Treating MRSA/MRSE infections in children

PIDSP annual convention, 20.2.2013

Shai Ashkenazi, MD, MSc

Chairman, Pediatrics A

Schneider Children's Center

The Pickel Professor for Pediatric Research

Sackler Faculty of Medicine, Israel

Chair, Education Committee

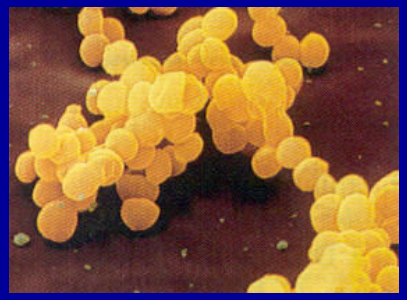
European Society for Paediatric Infectious Disease

Treating MRSA/MRSE infections

Thinking inside and outside the box

- **Prologue:** The genus *Staphylococcus*
- **MRSA MRSE**
  - Recent epidemiology
  - Clinical spectrum
  - Antibiotic therapy
- **Epilogue:** Future trends

The genus *Staphylococcus*



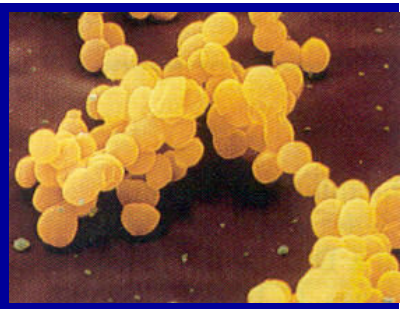
Greek:

