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VRE (VANCOMYCIN-RESISTANT ENTEROCOCCI): EPIDEMIOLOGY, SUSCEPTIBILITY AND TREATMENT

Outline

- What is VRE?
- Resistant mechanism
- The burden
- Molecular typing
- Drug susceptibilities
- Treatment
- Take home messages

Discovery of VRE

- First reported in 1988 from Europe
  - Related to the use of avoporcin
- Increased rapidly in USA in 1990s

Uttley AH, et al. Lancet 1988;1:57 – 8.

Leclercq R, et al. N Engl J Med 1988;319:157 – 61.

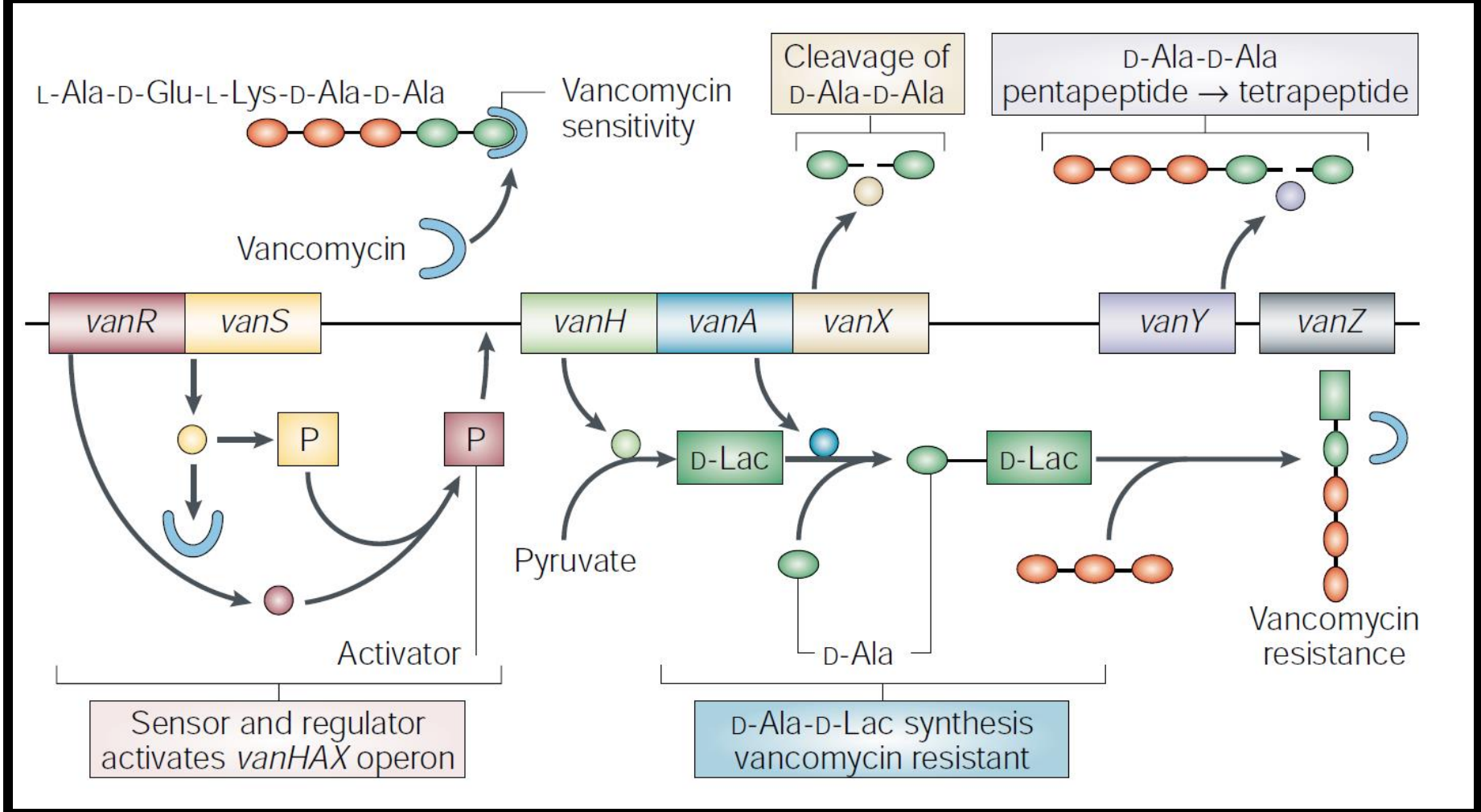
- Discovery of VRE in Taiwan: 1995

Chang SC, et al. Epidemiol Bull 1996;12:141 – 7.

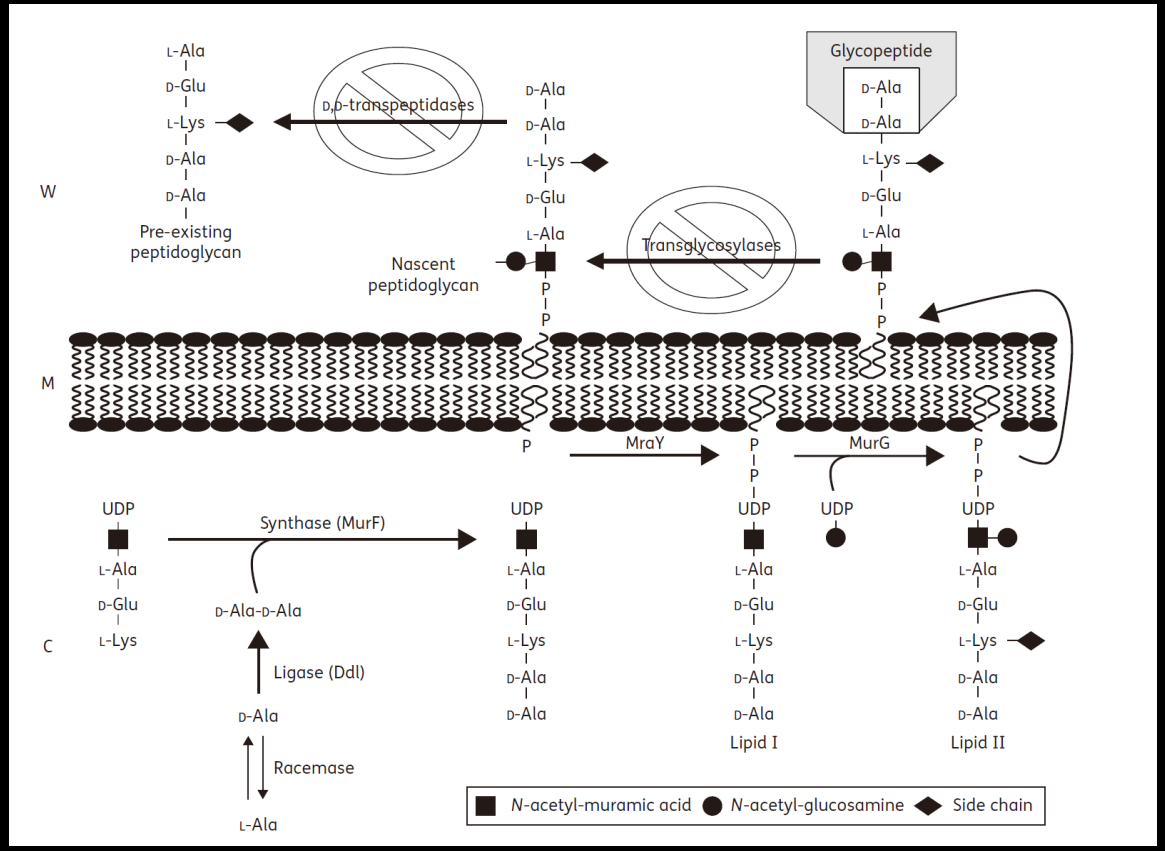
What is VRE?

Drugs	Zone diameter (mm)			MIC (mg/L)		
	S	I	R	S	I	R
Ampicillin	≥ 17		< 16	≤ 8		≥ 16
Vancomycin	≥ 17	15 – 16	≤ 14	≤ 4	8 – 16	≥ 32
Teicoplanin	≥ 14	11 – 13	≤ 10	≤ 8	16	≥ 32
Tetracycline	≥ 19	15 – 18	≤ 14	≤ 4	8	≥ 16
Doxycycline	≥ 16	13 – 15	≤ 12	≤ 4	8	≥ 16
Tigecycline (FDA)	≥ 19	-	-	≤ 0.25	-	-
Ciprofloxacin	≥ 21	16 – 20	≤ 15	≤ 1	2	≥ 4
Levofloxacin	≥ 17	14 – 16	≤ 13	≤ 2	4	≥ 8
Linezolid	≥ 23	21 – 22	≤ 20	≤ 2	4	≥ 8
Daptomycin	-	-	-	≤ 4	-	-
Fosfomycin	≥ 16	13 – 15	≤ 12	≤ 64	128	≥ 256

Illustration of Vancomycin Resistance



Nature Reviews Genetics. 2003;4:432–41.



