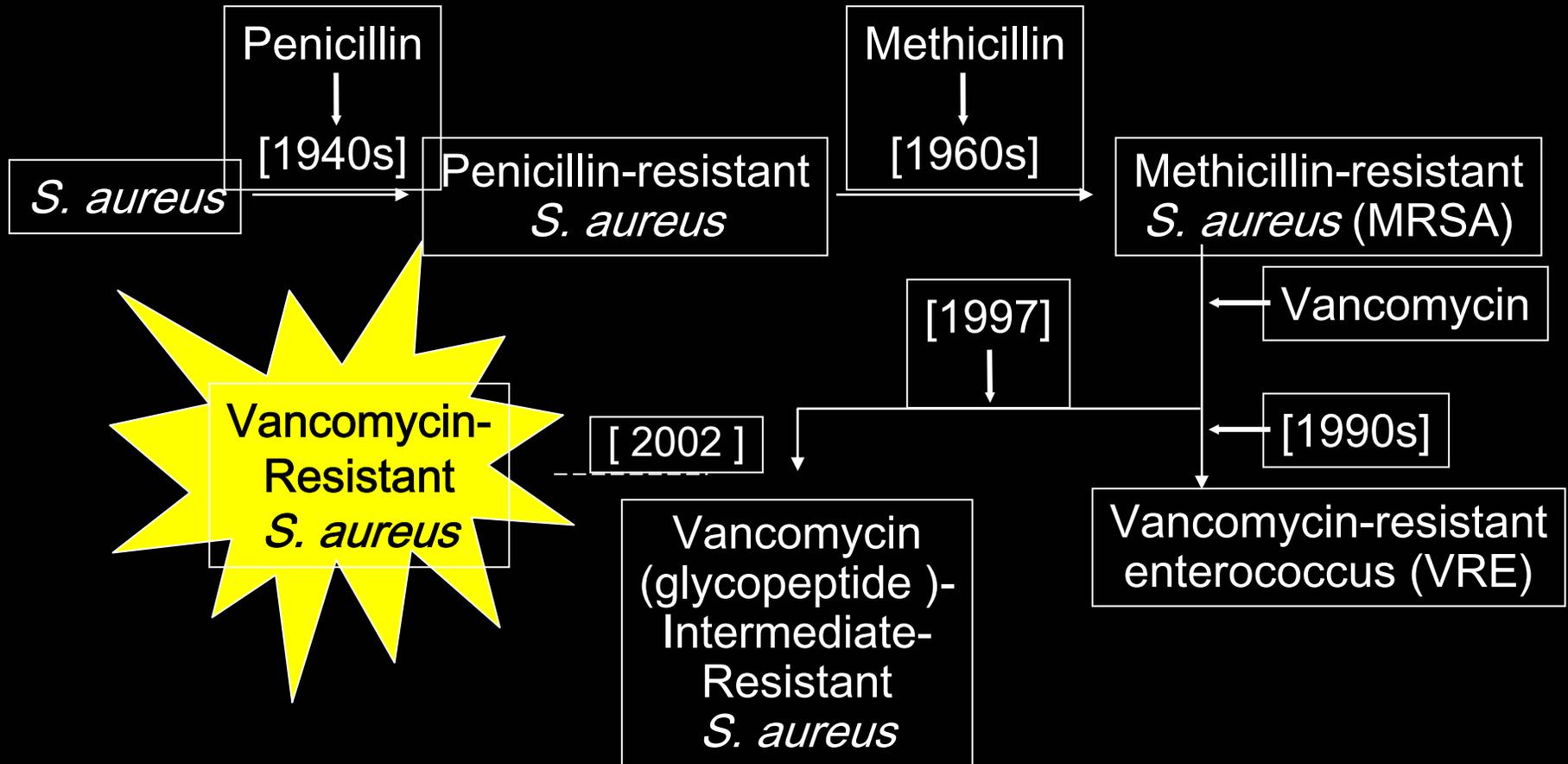


Methicillin-Resistant ***Staphylococcus aureus* (MRSA)**

Jan E Patterson MD

