
Staphylococcus aureus:
MRSA, VISA, and now VRSA

**Peter Appelbaum
Hershey Medical Center
Hershey, Pennsylvania
USA**

Staphylococcus aureus: Development of penicillin and methicillin resistance

- 1940s: Penicillin used to treat infection¹
- 1942: Penicillin-resistant *Staphylococcus aureus* recognized in hospitals²
- 1960s: > 80% of hospital and community acquired *Staphylococcus aureus* are penicillin resistant¹
- 1961: Introduction of methicillin, rapidly followed by reports of resistance³

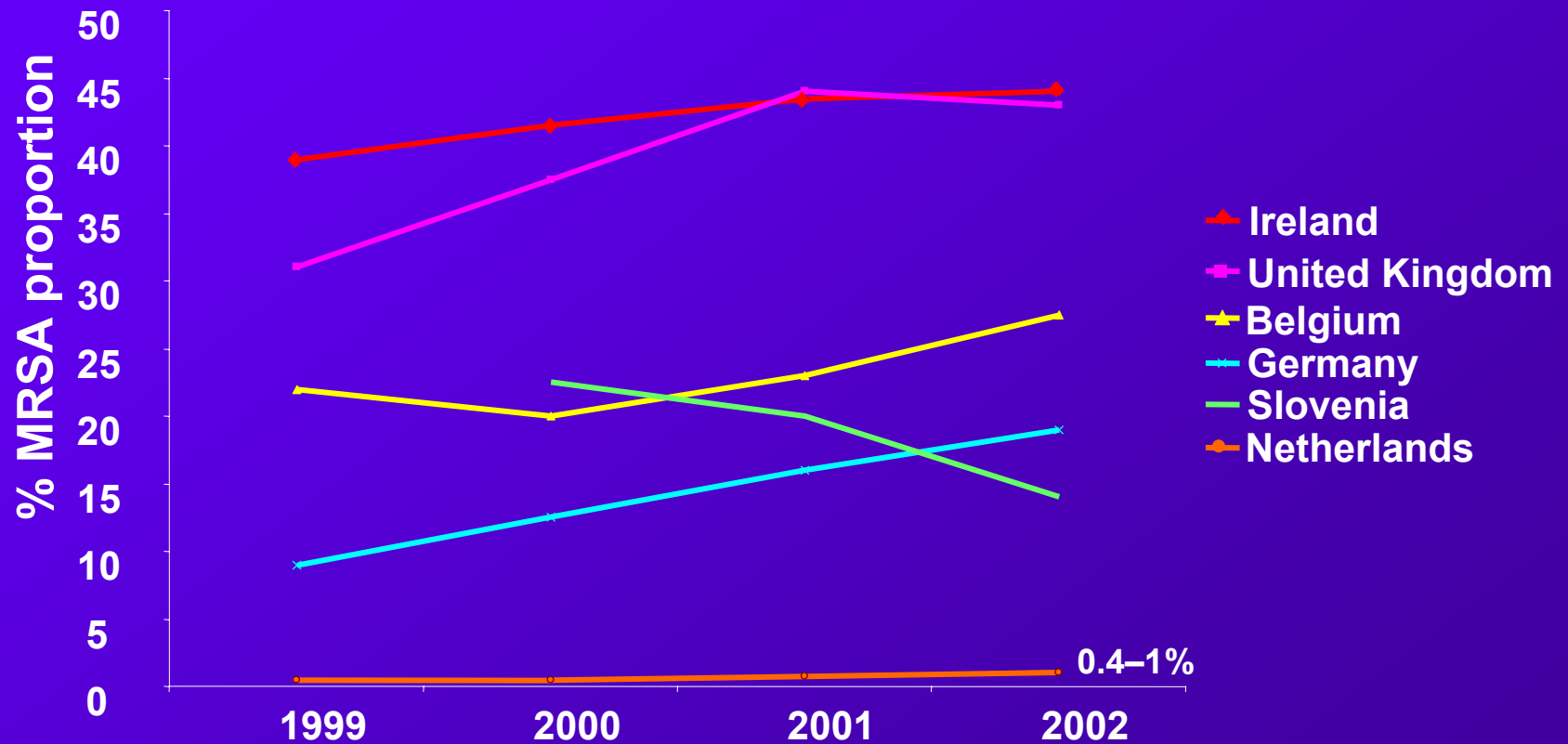
1. Lowy FD. *J Clin Invest* 2003; **111**: 1265–1273.