Cattoir V & Leclercq R. Jantimicrob Chemother 2013;68:731 – 42.

Table 1. Types of resistance to glycopeptides in enterococci[6,16–18]

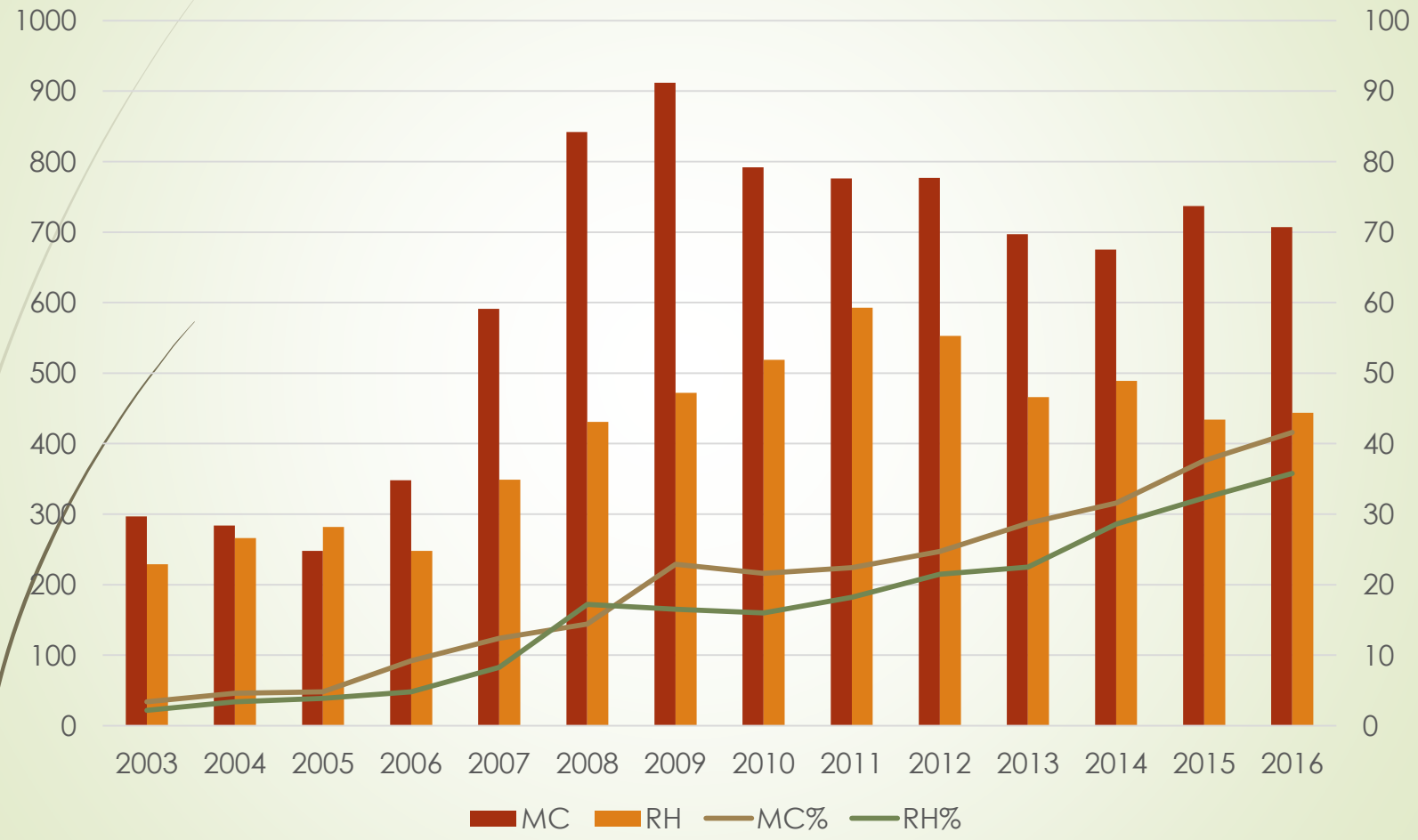
	Acquired resistance								Intrinsic resistance
	high level		variable	moderate	low level				low level
	VanA	VanM	VanB	VanD	VanE	VanG	VanL	VanN	VanC1/C2/C3
Susceptibility									
Vancomycin	R	R	r-R	R	r	r	r	r	r
Teicoplanin	R	R	S	r-R	S	S	S	S	S
Transferability	+	+	+	-	-	+	-	+	-
Main enterococcal species	A/B[a]	A	A/B	A/B	B	B	B	A	G/D
Expression	I	?	I	C	I/C	I	I	C	C/I
Genetic location	Plasmid (Chr)	Plasmid (Chr)	Chr (plasmid)	Chr (plasmid)	Chr	Chr	?	Chr	Chr
Precursors end	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser

R, high level of resistance (MIC >16 mg/L); r, low level of resistance (MIC = 8–16 mg/L); S, susceptible; A, *E. faecium*; B, *E. faecalis*; G, *E. gallinarum*; D, *E. casseliflavus*; I, inducible; C, constitutive; Chr, chromosome.
[a]Also other enterococcus species.

Mechanism of Resistance

- Genotype: major (C, D, E, G)
  - *vanA*: resides on Tn*1546*
  - *vanB*: resides on Tn*1547*, Tn*5382*
- Phenotype:
  - VanA: High level resistant to both vancomycin and teicoplanin
  - VanB: Still susceptible to teicoplanin

Proportion of VRE in ICUs

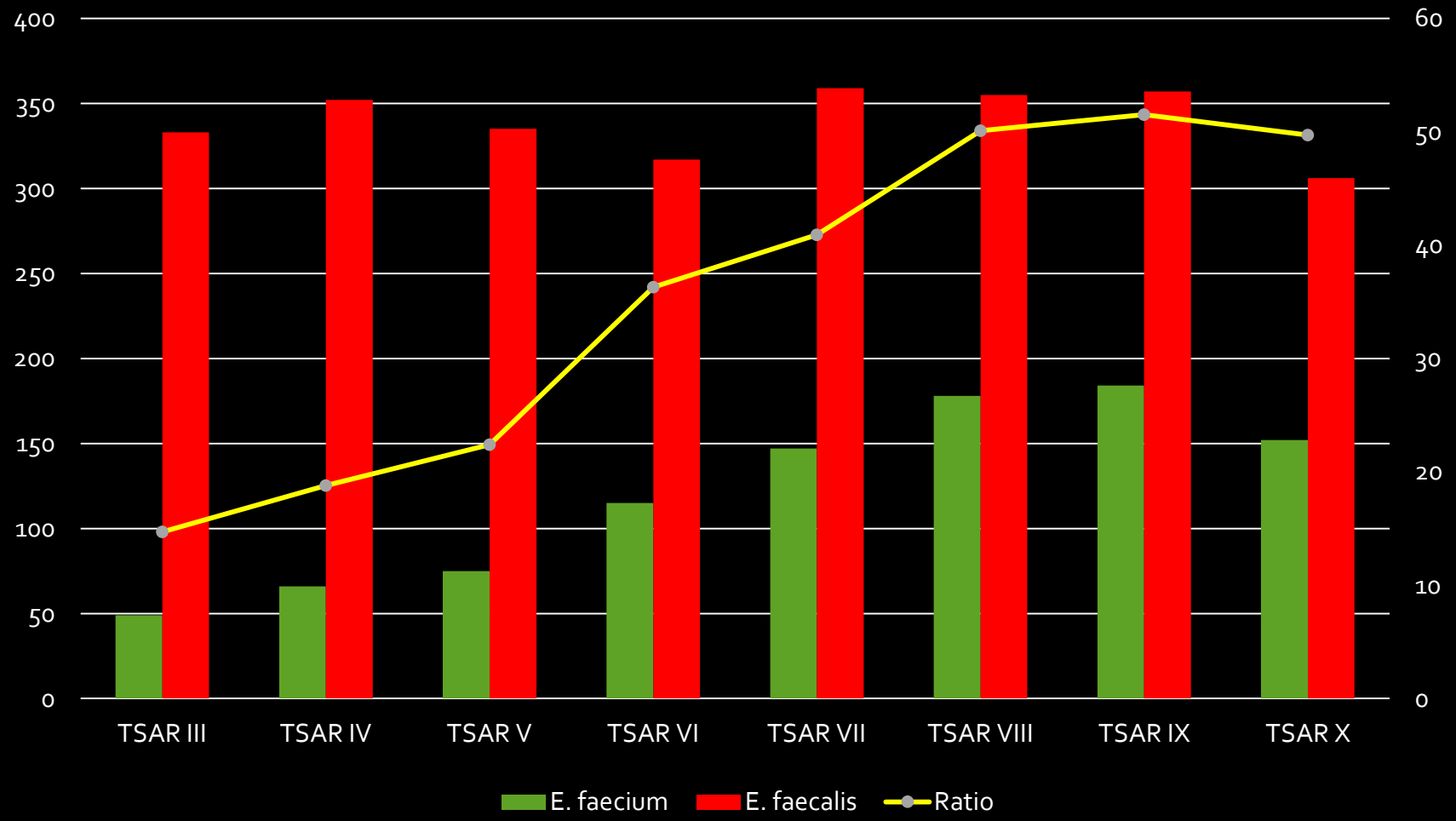


TNIS Surveillance data, CDC (Taiwan)