- **Staphyle:** bunch of grapes
- **Kokkos:** berry

CoPS, 1spp

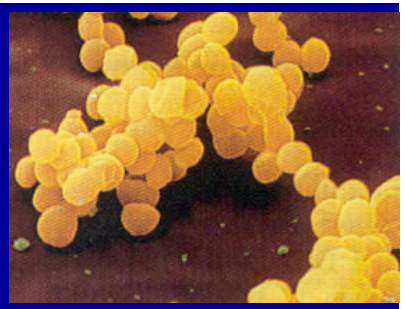
CoNS, >40spp

Staphylococci

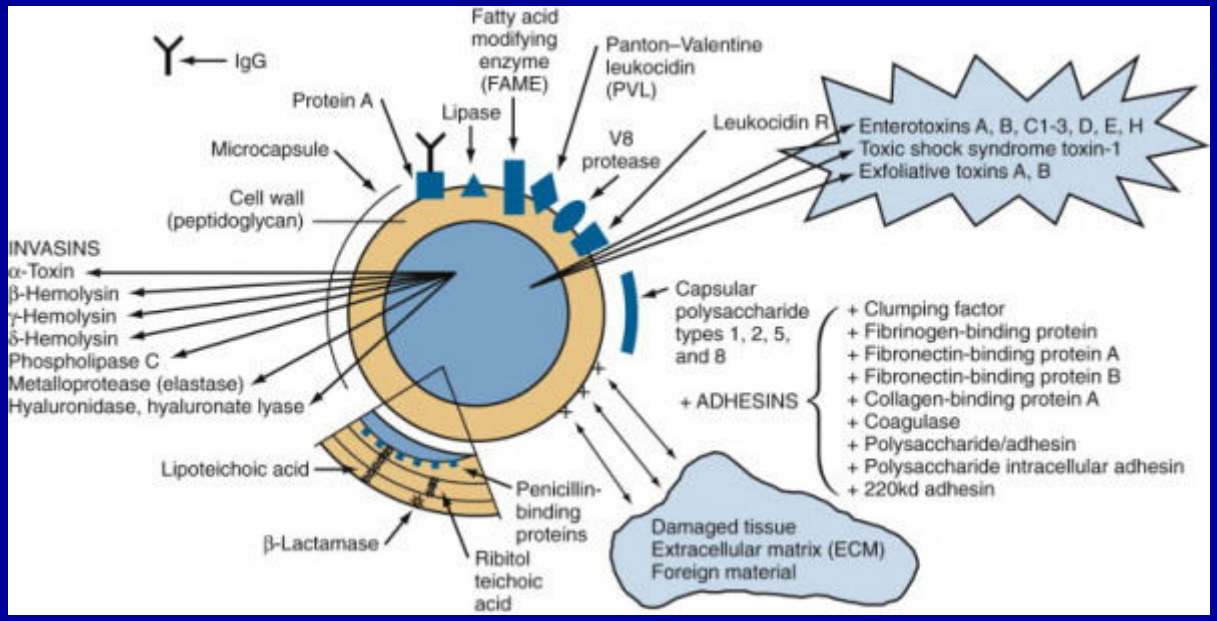


- Widely distributed in nature
- Part of human microbiome (Nature 2013;493:45)
  - SE found universally on skin and frequently in nasopharynx
  - SA carried (30%) on skin (face), nose and fingernails
- Survive non-physiologic conditions:
  - On dried clinical surfaces for months
  - Relatively heat-resistant
  - Tolerate high-salt media

Staphylococcus aureus

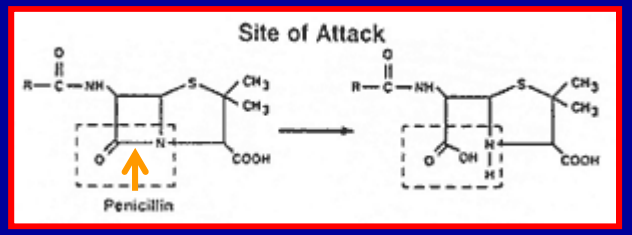


- Is a leading cause of SST, osteoarticular and bloodstream infections worldwide
- Can cause severe lower respiratory infection, TSS and endocarditis
- Virulence is complex, determined by attachment, penetration, evasion-controlled elements and toxins

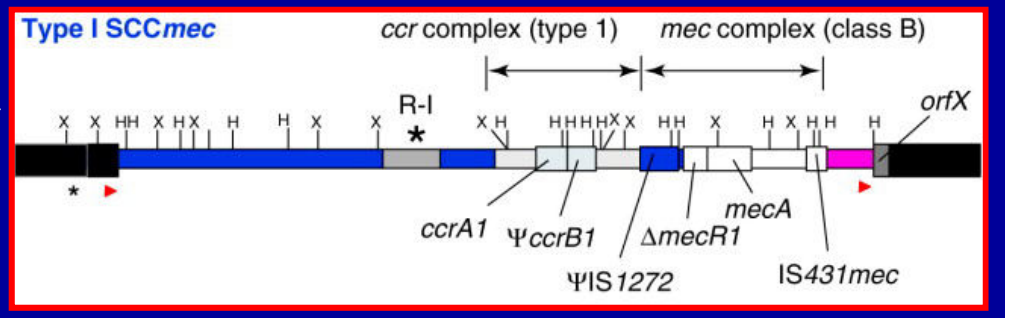


Evolution of antibiotic therapy of SA

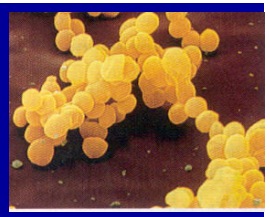
- 1941: Penicillin first successfully used to treat SA infection



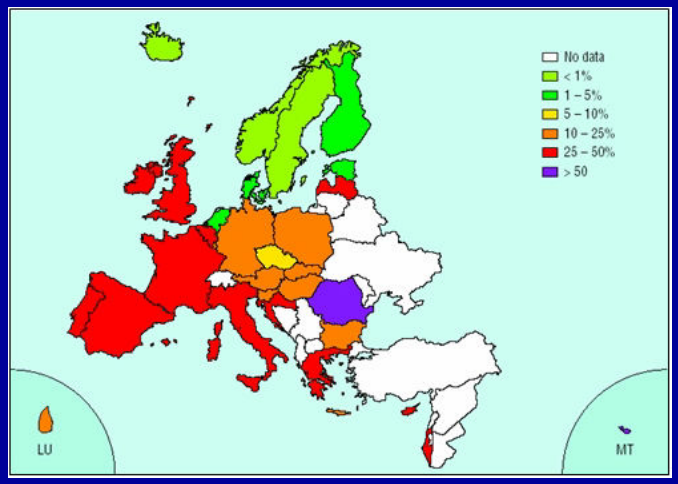
- 1950s: Plasmid-mediated β-lactamase
- 1980s: SCC-mediated MRSA
- 2000s: CA-MRSA
- 2010s: Vancomycin "creep"