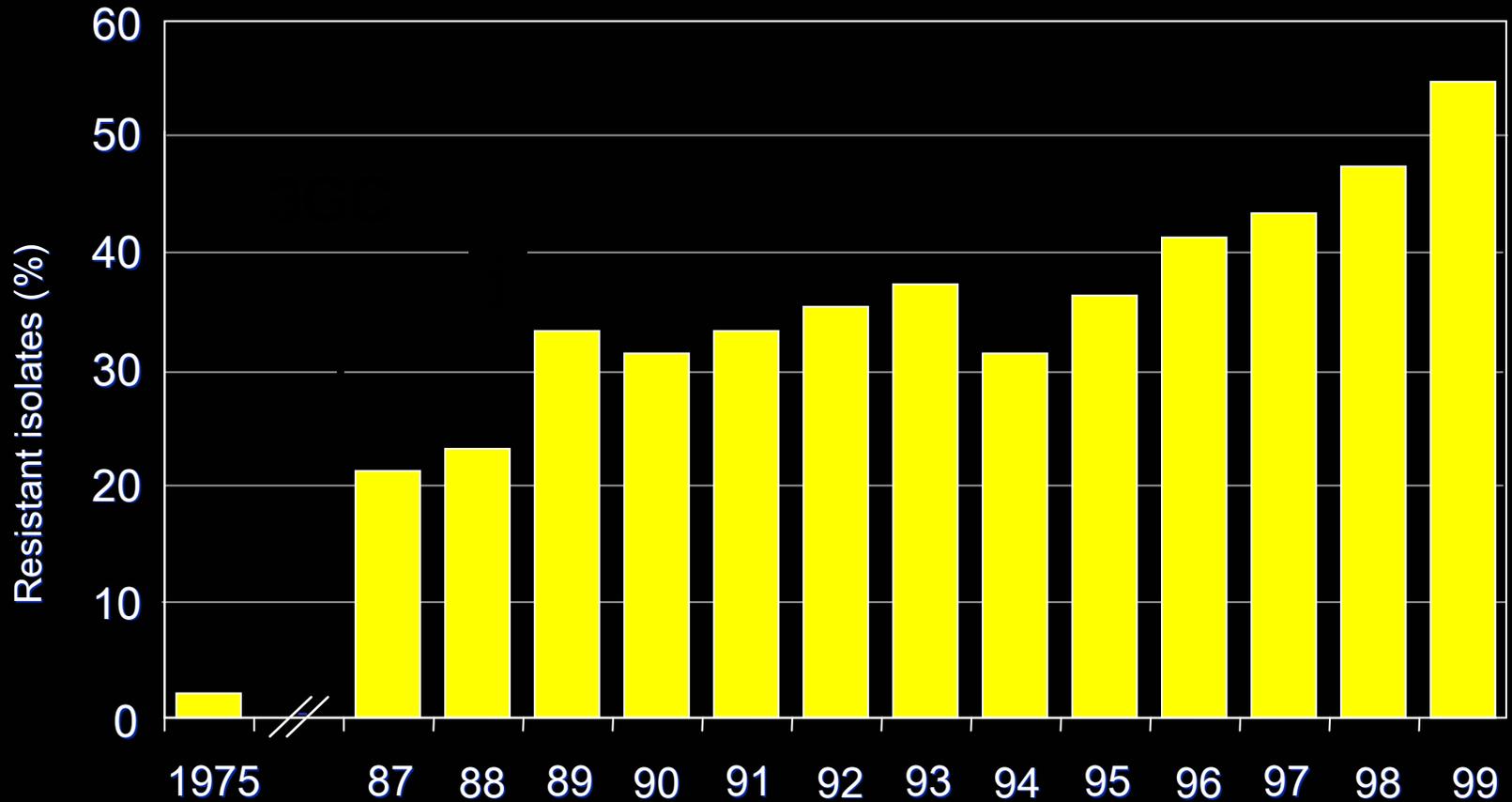
Evolution of Antimicrobial Resistance in Gram Positive Cocci