Proportion of VR*Efm* in ICUs

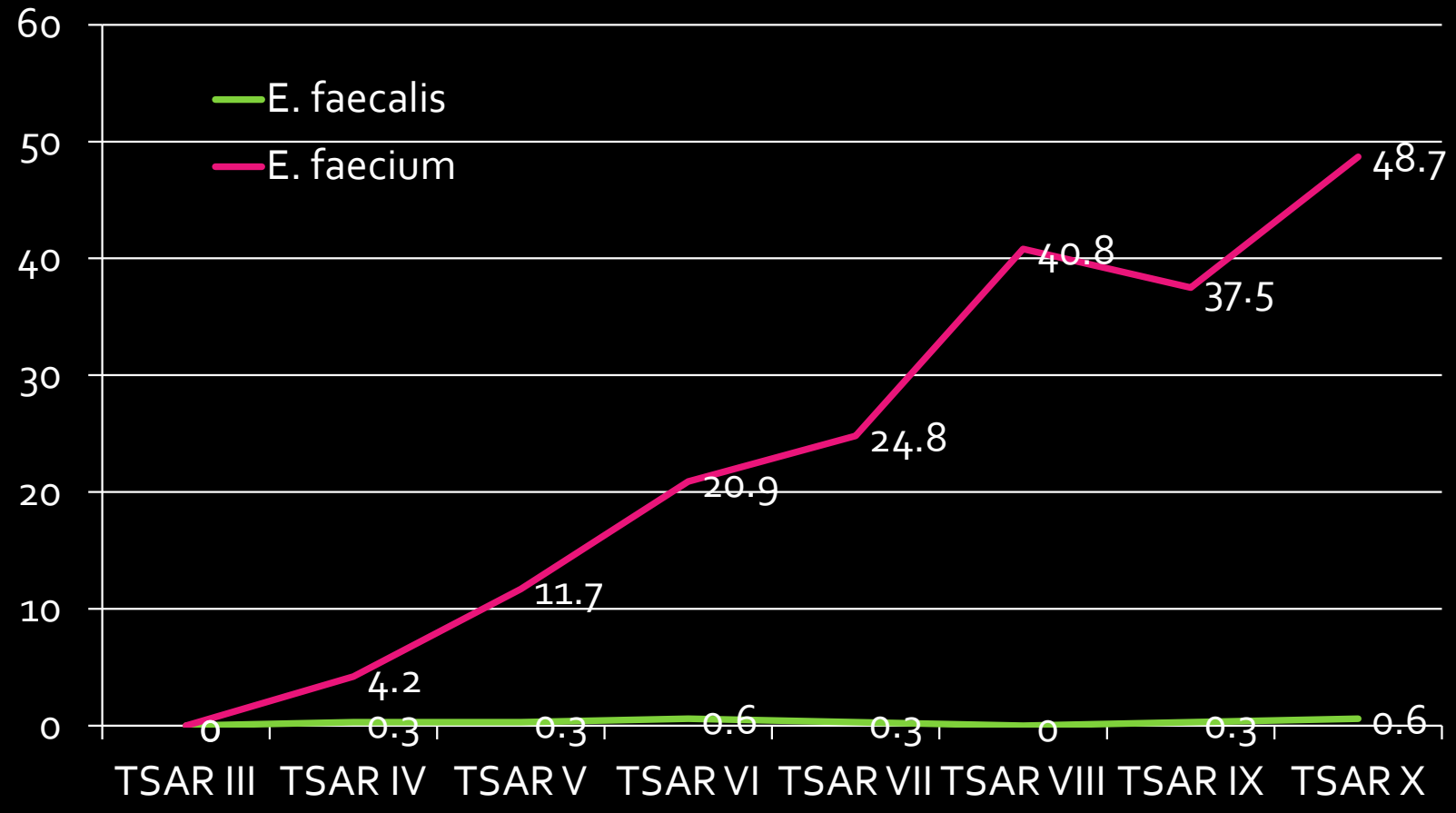
TNIS Surveillance data, CDC (Taiwan)

Enterococcus faecium Increasing
TSAR III (2002)- X (2016)



Kindly provided by Dr. Lauderdale TL

VRE, TSAR Data (> 90% *vanA*)



Kindly provided by Dr. Lauderdale TL

Risk Factors for VRE

Parameter	Odds ratio	95% C. I.		P
		Lower	Upper	
Length of risk	1.03	1.004	1.065	0.03
Prior use of 1st-generation cephalosporins	0.18	0.07	0.48	<0.001

Duration under risk
Antibiotics selective pressure

Pan SC, et al. PLoS One 2012;7:e47297.

Factor	OR	95% CI
Hospital		
Tertiary 2	Reference	Reference
Community	0.63	0.54–0.74
Tertiary 1	2.58	2.30–2.88
ICU stay	1.54	1.38–1.71
Charlson Comorbidity Index	1.04	1.02–1.06
Prior high-risk medication	8.19	5.96–11.26
Prior hospitalization	1.52	1.37–1.68
Renal failure	1.75	1.58–1.94
Maglignancy	1.46	1.29–1.66
Antibiotic use prior to infection	23.72	17.55–32.07
Sex		
Male	Reference	Reference
Female	1.29	1.17–1.43
Season		
Summer	Reference	Reference
Spring	1.16	1.02–1.33
Autumn	1.04	0.90–1.19
Winter	1.17	1.02–1.34
Length of stay prior to infection	1.03	1.02–1.03

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

Monteserin N, et al. J Hosp Infect 2016;94:236 – 41.

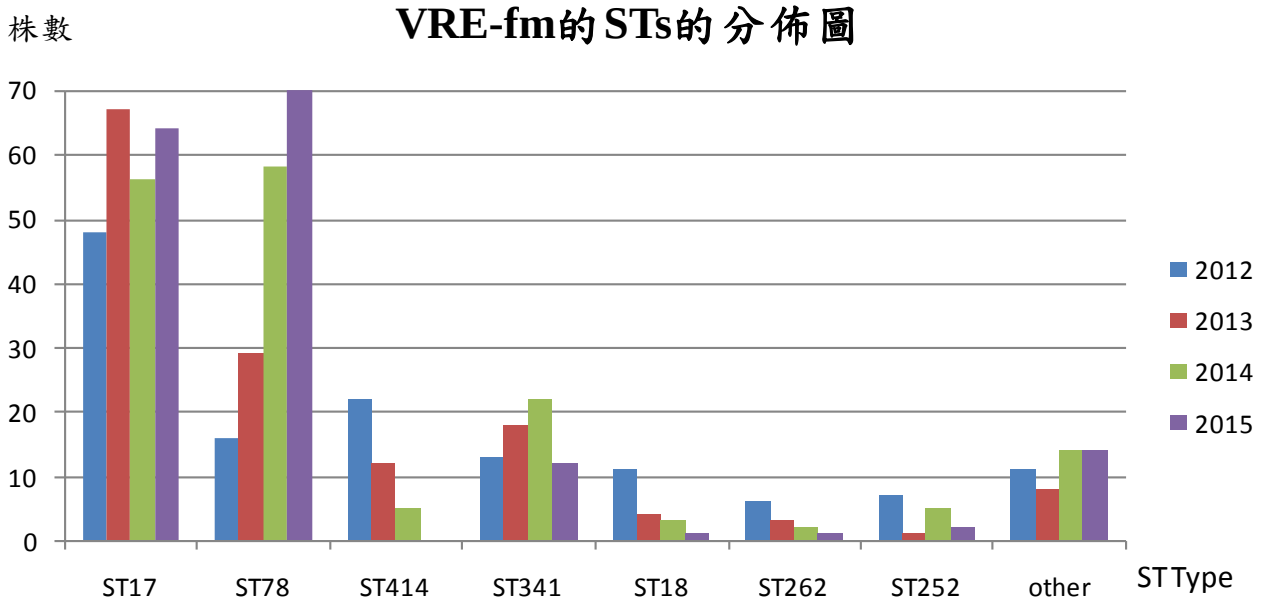
菌株*van*基因分析, Blood VR*Efm* 2012 - 2015

Bacteria	No.	*van*A genotype (%)		*van*B (%)	*van*C1/C2/C3
		VanA phenotype	VanB phenotype		
E. faecium	677	647 (95.6)	28 (4.1)	2 (0.3)	0
E. faecalis	2	2	0	0	0
E. avium	1	1	0	0	0
E. casslifavus	1	0	0	0	1
E. gallinarum	1	0	0	0	1
Total	682	650	28	2	2