2. Rammelkamp CH, Maxon T. *Proc Royal Soc Exper Biol Med* 1942; **51**: 386–389.

3. Jevons MP. *Br Med J* 1961; **1**: 124–125.

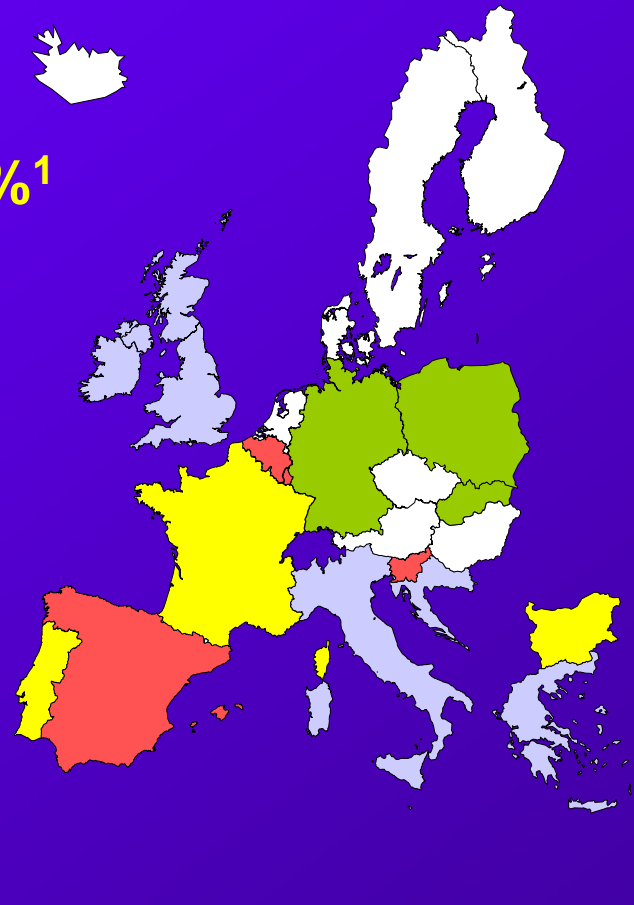
Nosocomial MRSA

- Significant trends ($p < 0.05$) in MRSA proportions across Europe

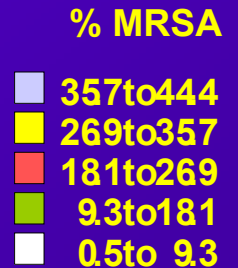


Percentage of MRSA isolates 1999–2002

- United States 26.6%–44.4%¹
- Taiwan 77%²
- Korea 64%³
- Australia 26%⁴



Europe
1999–2002⁵



1. Jones et al, IJAA 2003; 22: 406–419; 2. Hsueh et al, AAC 2004; 48: 1361–1364; 3. Kim et al, AAC 2004; 28: 1124–1127; 4. Douglas et al, Trop Med Int Health 2004; 9: 795–804; 5. Tiemersma et al, EID 2004;10: 1627–1634.

MRSA outside the hospital

- Methicillin resistance has moved outside the hospital environment
- MRSA clone isolated from U.S. football players (St. Louis Rams) in 2003
 - ◆ Susceptible to most antimicrobial agents except β -lactams and macrolides
 - ◆ Carried characteristic gene complex for methicillin resistance (mec IV) and gene for Panton-Valentine leukocidin
- Comparison of the strain involved with that involved in epidemiologically unrelated outbreaks demonstrated them to be indistinguishable
 - ◆ This clone may be widely distributed in the community

Differences between nosocomial and community acquired MRSA

Nosocomial MRSA

- ◆ Multi-drug-resistant (clindamycin, gentamicin, FQ)
- ◆ Contain SCCmec I, II, or III
- ◆ Usually PVL-negative

Community acquired MRSA

- ◆ Usually only resistant to pen, ox ± eryth ± FQs
- ◆ Contain SCCmec IV
- ◆ Usually produce PVL, especially in the US
- ◆ Virulent (osp, skin and lung)

The Tip of the Iceberg

- **MRSA strains now distributed worldwide**
- **3 pandemic clones traced to original Danish isolates¹**
- **Generally MDR**
- **Dramatic increase in MRSA linked to expanding reservoir of community-onset MRSA²**

1. Cristomo et al, *Proc Natl Acad Sci USA* 2001; **98**: 9865–9870.

2. Carleton et al, *JID* 2004; **190**: 1730–1739.

LIFE-THREATENING COMRSA INFECTIONS

1) Neonatal sepsis: 8/17 S.aureus bacteremia due to MRSA; 6/8 carried SCC mecIV. Three fatalities and three had complications requiring prolonged therapy.