Methicillin-resistant *S aureus* (MRSA)



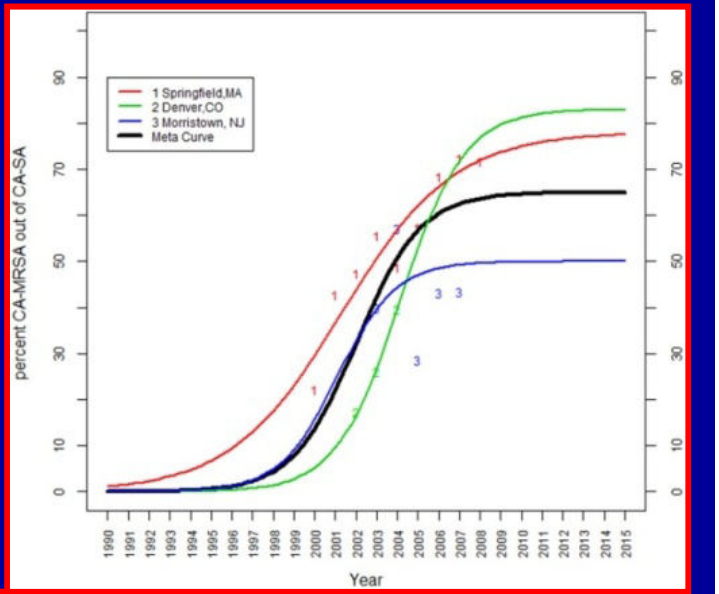
- Caused by mecA gene-encoding PBP2a with low affinity
- Situated on a mobile genetic element SCCmec, types 1-8; constitutive or inducible
- MRSA are resistant to all β-lactams
- Some SCCmec contain genes encoding resistance to non-β-lactam antibiotics
- Was typically confined to HCA infections

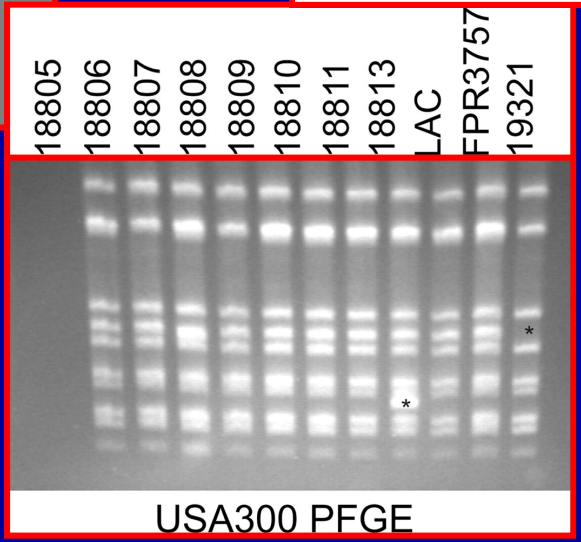


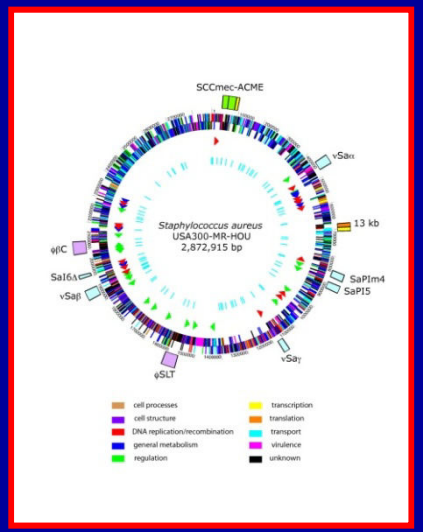
Community-associated (CA)-MRSA Frequency

PLoS One 2013;8:e52722
PIDJ 2013;32:124-8

- Increased in the last 10y reaching 80% of all CA-SA
- 10%-22% carriage
- >80% USA300 clone by PFGE