Thank Dr. Wu TL for her kindly providing this slides

Molecular Typing by Multi-locus Sequence Typing

- 682 VR*Efm*的MLST分型結果，共35型-皆屬於clone complex 17(CC17)
  - ST17、ST78最多，各占235株(38.5%)、179株(29.3%)、其次為ST341 占65株(10.3%)，ST414占39株(5.9%)
  - 新型的16型ST共有19株VRE-fm



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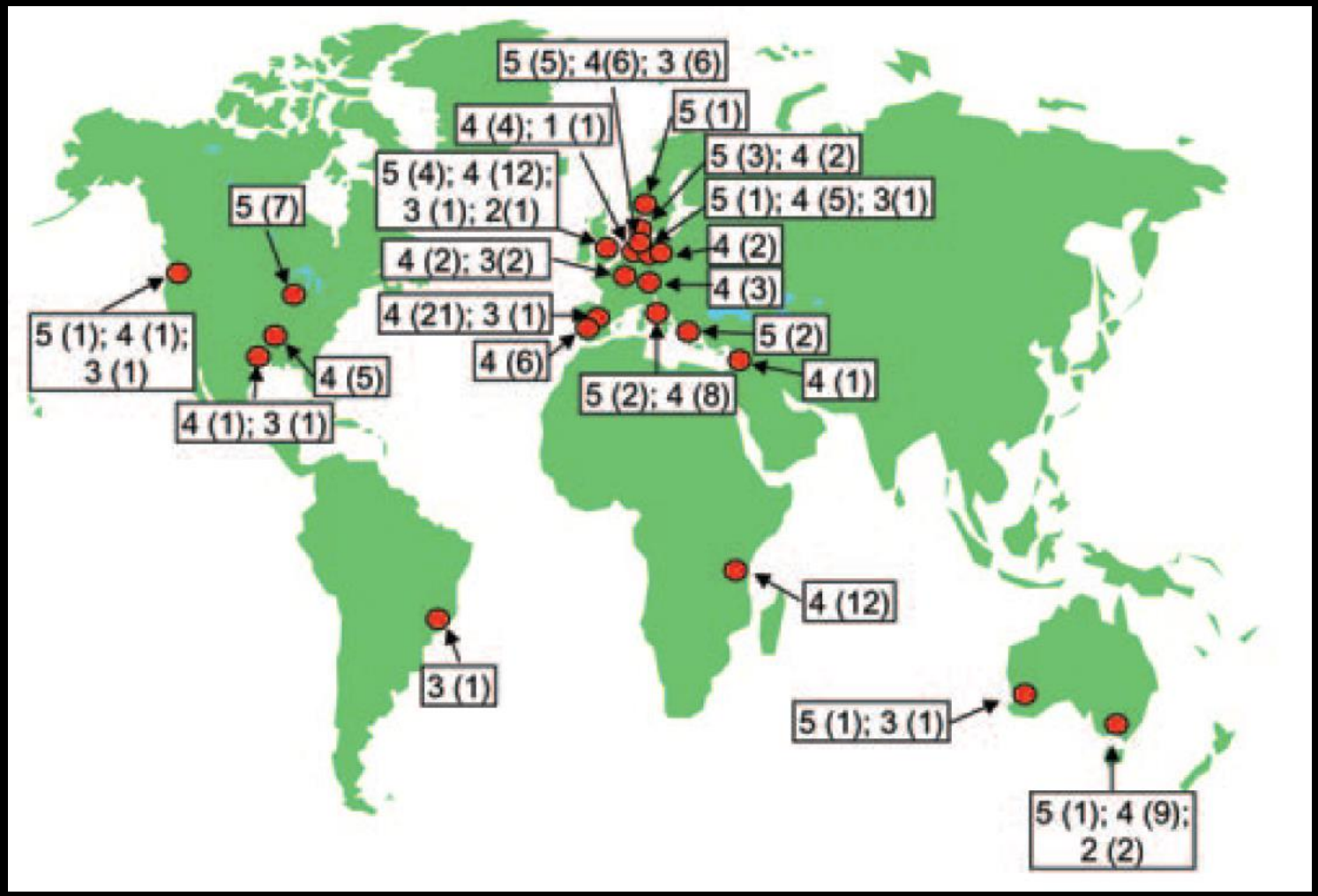
Global Spread of CC17 VRE



Willems RJ, et al. Emerg Infect Dis 2005;11:821-8

MIC&抗藥基因檢測

- 2012~2015年含*van*A抗藥基因的VRE菌株(678株)之各種抗生素抗藥性比較

抗生素	2012~2015年			抗藥性% (株數)				
	範圍	MIC_{50}	MIC_{90}	4年	2015年	2014年	2013年	2012年
Vancomycin	>256	>256	>256	100	100	100	100	100
Teicoplanin	3~>256	24	64	96.2	95.8	94.5	97.2	97.7
Tigecycline	0.016~12	0.125	0.19	5.6(38)	3.8(9)	4.2(7)	9.0(13)	6.8(9)
Daptomycin	0.64~32	2	3	1.0(7)	0.8(2)	2.4(4)	0.7(1)	0
Linezolid	0.25~2	1.5	1.5	0	0	0	0	0

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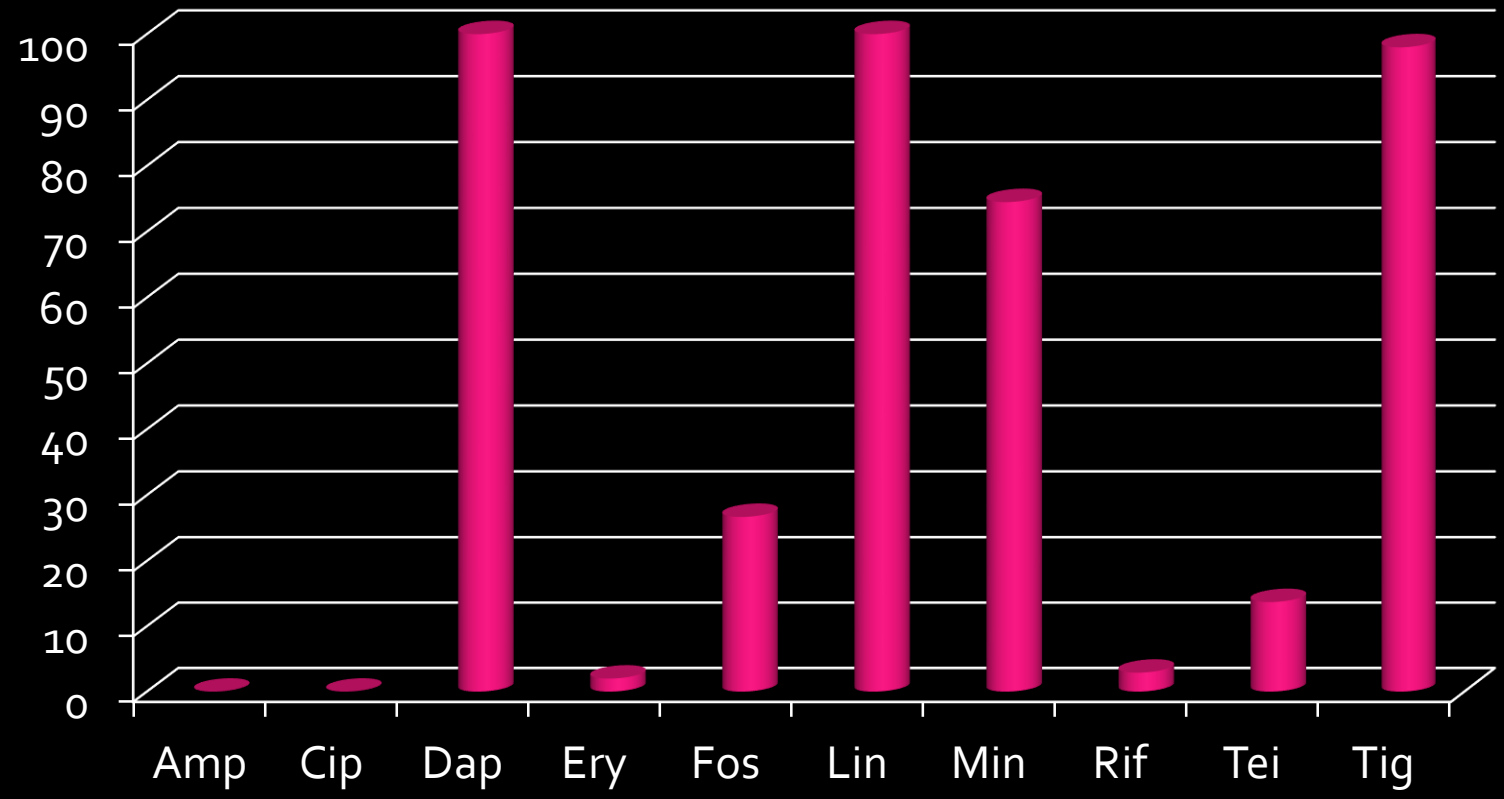
VR*Efm* Blood Isolates Susceptibilities