Healy et al (2004) Clin Infect Dis 39: 1460

2) Community-acquired pneumonia. Four patients, all strains PVL + with SCC mecIV. Two patients with concomitant influenza A. One fatality; the other 3 requiring prolonged hospitalization with severe complications

Francis et al. 2004. Clin Infect Dis 40: 100.

The Consequences of Increasing Resistance: 2

- Seventeen infants (47%) with bacteremia at a tertiary care NICU in Houston had MRSA¹
- Isolates from 6/8 infants (75%) carried SCCmec genes (community MRSA); 4 had mecIVa
- All six isolates were β -lactam and erythro-resistant; one also clinda-resistant
- One isolate non-typeable, carried SCCmec type II gene (nosocomial strains) but was vancomycin-susceptible
- Seven (88%) of 8 infants presented with septic shock
- Despite vancomycin treatment, three (38%) died and the survivors required prolonged antibiotic therapy

The Consequences of Increasing Resistance (3)

- During 2003 US football season 8 MRSA infections amongst 5/58 team players (St. Louis Rams)
- Lesions at turf-abrasion sites; subcutaneous abscesses
- MRA isolated from whirlpools, taping gels and nasal swabs from players and staff members (42%)
- MRSA from a competing football team and other community clusters and sporadic cases had PFGE patterns indistinguishable from those of the Rams' MRSA
- All MRSA carried PVL and mec IV

Current Issues in Staphylococcal Resistance: from VISA to VRSA

The Emergence of hVISA: the Precursor to VISA

- **1996: First report of hVISA in Japan – Mu3 Case history**
- **64-year old Japanese man who had MRSA pneumonia**
- **Treatment with vancomycin for 12 days was ineffective**
- **Subsequently treated successfully with 10 day course of aminoglycoside + ampicillin/sulbactam**
- **Sputum sample revealed MRSA (Mu3) with vancomycin MIC of 4 µg/ml on BHIA plates**
 - ◆ **Subpopulations grew in the presence of 5–9 mg/L vancomycin**

The Emergence of VISA

- **1997: First report of VISA in Japan – Mu50 Case history**
- **4 month old Japanese infant who underwent heart surgery**
- **2 weeks post-op, patient became febrile and developed a purulent discharge from incision site**
- **Treated with vancomycin for 29 days; fever and discharge persisted**
- **Aminoglycoside added to treatment regimen for 12 days; wound healed**
- **Abscess developed 12 days later, and treated with aminoglycoside + ampicillin/sulbactam**
- **Debridement sample revealed MRSA (Mu50) with vancomycin MIC of 8 µg/ml by broth microdilution method**