CA-MRSA

PIDJ 2011;30:418-21
PIDJ 2013;32:124-8

Severity – "new" syndromes

- Bacteremia & septic shock
- Purpura fulminans
- Necrotizing pneumonia/empyema
- OM-multiple sites, DVT
- Pyomyositis
- Orbital cellulitis
- Necrotizing fasciitis

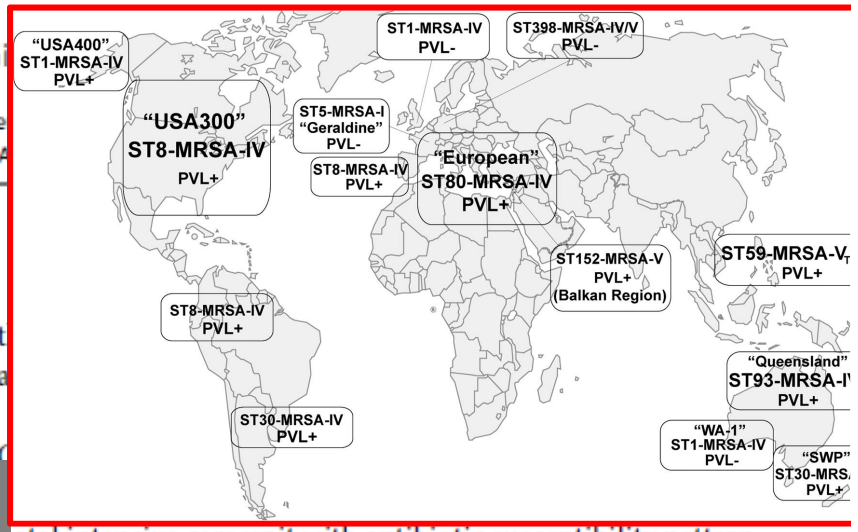
TABLE 5. Hospital course and outcome of children with invasive CA-MRSA and CA-MSSA infection

Outcome	MRSA (n = 46)	MSSA (n = 53)	P
Cure/improvement	45	52	NS
Death	1	1	
Febrile days			
Mean ± SD	3.93 ± 4.12	1.81 ± 1.69	0.07
Median	3 (0–14)*	2 (0–6)	
Hospital days			
Mean ± SD	12.02 ± 7.64	9.02 ± 8.54	0.005
Median	9 (3–37)	7 (0–44)	
PICU days	n = 8	n = 3	
Mean ± SD	6.50 ± 4.75	9 ± 4.36	0.49
Median	9 (1–15)	7 (6–14)	
Days of BC+	n = 16	n = 18	
Mean ± SD	3.38 ± 2.45	1.50 ± 1.04	0.04
Median	2 (1–11)	1 (1–4)	
Days of BC+†	n = 15	n = 18	
Mean ± SD	2.87 ± 2.45	1.50 ± 1.04	0.084
Median	1 (1–8)	1 (1–4)	

Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections in Israel*

Alon Nevet MD PhD[1], Shai Ashkenazi MD MSc[1,2], Zmira Samra PhD[3] and Gi

[1]Department of Pediatrics A and [2]Unit of Pediatric Infectious Diseases, Schneider Children's Medical Ce
(Beilinson Campus), Petah Tikva, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat A



ABSTRACT: **Background:** Community-associated methicillin-resistant *Staphylococcus aureus* infections are increasingly being documented worldwide. In Israel, however, CA-MRSA

atal intensive care unit with antibiotic susceptibility pattern
imilar to CA-MRSA have been described in Israel [5]. In this
ork, we present three children with soft tissue infections
aused by CA-MRSA. Our aim was to prompt physicians to
e more alert to the possibility of infection with CA-MRSA,

- European study in 10 countries
- 19 (12%) CA-MRSA of 155 CA-SA
- No significant clinical differences between CA-MRSA and CA-MSSA