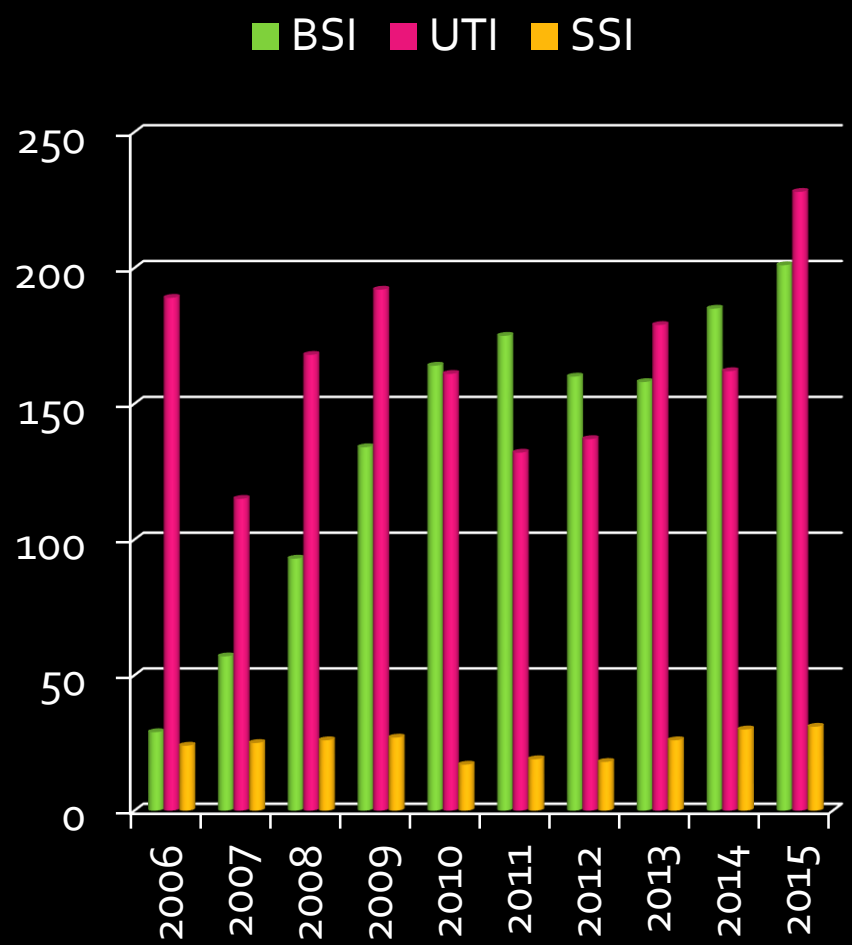


Lee SC, et al. BMC Infect Dis 13:163.
Lu CL, et al. J Antimicrob Chemother 2012;67:2243-9.
Lu CL, et al. Antimicrob Agents Chemother 2011;55:4295 – 4301

Treatment of VRE Infection

- Local epidemiology
  - VanA phenotype predominant, the role of teicoplanin is limited
- Tissue penetration
  - Bloodstream infection and urinary tract infection
    - Tigecycline is not suitable, usually
- Characteristics of antibiotics:
  - Bactericidal v.s. bacteriostatic

Major Sites of Infection by VREfm, TNIS (Left, MC; Right, RH)



Possible Drugs of Choice for VRE Infections

- Ampicillin:
  - Drug of choice, if susceptible
    - Adding gentamicin for bactericidal effect if not highly resistant (MIC > 2000 mg/L)
  - High-dose, maybe, if MIC 16 – 64 mg/L

Malathum K, et al. 1999 Drug Resist Uptdate 1999;2:224 – 43.
Mekonen ET, et al. Microb Drug Resist 1995;1:249 – 53.

- Fosfomycin:
  - > 90% susceptibilities
  - Limited clinical data, maybe for simple UTI

Perri MB, et al. Diagn Microbiol Infect Dis 2002;42:269 – 71.
Allergerger F, et al. J Antimicrob Chemother 1999;43:211 – 7.
Shrestha NK, et al. Scand J Infect Dis 2003;35:12 – 4.
Nicolee LE. Am J Med 2002;113(Suppl IA):35S – 44S.

Possible Drugs of Choice for VRE Infections

- Nitrofurantoin:
  - Around 80% susceptible rate in the surveillance data
  - Maybe for simple UTI
  - Very limited clinical data

Nicolee LE. Am J Med 2002;113(Suppl IA):35S – 44S.

Shrestha NK, et al. Scand J Infect Dis 2003;35:12 – 4.

Mutnick AH, et al. Diagn Microbiol Infect Dis 2003;46:63 – 8.

- Doxycycline / tetracycline
  - Susceptible rate: 50 – 87%, variable
  - Limited clinical data

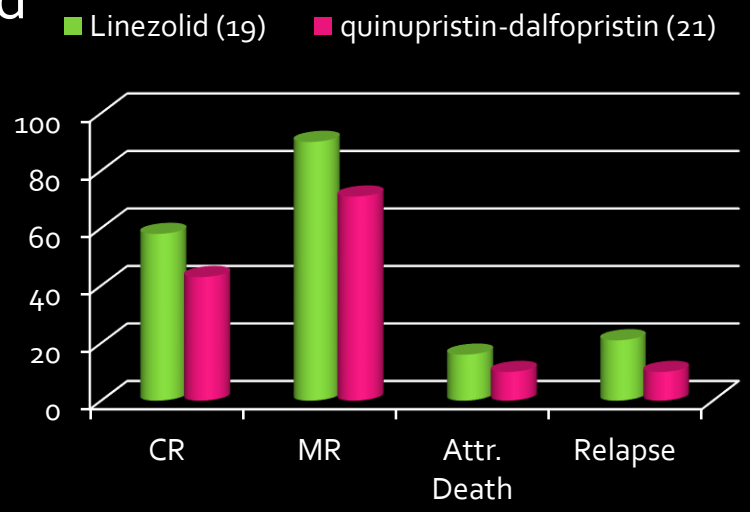
Howe RA, et al. J Antimicrob Chemother 1997;40:144 – 5.

Montecalvo MA, et al. Antimicrob Agents Chemother 1995;39:794.

Chia JK, et al. Clin Infect Dis 1995;21:1520.