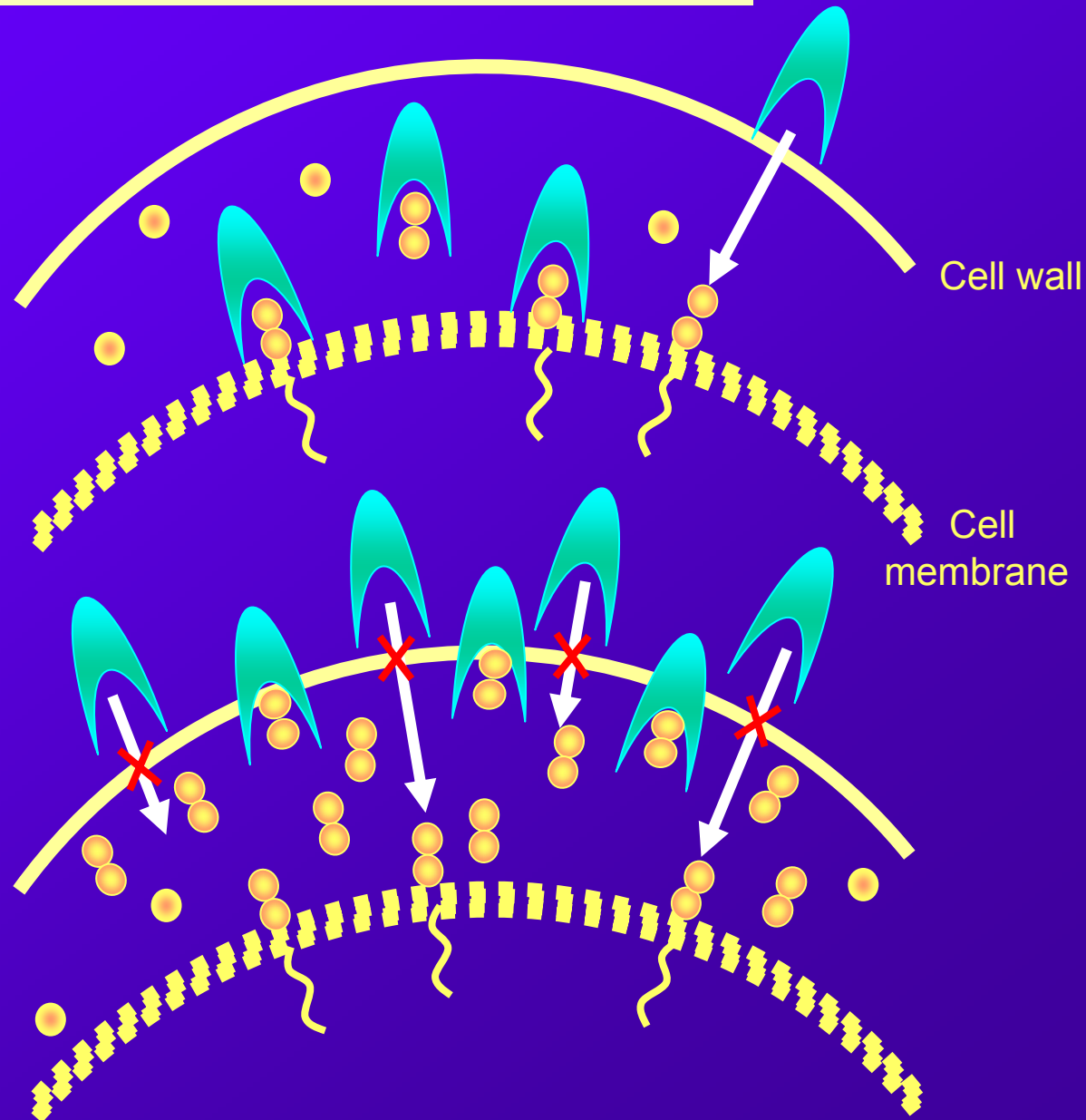
VISA: Mechanism of Resistance

Susceptible cell

Cell wall synthesis is inhibited and glycopeptides have access to cell wall synthesis sites

VISA

Cell wall synthesis continues and glycopeptides are unable to access cell wall synthesis sites



INCIDENCE OF VISA IN ANKARA TURKEY

- **Amongst 256 MRSA (1998-2002), 145 grew on BHI-V4**
- **46 of these 145 yielded vancomycin MICs of 4-12 µg/ml and teicoplanin MICs of 8-16 µg/ml by E test**
- **CLSI microdilution showed all strains to be S**
- **Incidence of these strains rose from 1.6% in 1998 to 36% in 2001**
- **Most VISA strains were isolated from blood and pus**

The emergence of VRSA

- **2002: Emergence of VRSA in the USA Case history**
- **40 year old man from Michigan, with diabetes, PVD and CRF**
- **Amputation of gangrenous toe in April 2002; subsequently developed MRSA bacteremia caused by infected arteriovenous hemodialysis graft**
- **Treated with vancomycin, rifampicin, and removal of the graft**
- **Developed suspected catheter exit-site infection in June; catheter subsequently removed**
- **Catheter tip cultures grew Staphylococcus aureus resistant to oxacillin and vancomycin**
- **Later, chronic foot ulcer appeared infected; cultures grew VRSA, VRE, and Klebsiella oxytoca**

The Common Denominator: Chronic Ulceration

VRS1 (Detroit)¹

- Diabetic PVD & Chronic Renal Failure, hypertensive
- From 4/01 Multiple Rx including vancomycin for chronic foot ulceration
- April 2002 amputation of Gangrenous toe, developed MRSA bacteraemia from infected graft (Rx vancomycin, rifampicin)
- June 2002 – catheter exit site infection, MRSA, VRSA
- After 1 week VRSA, VRE, *K. oxytoca* from foot ulcer
- Successfully treated with debridement, SXT/metronidazole

