a	6mg/kg/q48hrs	0%	Percutaneous drainage of collections. Morbid obesity. Salvage therapy with tigecycline successful. MIC rose on daptomycin therapy. Renally adjusted dosing.
Le <i>et al</i> (40)	2	<i>E. faecium</i> (post neurosurgical meningitis)	2 -3 ^b	9 - 12 mg/kg/day	100%	Gentamicin co-therapy.
Hidron <i>et al</i> (41)	1	<i>E. faecalis</i> (BSI, mechanical prosthetic valve endocarditis)	4 - > 8 ^b	Unknown	0%	No surgical intervention. Linezolid salvage therapy failed and patient died. Two isolates with different MICs.

Sabol <i>et al</i>	1	<i>E. faecalis</i> (UTI, BSI)	≥ 32 ^a	6mg/kg/day	0%	Vascular catheter removed. Initial urine isolate had MIC = 2 µg/mL, blood isolates MIC ≥ 32 µg/ml. Linezolid salvage therapy resulted in cure
Munoz-Price <i>et al</i> (42)	1	<i>E. faecalis</i> (hemodialysis related BSI)	1 - 16 ^a	400mg q48hr	0%	Hemodialysis vascular catheter replaced. Patient expired. Dose was renally adjusted. Initial isolate MIC of 1 µg/mL, final isolate MIC of 16 µg/ml. Amikacin co-therapy.
Barber <i>et al</i> (43)	1	<i>E.gallinarum</i> (CLABSI)	1 ^b	6 mg/kg/day	100%	Intravascular catheter changed. Malignancy with neutropaenia post-chemotherapy. Gentamicin co-therapy.

BSI = bloodstream infection, UTI = urinary tract infection, MIC = minimum inhibitory concentration (µg/ml), ^aBMD, ^bEtest, ^cmethod not described, ^dautomated

*Subjects only included where MIC and correlating clinical outcome could be derived from published study findings, CLABSI = central line associated blood stream infection

¶cure defined as clearance of bacteremia or other cultures unless otherwise stated, SSTI = skin and soft tissue infection, Q/D = quinupristin-dalfopristin

Supplemental Table References

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