Possible Drugs of Choice for VRE Infections

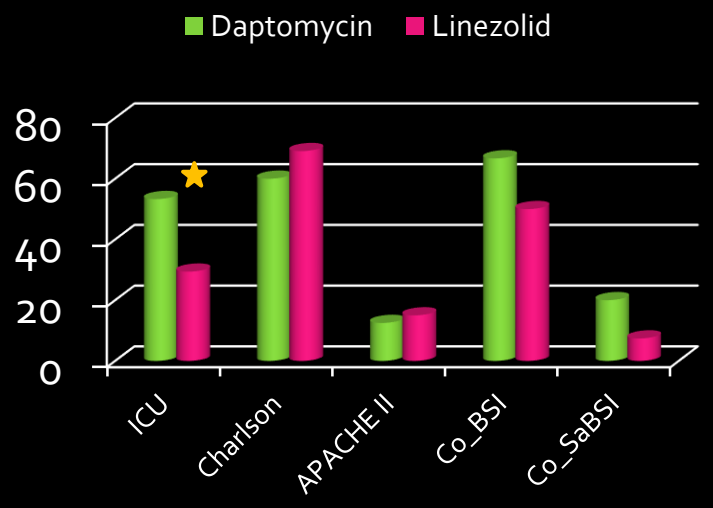
- Quinupristin-dalfopristin
  - FDA approves for VRE infection in 1999
  - However,
    - *E. faecalis* Intrinsically resistant to this drug
    - Not availabe in Taiwan
    - With comparison to linezolid
      - One RCT: better
      - One retrospective study:
        - A trend toward worse
        - ORs=5.45, univariate



Raad I, et al. J Antimicrob Chemother 2004;53:646 – 9.
Erlandson KM, et al. Clin Infect Dis 2008;46:30 – 6.

Possible Drugs of Choice for VRE Infections

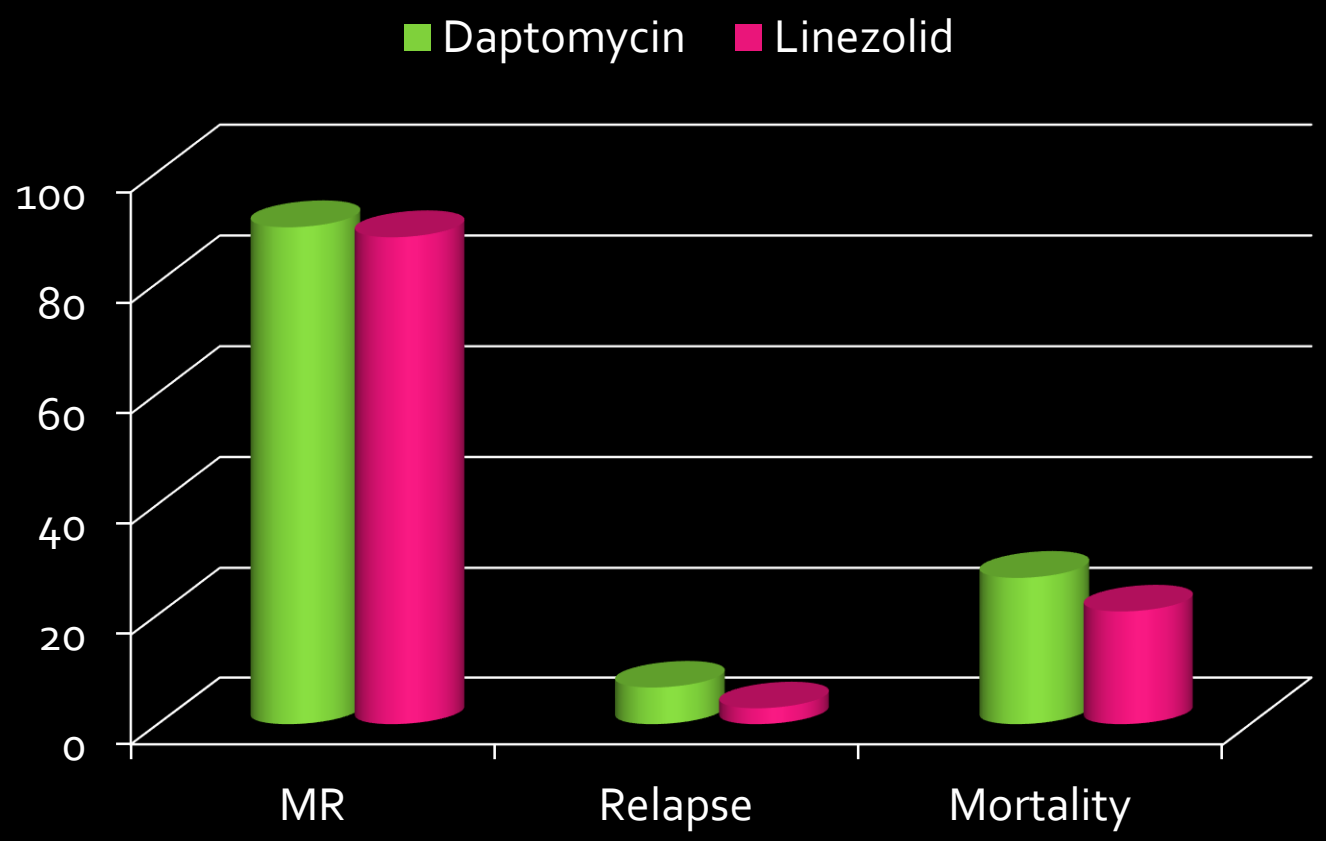
- Linezolid:
  - Approved by FDA for VRE infection in 2000
  - Good in vitro activity
  - Bacteriostatic, emergence of resistance, BM suppression



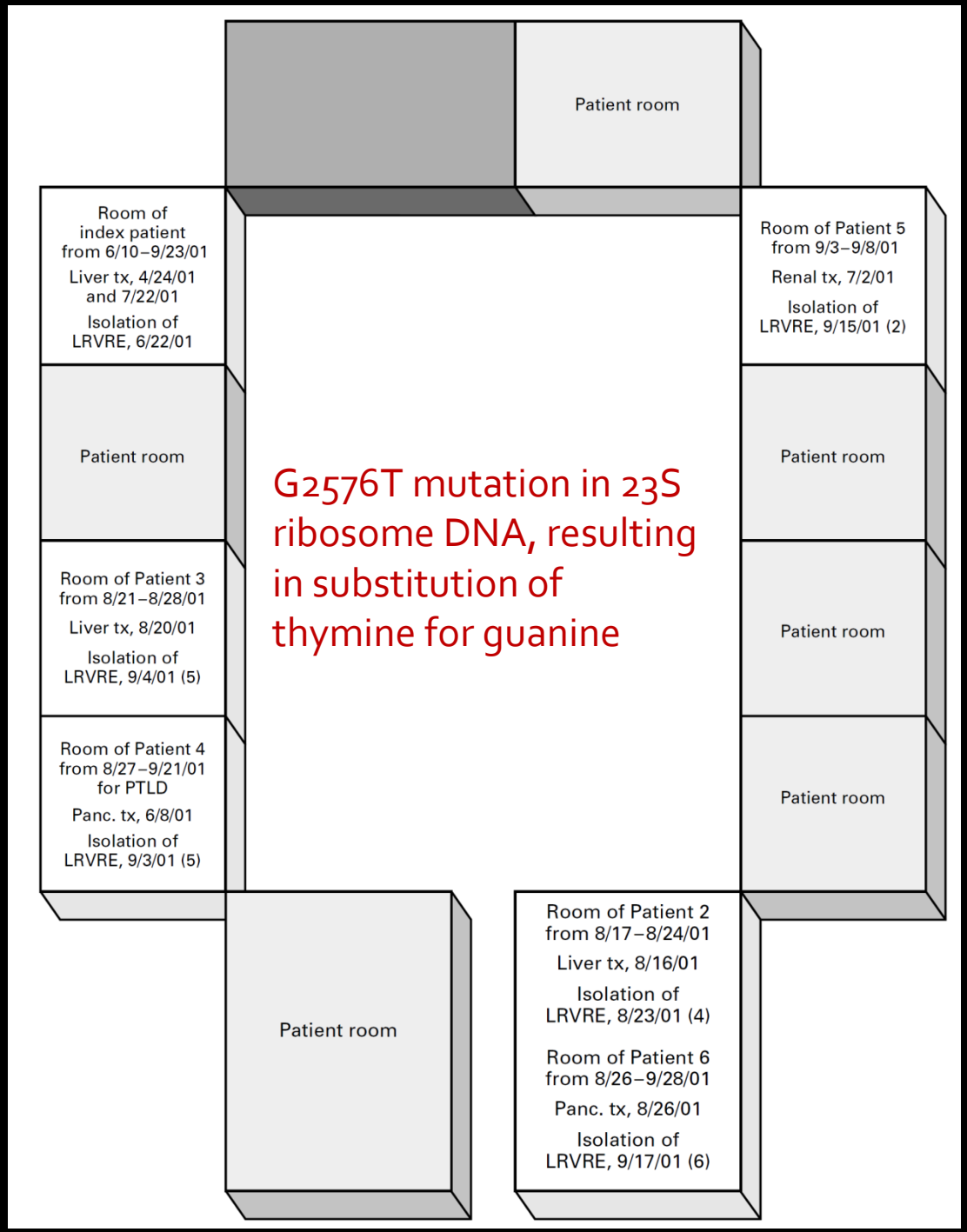
- 98 adult patients with VRE BSI
  - 2003.9 – 2007.12
  - 30 with daptomycin
  - 68 with linezolid
- Retrospective, obervational

Mave V, et al. JAC 2009;64:175 – 80.