VRS2 (Hershey)^{2,3}

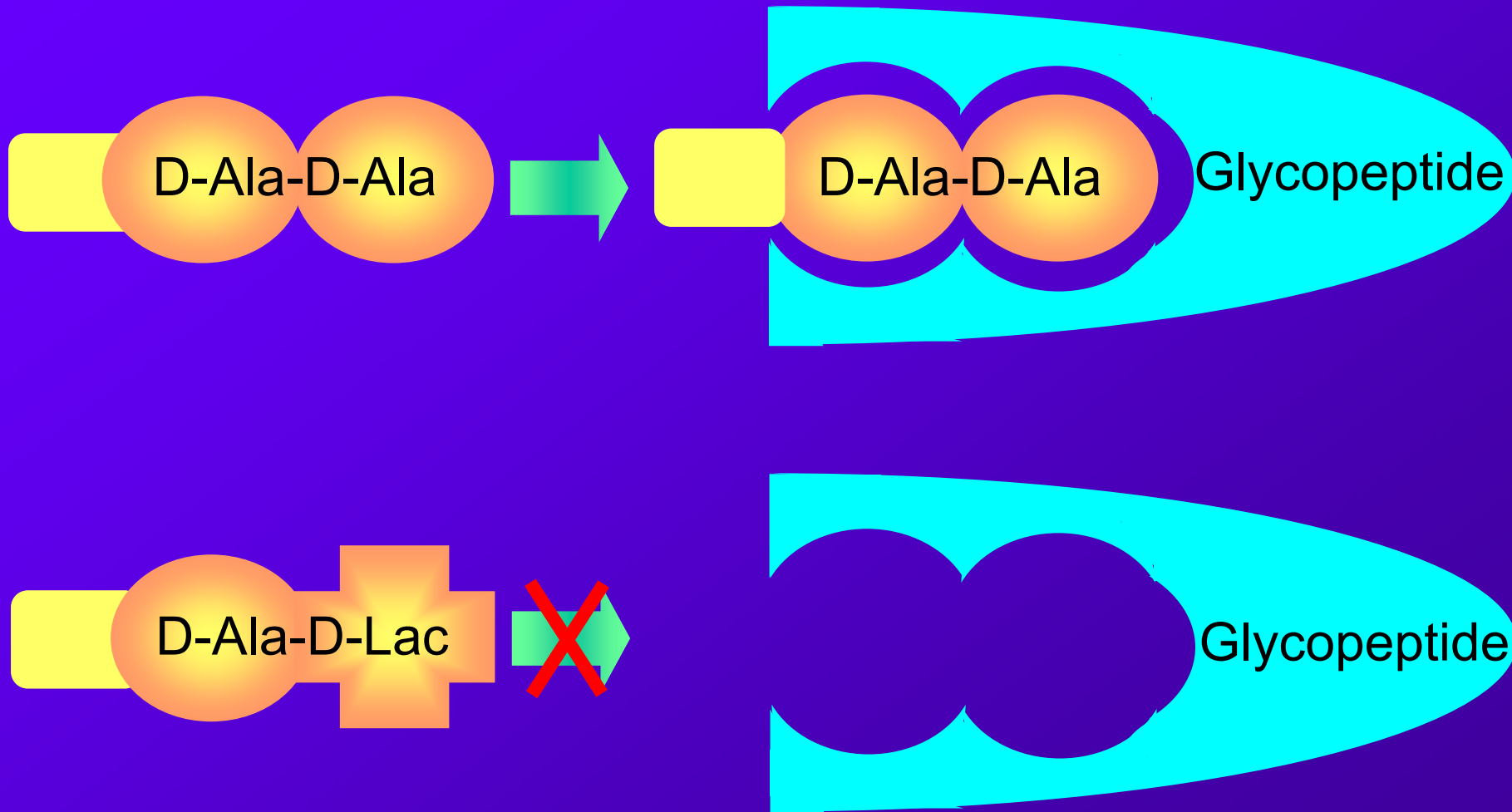
- Emergency admission – nausea, vomiting, purulent right heel ulcer
- 70 year-old chronic hypertensive below- left knee amputation
- Heel cultures – GBS, *P.aeruginosa*, *S. maltophilia*, MRSA, VRSA
- Rx – linezolid, pip/tazo, SXT (4-6w)
- Debridement – *P. aeruginosa*, *C. albicans*, CNS, No MRSA, VRSA, VRE
- Post-op Rx imioenem, tobramycin, fluconazole
- Died CPF