MRSA Multidrug Resistance

- Penicillins
- Cephalosporins
- Erythromycin (Macrolides)
- Clindamycin
- Tetracycline
- Fluoroquinolones
- Trimethoprim/sulfamethoxazole
- Gentamicin
- Vancomycin (emerging)
- Linezolid (emerging)

Prevalence of Methicillin Resistance: *Staphylococcus aureus*



Lowy, *New Engl J Med* .1998;339:520-532.

NNIS Antimicrobial Resistance Surveillance Report. Dec 2000.
(www.cdc.gov/ncidod/hip/NNIS/AR_Surv1193.htm).

Global MRSA Prevalence

- North America
 - Canada (Ottawa) 1%
- Europe
 - Netherlands 1.5%
 - Switzerland 4 to 68/10,000 adm (Up to 12%)
 - Poland 3-11%
 - UK 25% and Italy, France 30-50%
- Latin America
 - Brazil 70%
- Asia - Japan 60%

Risk Factors for MRSA

- Invasive devices
- Time at risk
- ICU stay
- Coma
- Surgery

Law. Epidemiol Infect 1988; Ascensio. ICHE 1996
Crowcroft JHI. 1996; Crossley. JID. 1979
Peacock. Ann Intern Med 1980

Fluoroquinolones and MRSA

- In vitro and in vivo rapid emergence of FQ resistance in MRSA
- Duration of exposure and serial passages may yield conflicting results
- Cipro > Levo > Gati ≥ Moxi
- FQ use associated with clinical isolates of MRSA?

Venezia RA, et al. *J Antimicrob Chemother.* 2001;48:375-381.

Venezia RA, et al. 7th International Symposium on New Quinolones (abstract). UK, 2001.

Gilbert DN, et al. *Antimicrob Agents Chemother.* 2001;45(3):883-892.

Evans ME, Titlow WB. *J Antimicrob Chemother.* 1998;41:285-288.

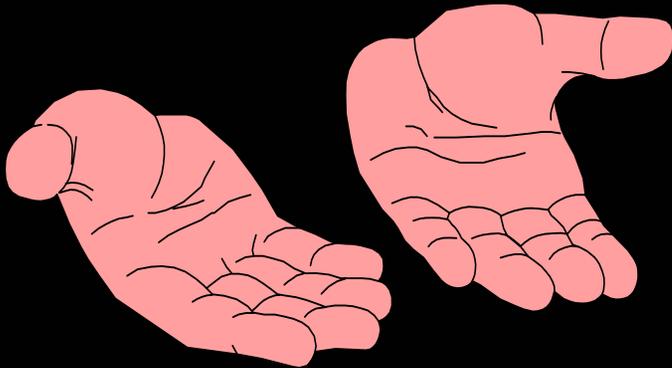
MRSA Transmission

- Methicillin resistance gene
 - Chromosomally-mediated
 - Not generally transferable
 - Mobilization of cassette in recent MRSA
 - Antibiotic selection
- Spread is clonal and transmitted by direct person-to-person contact
 - Sites of colonization
 - Nares, axilla, skin
 - Antibiotic concentrations negligible here except FQ

MRSA Transmission

- Transient hand carriage by personnel
 - Infected or colonized patient
 - Infected or colonized HCW
- Environment
 - Burn units
 - Dermatology wards

Decrease MRSA Transmission



MRSA Control Measures

- Acute Care Hospital
 - Microbiologic surveillance
 - Standard Precautions
 - Contact Precautions
 - Antisepsis
 - Standard housekeeping
- Local assessment

Surveillance Cultures

- Elimination of MRSA from Finland hospitals
 - 2 outbreaks MRSA 1991-2
 - 1991-2002
 - 202 persons with MRSA in medical district
 - Strict control measures for all 30 district hospitals
 - Contact precautions for colonized patients
 - Systematic screening for contacts of MRSA pts
 - Cohorts of MRSA+ and MRSA exposed pts
 - Continuous staff education