Possible Drugs of Choice for VRE Infections



Despite a trend towards worse outcomes, daptomycin was as effective as linezolid in treating VRE BSI. A randomized clinical trial is needed

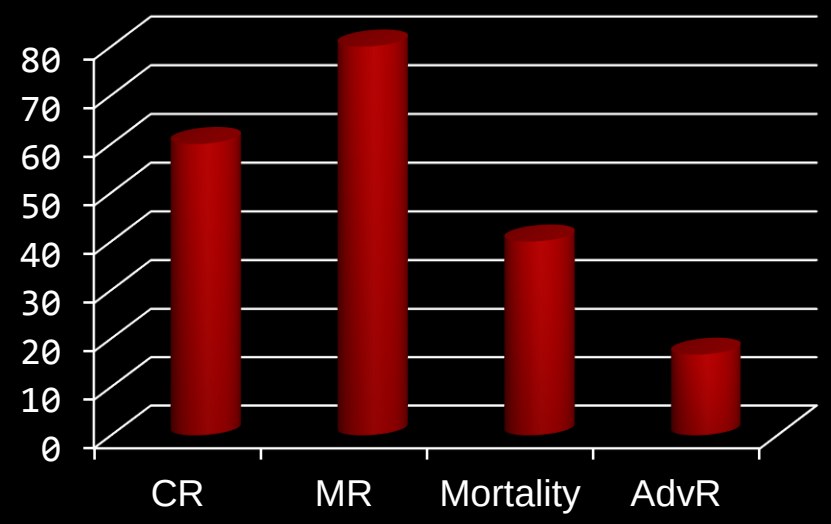


Emergence of linezolid-resistant VRE even leading to nosocomial outbreak

Herrero IA, et al. N Engl J Med 2002;346:867 – 9

Possible Drugs of Choice for VRE Infections

- Daptomycin:
  - Not proven by FDA for VRE BSI
  - Good in vitro activity, the only one bactericidal agent for VRE, Presence of clinical evidence



- Jan. 2004 – Jul. 2007
- 30 adult patients, VRE bacteremia
  - Median age, 59 (19 – 79) years
  - Male to female ratio, 1:1
- Independent factor for CR
  - Lower APACHE II score
  - Daptomycin dose ≥ 6 mg/kg.day
- Independent factor for MR
  - Lower APACHE II score

Gallagher JC, et al. Pharmacotherapy 2009;29:792 – 9.

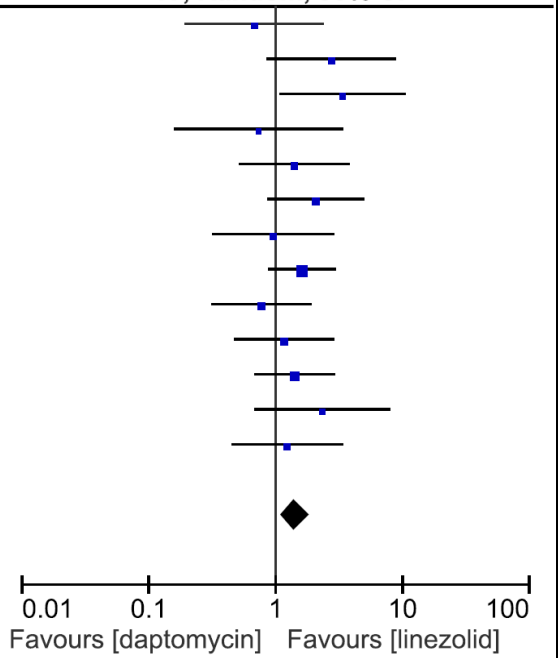
Preliminary Meta-analysis

(a)

Study or Subgroup	daptomycin Events	daptomycin Total	linezolid Events	linezolid Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Furuya et al. 2005	5	14	18	40	4.4%	0.68 [0.19, 2.39]	2005
El-Lababidi et al. 2007	12	28	6	28	5.1%	2.75 [0.85, 8.88]	2007
Dubrovskaya et al. 2008	13	40	5	40	5.3%	3.37 [1.07, 10.61]	2008
Marion et al. 2008	11	21	6	10	3.0%	0.73 [0.16, 3.38]	2008
Mave et al. 2009	8	30	14	68	7.0%	1.40 [0.52, 3.81]	2009
Crank et al. 2010	31	67	10	34	9.0%	2.07 [0.86, 4.98]	2010
Kraft et al. 2011	10	43	7	29	5.7%	0.95 [0.32, 2.88]	2011
McKinnell et al. 2011	32	86	28	104	18.5%	1.61 [0.87, 2.98]	2011
Bio et al. 2011	12	37	18	47	8.5%	0.77 [0.31, 1.91]	2011
Lu et al. 2012	11	29	22	64	8.5%	1.17 [0.47, 2.90]	2012
Twilla et al. 2012	15	63	25	138	13.4%	1.41 [0.68, 2.91]	2012
Chou et al. 2012	9	16	11	31	4.6%	2.34 [0.68, 8.01]	2012
Barbour et al. 2013	23	58	8	23	6.9%	1.23 [0.45, 3.37]	2013
Total (95% CI)		**532**		**656**	**100.0%**	**1.43 [1.09, 1.86]**	
Total events	192		178				

Heterogeneity: Tau² = 0.00; Chi² = 9.41, df = 12 (P = 0.67); I² = 0%

Test for overall effect: Z = 2.63 (P = 0.009)



Chuang YC, et al. BMC Infect Dis 2014;14:687.

Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in VRE BSI: A National Cohort Study of Veterans Affairs Patients

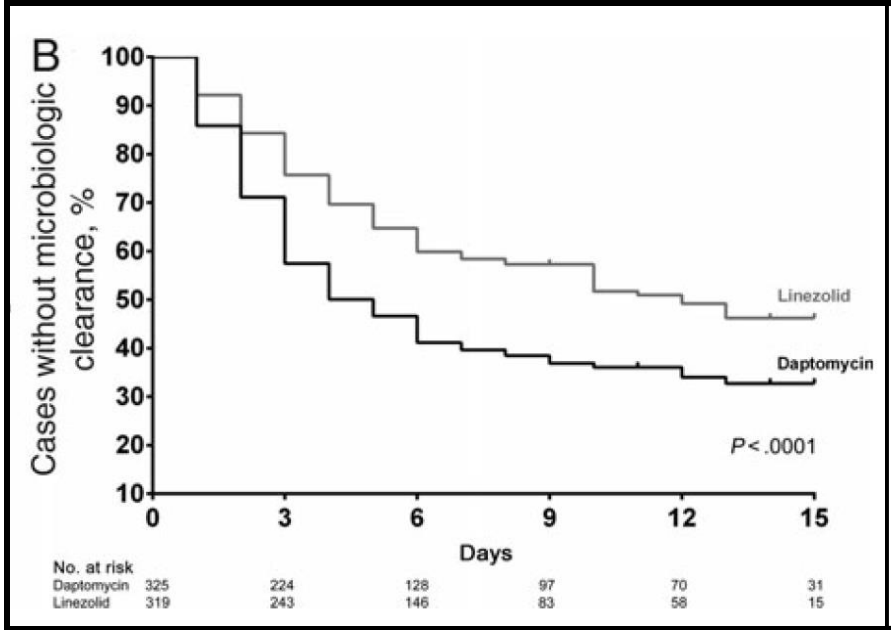
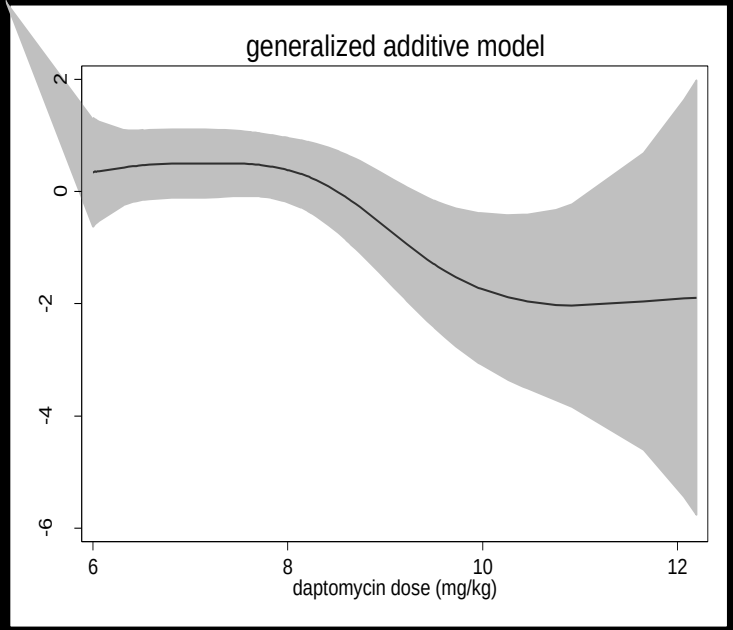