1. MMWR 2002; 51: 565.

2. MMWR 2002; 51: 902.

3. Tenover FC et al. Antimicrob Agents Chemother 2004; 48: 275–280

VRSA: Mechanism of Resistance



Vancomycin Resistant *S. aureus* Isolated in Michigan (1)

- **High level vancomycin resistant strains isolated leg ulcer and catheter tip of same patient in June 2002**
 - ◆ ***S. aureus* (VRSA) : vancomycin MIC 1024 µg/ml**
 - ◆ ***E. faecalis* (VRE)**
- **Localisation of vanA gene in both strains**
 - ◆ **60kb plasmid**
- **Conjugative transfer to *E. faecalis* JH2-2**
 - ◆ **Negative with VRSA**
 - ◆ **Positive with VRE**

Vancomycin Resistant *S. aureus* Isolated in Michigan (2)

- **vanA-positive (vancomycin MIC=1024 µg/ml)**
- **mecA-positive**
- **Susceptible to:**
 - ◆ **TMP-SMX**
 - ◆ **Minocycline**
 - ◆ **Linezolid**
 - ◆ **Quinupristin/dalfopristin**

Vancomycin Resistant *S. aureus* Isolated in Michigan (3)

- **Case report (1)**
 - ◆ **40-year-old woman**
 - ◆ **Diabetes, Peripheral vascular disease**
 - ◆ **Hypertension, Chronic renal failure**
 - ◆ **Chronic foot ulceration (since April 2001)**
 - ◆ **Amputation of a gangrenous toe (April 2002)**
 - ◆ **Bacteremia caused by infected graft (MRSA)**
 - ◆ **Treatment with vancomycin, rifampin**
 - ◆ **Foot ulceration persisted**

Vancomycin Resistant *S. aureus* Isolated in Michigan (4)

- **Case report (2)**
 - Catheter exit-site infection (June 2002)
 - Cultures from exit site and catheter tip
 - *S. aureus* (Methicillin and vancomycin resistant)
 - Culture from foot ulcer (one week later)
 - VRSA, VRE, *K. oxytoca*
 - Treatment and outcome
 - Operative debridement,
 - TMP-SMX and metronidazole,
 - ulcers had healed.

Case Report (1)

- **VRSA isolated from right foot ulcer September 20, 2002 in Hershey Medical Center**
- **70 year old male patient**
- **Chronic hypertension**
- **Left below the knee amputation**
- **Morbid obesity (over 200 kg)**
- **Right cataract surgery**

Case Report (2)

- Presented and admitted to hospital with
 - ◆ Nausea, vomiting
 - ◆ Somnolence, fever, chills, dyspnea
 - ◆ Purulent drainage from chronic right heel ulcer
- Laboratory
 - ◆ WBC 15.8 K/ μ L, Platelet count 262 K/ μ L
 - ◆ Hemoglobin/hematocrit 11.3g/dL/35.5%
 - ◆ Swab heel cultures
 - ~ GBS, *P. aeruginosa*, *S. maltophilia*,
 - ~ *S. aureus* (methicillin and vancomycin resistant)

Case Report (3)

- **Treatment**
 - ◆ **Linezolid (4 weeks). Stopped due to transient bone-marrow suppression**
 - ◆ **Piperacillin-tazobactam (6 weeks)**
 - ◆ **TMP-SMX (6 weeks)**
- **Heel ulcer persisted**
 - ◆ **Operative debridement (November 7)**
 - ◆ **P. aeruginosa, Candida albicans, CNS**
 - ◆ **No VRSA, MRSA, VRE**

Case Report (4)

- **Post-operative treatment**
 - ◆ **Imipenem-cilastin, tobramycin, fluconazole**
- **Respiratory failure, ventilatory support**
- **Demand no further intubations**
- **Died at home from obesity-related progressive cardiopulmonary failure (December 6)**

SIX VRSA STRAINS

- 1) Michigan 1: leg ulcer (2002)
- 2) Hershey: leg ulcer (2002)
- 3) New York: urine from an elderly patient in long-term care (2004)
- 4) Michigan 2: toe ulcer from an elderly diabetic with heavy prior antibiotic use. Surveillance culture from the patient yielded a vanc-R *E. faecalis* (2005)
- 5) Michigan 3: Toe wound from elderly diabetic with prior vanco use. Van-R *E. faecalis*
- 6) Michigan 4: Wound, VRE (preliminary)

Saderi et al.