VISA (GISA)

- Intermediate resistance to vancomycin
 - MIC 8 µg/ml
 - Japan: ≤ 20% prevalence among noso MRSA
 - Cases in all continents
 - ?Continuum of strains with decreasing susceptibility to vancomycin
- Risk factors
 - Exposure to vancomycin
 - Prior MRSA infection
 - Renal failure

Hiramatsu 1997, CDC 1997-98

Vancomycin-Resistant *S. aureus*

- 3 VRSA isolates reported in US, 2002
- June 2002
 - Catheter exit infection
 - MRSA, vanco MIC 1024 µg/ml
 - Susc TMP/S, Clinda, tetracycline, minocycline, linezolid, quinu/dalfo
 - VRE *vanA* gene detected in the VRSA isolate
 - Rx TMP/S and removal of catheter

Vancomycin-Resistant *S. aureus*

- June 2002
 - Catheter exit infection
 - MRSA, vanco MIC 1024 $\mu\text{g/ml}$
 - Susc TMP/S, Clinda, tetracycline, minocycline, linezolid, quinu/dalfo
 - VRE and *K. oxytoca* from foot ulcers
 - *vanA* gene detected in the VRSA isolate
 - Rx TMP/S and removal of catheter

Community MRSA

- 1980's Detroit
 - Outbreaks of CA-MRSA in IDU
- 1990's
 - Cincinnati
 - 1977-81 6% MRSA CA
 - 1987-90 28% MRSA CA
 - New Haven
 - 1981 2.5% MRSA present on admission
 - » 1991 37% MRSA present on admission

Cushing 1991; Saravolatz 1991; Linneman 1991; Layton 1992

Epidemiology of MRSA

- MRSA increased
 - 11% in 1992 to 18% in 1993
- 21 mos. surveillance ; 170 MRSA pts
- 58% present on admission (not transfers)
- Distinct PFGE patterns
 - 68% community; 44% nosocomial
 - Several small clusters identified
- Risk factors did not distinguish MRSA vs. MSSA

Community MRSA in Children

- Chicago hospital
- Children admitted with CA MRSA disease
 - 10/10,000 adm in 1988-90
 - 259/10,000 adm in 1993-95
- Risk factors
 - Previous antibiotics
 - Hospitalization
 - Chronic disease
 - Prior surgery
 - Chronic urinary catheter

Community MRSA in Children

- Dallas, Texas
- Proportion of CA MRSA
 - 20% in 1992 to 75% in 1996
- Prevalence of MRSA at 2 day care centers
 - Center X: 2/61 (3%) colonized with same strain
 - Center Y: 9/40 (24%) colonized
 - 6 children strain A
 - 4 children strain B
- No identified risk factors

Community MRSA

- Serious community onset infections
 - Skin and soft tissue infections
 - Abscesses, cellulitis
 - Otitis externa, media
 - Previously healthy children
 - Risk factors similar to MSSA
 - Not multiresistant
 - Contain novel *SCCmec* IV gene

Eady 2003; Santo 200; Fergie 2001

Community MRSA

- Risk factors in children, MRSA vs. MSSA
 - Monthly rates of methicillin resistance
 - 35-51%
 - No significant difference in risk factors
 - Deep-seated infections
 - MSSA 30%
 - MRSA 11%
 - CA MRSA susc to clinda, TMP/S

Community MRSA

- Serious community onset infections
- Other settings
 - Skin and soft tissue infections
 - Abscesses, cellulitis
 - Detention facilities
 - School athletic programs
 - Most susceptible to clindamycin
 - Distinct MRSA strain

Therapy

- Vancomycin
 - 10-15 mg/kg optimal dose
 - Keep troughs in range of 15 for serious infection
 - Monitor ototoxicity in elderly
 - No po or IM route
 - Resistance now reported
 - Tolerance more widespread problem