Table 4. Cox Proportional Hazards Model of Factors Associated With 30-Day Mortality Among Patients With Vancomycin-Resistant *Enterococcus* Bloodstream Infection

Factor (N = 644)	Hazard Ratio (95% CI)	*P* Value
Linezolid treatment	1.36 (1.05–1.76)	.021
Age ≥65 y	1.27 (.97–1.67)	.088
Intensive care unit admission	1.90 (1.29–2.80)	.001
Severe liver disease	1.83 (1.26–2.66)	.002
Hematologic malignancy	1.57 (1.11–2.22)	.011
Thrombocytopenia	1.52 (1.07–2.16)	.019
Unknown infection source	1.69 (1.25–2.28)	<.001
APACHE II score	1.03 (1.01–1.05)	<.001

Britt NS, et al. Clin Infect Dis 2015;61:871 – 8.

Risk Factors for Mortality among Patients with VRE BSI



Variables	OR (95% C.I.)	P
Steroid	3.43 (1.42 – 8.31)	0.006
Platelet	0.94 (0.91 – 0.98)	0.002
Pitt score	1.27 (1.13 – 1.43)	<0.001
Linezolid vs daptomycin	0.45 (0.21 – 0.96)	0.04
Using low-dose (< 9mg/day) daptomycin as reference		
High daptomycin	0.26 (0.09 – 0.74)	0.01
Linezolid	0.36 (0.17 – 0.79)	0.01

Chuang YC, et al. Clin Microbiol Infect 2016;22:890 e1 – 7.

Does MIC Level Matter?

Logistic regression for microbiologic failure (by Etest):

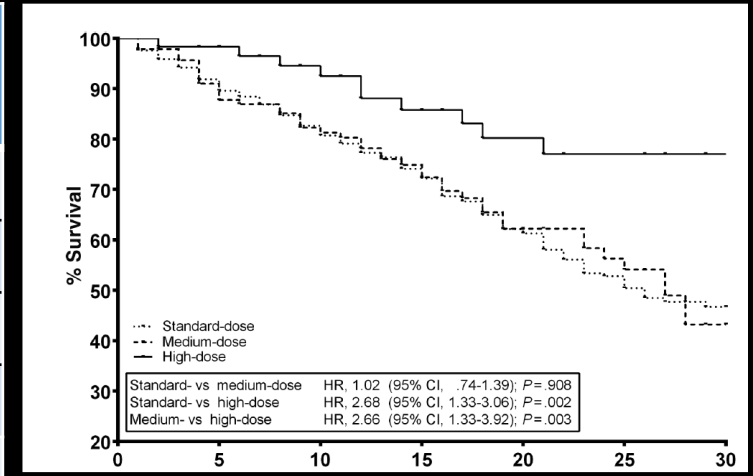
	Clearance < 4 d (28)		Clearance ≥ 4 d (34)		P	OR	95% C.I.		P
MIC, 3 – 4 mg/L	9	32.1%	22	64.7%	.011	4.70	1.37	16.12	.014
MIC ≤ 2 mg/L	19	67.8%	12	35.3%	.011				
Charlson score	11	39.3%	11	32.4%	.05	0.29	0.08	0.99	.047
Immusuppression	17	60.7%	31	91.2%	.004	5.32	1.20	23.54	.028

Logistic regression for in-hospital mortality:

	Clearance < 4 d (28)		Clearance ≥ 4 d (34)		P	OR	95% C.I.		P
ICU stay	11	29.7%	14	56.0%	.039	1.82	0.55	6.02	.328
AKI	8	21.6%	14	56.0%	.006	2.57	0.70	9.43	.156
Abd. source	8	21.6%	13	52.0%	.013	2.36	0.68	8.20	.178

Shukla BS, et al. Clin Infect Dis 2016;62;1514 – 20.

Risk factor for mortality	HR	95% C.I.		P
		Lower	Upper	
Age ≥ 65 y	1.76	1.37	2.28	<0.001
ID consultation	0.58	0.46	0.75	<0.001
Severe liver disease	1.22	1.09	1.37	0.001
Thrombocytopenia	1.61	1.25	2.08	<0.001
Charlson comorbidity index	1.05	1.01	1.08	0.015
Daptomycin ≥ 10 mg/kg.day				
8 mg/kg.day	2.52	0.09	0.74	0.008
6 mg/kg.day	2.58	0.17	0.79	0.004

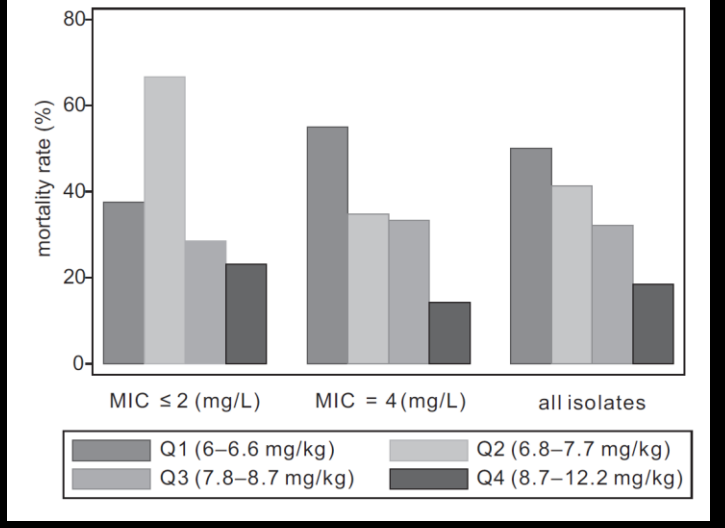


Days

Britt NS, et al. Clin Infect Dis 2017;64:605 – 13.

Variable	Multivariable Odds Ratio[a] (95% Confidence Interval)	*P* Value
Steroid use	7.39 (1.82–29.96)	.005
Pitt bacteremia score	1.26 (1.07–1.48)	.007
Platelet count ($\times 10^4/\mu L$)	0.93 (0.88–0.98)	.01
Daptomycin dose		
<7 mg/kg	Reference	
7–9 mg/kg	0.47 (0.16–1.40)	.18
≥9 mg/kg	0.09 (0.02–0.44)	.003

[a]Hosmer-Lemeshow goodness-of-fit test, $P = .94$.



Chuang YC, et al. Clin Infect Dis 2017;64:1026 – 34.

Combination Therapy

- Daptomycin + ampicillin
  - case report only
- Daptomycin + ceftaroline
  - Case report only
- Daptomycin + tigecycline
  - Most frequently reported
- Daptomycin + fosfomycin
  - In vitro study and animal study only

Barber KE, et al. Expert Rev Anti infect Ther 2015;13:363 – 77.

Treatment for VRE Infection

- Summary:
  - Old drugs:
    - Ampicillin, if susceptible
    - Other drugs are limited for
      - Adverse effect, limited susceptibilities
      - Very limited clinical data
  - New drugs (in current Taiwan):
    - Daptomycin and linezolid may be drug of choices
    - Tigecycline will be restricted for its low tissue concentration in the common foci of VRE infection

Take Home Message

- Most VRE carrying *vanA* gene and expressing VanA phenotype in current Taiwan
- VR*Efm* is predominant in current Taiwan
- The burden is high and increasing
- Major sequence types: 17 & 78, all belonging to CC17
- Most convincing agents in vitro:
  - Linezolid, daptomycin, tigecycline
- For VRE BSI
  - Linezolid vs. daptomycin: needs further study
  - High-dose daptomycin for VRE BSI might be needed