<http://www.ams.ac.ir/AIM/0582/007.htm>

- **Five out of 139 clinical *S.aureus* strains isolated in multiple Tehran hospitals during 2003 had vancomycin MICs ≥ 256 $\mu\text{g/ml}$ by CLSI agar dilution and confirmed by E test**

Antimicrobial Susceptibility (1)

- **Multi drug resistant to**
 - ◆ **Vancomycin (32 µg/ml)**
 - ◆ **Beta lactams**
 - ◆ **Macrolides**
 - ◆ **Aminoglycosides**
 - ◆ **Fluoroquinolones**
 - ◆ **Tetracycline**

Antimicrobial susceptibility (2)

Drugs that inhibit VISA and VRSA
(MICs $\mu\text{g/ml}$)

- ◆ **Commercially available**

antibacterial

- Linezolid (1)
- Quinupristin/
dalfopristin (0.25)
- TMP-SMX (0.25)
- Rifampicin (<0.06)
- Tigecycline (0.12)

- ◆ **Daptomycin (0.5)**

Antimicrobial susceptibility (3)

- **Cell wall inhibitors**

- **Ceftobiprole (1)**
- **TAK-599 (1)**
- **Dalbavancin (0.5)**
- **Telavancin 0.5**

MICs for VRSA and VRSA-1

MIC (μgml)

Drug	VRSA	VRSA-1
Vancomycin	32	4
Teicoplanin	4	4
Daptomycin	0.5	0.5
Oritavancin	0.25	0.25
Ramoplanin	0.12	0.12
Dalbavancin	0.5	0.06

Comparison of VRSA Strains

	VRS1	VRS2	VRS3
	Michigan	Hershey	New York
MIC	1024 µg/ml	32 µg/ml	64 µg/ml
Vancomycin treatment	Yes	No	?
VRE	Yes	No	Yes
Plasmid	60 kb	120 kb	120 kb
Transfer	No	No	?
Carrier	No	No	?

VRS in Healthy Carriers

- Strains isolated from populations both inside and outside of hospital environment
- Various *Staphylococcus* strains isolated
 - ◆ *S. capitis*
 - ◆ *S. ureolyticus*
 - ◆ *S. epidermidis*
- All strains demonstrated unstable heteroresistance to vancomycin
- The strains isolated had significantly thicker cell walls than the control strains ($p < 0.001$)

VRS in Healthy Carriers

- Vancomycin resistance in the CoNS isolates studied proved unstable, resistance tending to return upon exposure to vancomycin
- Vancomycin resistance was not restricted to oxacillin-resistant strains
- Presence of VRS in carriers, particularly outside of the hospital environment, is cause for concern
 - ◆ Patients at risk include those in long-term facilities with chronic leg or decubitus ulcers

VRS? The Tip of the Iceberg

- Because no systematic screening for VRS has been performed in at-risk patients (nursing home and long care patients; chronic leg and decubitus ulcers) we have no way of knowing how extensive this problem really is. Such studies are urgently needed

The Consequences of Increasing Resistance

- **Reduced vancomycin susceptibility increases the possibility of antimicrobial failure**
- **Clinical implications of heteroresistance unclear**
- **Are VISA and VRSA being missed?¹**

TREATMENT OF COMRSA, VISA, VRSA

- 1) There is an urgent need for non-glycopeptide treatment of COMRSA
- 2) Currently SXT, rifampin (perhaps + fusidic acid), minocycline, linezolid, tigecycline
- 3) Systemic infections (bacteremia, endocarditis) caused by VISA, VRSA: quinupristin/dalfopristin (toxic); daptomycin or dalbavancin (not FDA approved); tigecycline (static), linezolid (not FDA approved and static)