Therapy

- ▣ Linezolid
- ▣ Oxazolidinone
- ▣ IV or po
- ▣ AEs: cytopenias, HA
 - Longterm: uveitis, peripheral neuropathy
- ▣ Serotonin syndrom with SSRI (rare)
- ▣ Cost
- ▣ ?Better for MRSA pneumonia

Therapy

- Minocycline
 - Most active tetracycline to date
 - IV or po form
 - Most useful in po form
 - Used in Japan for MRSA and MRCNS

Community MRSA Infections

- Therapy skin & soft tissue infection
- Local drainage
- 2 drugs: clinda + TMP/S
- Chlorhexidine baths
- Mupirocin nasal eradication
- Treat affected family members

MRSA Nasal Eradication

Route and efficacy

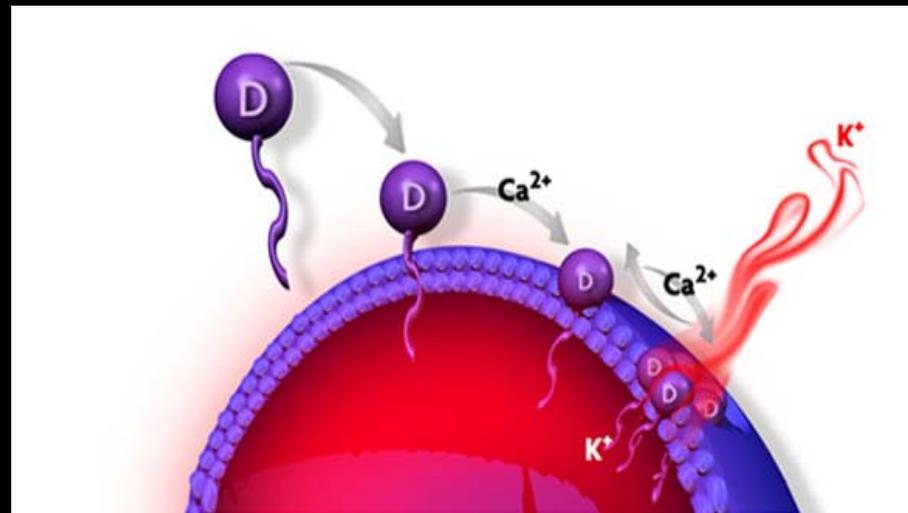
- Intranasal
 - Mupirocin anterior nares BID X 7 days
 - 95%
- Oral +/- intranasal
 - RIF +TMP/SMX + Bacitracin (intranasal) X 5 days
 - 90%
 - RIF + TMP/SMX X 5 days
 - 50-75%
 - MIN + RIF X 14 days + MUP X 3 days
 - 90%

Daptomycin

- Cyclic lipopeptide
- Gram-positive activity
 - *S. aureus*, *S. pneumo*, enterococcus
 - VRE, MRSA, PRSP
- Bactericidal, including enterococci
- Unique mechanism – disrupts plasma membrane function
- AE – myopathy
- For submission soon
 - Skin/soft tissue, ?CAP

Daptomycin Mode of Action

- Binds to Gram-positive bacterial cell membrane
 - Calcium-dependent insertion of lipid tail
- Rapidly depolarizes the cell membrane
 - Efflux of potassium
 - Destroys ion-concentration gradient
- Cell death
 - Multiple failures in biosystems, DNA, RNA, protein synthesis



Tigecycline

- Glycylcycline
- Gram-positive activity
 - MSSA, MRSA, GISA, *S. pneumo*, PRSP, enterococcus, VRE
 - Non-tuberculous *Mycobacteria*
- Gram-negative activity
 - ? *Acinetobacter*
 - NOT *Pseudomonas*

Summary

- Major nosocomial pathogen
- Community onset cases increasing
- Controlled by antiseptics
- Surveillance cultures in some settings
- Contact vs. Standard Precautions
- Vancomycin resistance
- New options for therapy