DEFINITION OF VANCOMYCIN SUSCEPTIBILITY IN *S.AUREUS*

- **VANCOMYCIN SUSCEPTIBLE *S.AUREUS* (VSSA):**
VANCOMYCIN MICs ≤ 2 $\mu\text{g/ml}$
- **VANCOMYCIN INTERMEDIATE *S.AUREUS* (VISA):**
VANCOMYCIN MICs 4-8 $\mu\text{g/ml}$
- **VANCOMYCIN RESISTANT *S.AUREUS* (VRSA):**
VANCOMYCIN MICs ≥ 16 $\mu\text{g/ml}$

CAUTION

- BUT:
- 1) Insufficient numbers of VRSA tested to validate the R level
- 2) Paper by de Lassence et al (CID 2006; 42: 170) describing clonal spread of and fatalities caused by a GISA strain which yielded vanco 2 µg/ml (teico 4 µg/ml) by CLSI BUT vanco 4-6 µg/ml (teico 12 µg/ml) by E test (NOT recommended by CLSI)

Etest Macromethod

Values (mg/L)

MIC on MH (mg/L)

PAP (11%)

Identification (n)

VAN

TEC

VAN

MSSA-GSSA (6)

4-6

4-16

1-4

MSSA-hGISA (7)

4-8

4-24

4-6

MRSA-GSSA (33)

4-8

4-16

1-4

MRSA-hGISA(248)

2-16

4-48

2-8

ACCEPTABLE METHODOLOGY

Non-automated methodology:

- **NCCLS broth microdilution**
- **Agar dilution**
- **E test (0.5 MacFarland, 24 h incubation)**

UNACCEPTABLE METHODS

- **Disk diffusion alone (may be acceptable for VRSA)**
- **Automated methods, e.g. Vitek and Microscan: neither method accurately identified Hershey and NYC VRSA with a Van MIC 32-64 µg/ml.**

**LABORATORIES USING THE ABOVE MUST ADD
A VANCOMYCIN AGAR SCREENING PLATE**

hVISA

In my personal opinion, with the new current CLSI vancomycin breakpoints, all hVISAs are really VISAs so the differentiation is of less importance. This was only the case with MICs between 2 and 4 µg/ml

SFM AND DIN

**Screening with a MHA plate
containing 6 µg/ml teicoplanin**

VRSA

VRSA-1



Disk diffusion test with 30 µg vancomycin



How to Avoid Dissemination?

- **HANDWASHING!!!**
- **WHAT WAS GOOD IN THE TIME OF SEMMELWEISS IS JUST AS APPLICABLE TODAY: BASIC TRUTHS DO NOT CHANGE**

How to avoid dissemination?

- **Rational and restricted use of vancomycin and (if available) teicoplanin or any other glycopeptides**

INFECTION CONTROL PROCEDURES HMC

MRSA

- Private room
- Gloves to enter
- Gowns if close contact
- Dedicated stethoscope
- Wash hands on exit
- No specific nursing
- No routine mask
- No log-in sheet
- No routine contact invest

VISA/VRSA

- Private room
- Gloves to enter
- Gowns to enter
- Dedicated stethoscope
- Wash hands on exit (alc rub)
- One-to-one nursing
- Mask if necessary
- Log-in sheet
- Contact investigation, weekly while patient is in hospital

OUTPATIENT FOLLOW-UP HMC

- Patient comes as last patient of the day
- Have all healthcare workers come to one location
- Terminal cleaning of room when patient leaves
- MRSA patients are placed in contact isolation for life
- VISA/VRSA patients are in special isolation for life (see above)

NURSING HOME/LONG TERM CARE FACILITY PROBLEM

- **In my opinion chronic leg or decubitus ulcers in the elderly are the primary source of VRSA and maybe also VISA. How does one adhere to proper hospital control measures in such institutions???? In the US, also VA hospitals**
- **What else can be done except rigorous handwashing and the above mentioned hospital control measures?**
- **The Dutch method: the best but not possible everywhere (and certainly not ni the US!)**

How to avoid dissemination ?

- **Carriers**

- ◆ **Nasal carriers**

- ◆ **Perineal carriers**

- **Infection control**

- ◆ **Screening and isolation of patient with VRE, MSRA, VRSA**

- ◆ **Chronic foot ulcers**

VICONS

Vancomycin intermediate strains of *S.haemolyticus* have been reported.

Screening of VICONS??

PAUL EHRLICH'S RECIPE FOR SUCCESS

- **GELD** (Money)
- **GEDULD** (Patience)
- **GESCHICK** (Fate)
- **GLUECK** (Luck)

Our Future Without New Antibiotics