ESPID Annual Meeting
June 2012

CA-MRSA

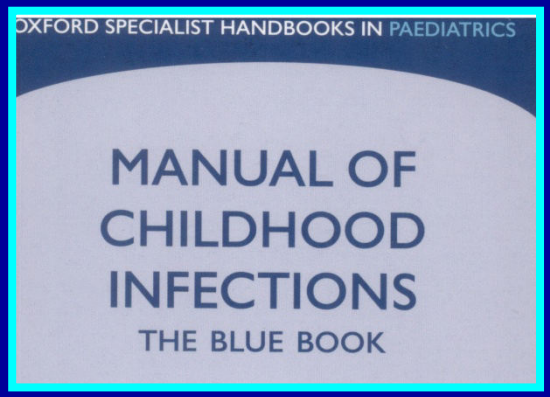
Antibiotic susceptibility

- CA-MRSA usually encodes by the small type 4 SCCmec that doesn't include other resistance genes
- Therefore, usually susceptible to non-β-lactams: clindamycin, T-S, aminoglycosides, tetracyclines, FQ
- In contrast to HA-MRSA
- TCH: clindamycin non-susceptibility of CA-MRSA increased over a decade from 2% to 11%

Treatment of MRSA

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

***CID* 2011;52:285-92**



Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK

***JAC* 2006;57:589-608**

The principles are similar

Treatment of CA-MRSA

US guidelines - CID 2011;52:285
UK guidelines - JAC 2006;57:589

1. **No antibiotics: for cutaneous abscess, I&D is the primary treatment and likely to be adequate alone (A2)**
   - DB study of T-S vs placebo after I&D with a 90d F/U call. Noninferiority of placebo (Ann Emerg Med 2010;55:401-7)
   - RCT of cephalexin vs clindamycin for uncomplicated SSTIs in 200 children (>6mo), 69% MRSA

     On d7, resolution of MRSA infections: 97% on cephalexin, 94% on clindamycin (Pediatrics 2011;127:e573-80

Treatment of CA-MRSA

CID 2011;52:285

2. Antibiotic therapy is recommended for cutaneous abscesses with the following conditions (A3):
   - Severe local disease (multiple sites, rapidly progressed cellulitis, septic phlebitis)
   - Systemic illness
   - Comorbidities
   - Immunosuppression
   - Difficult to drain sites (face, hands, genitalia)
   - Lack of response to I&D

Treatment of CA-MRSA

CID 2011;52:285

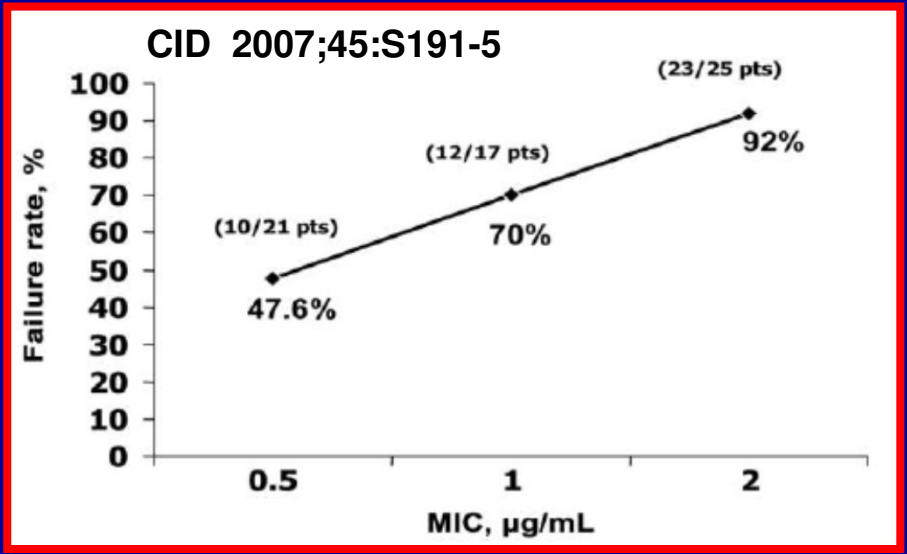
- **In hospitalized children with invasive disease, vancomycin is recommended (A2)**
  - **If the patient is stable without ongoing bacteremia or intravascular infections, empiric therapy with IV clindamycin is an option if the clindamycin resistance rate is low (eg <10%), with transition to oral therapy if the strain is susceptible (A2)**
  - **Empiric clindamycin alone?**
  - **"A minimum 3-4 w course is recommended for septic arthritis and a 4-6 w course for OM"**
  - **Shorter courses acceptable (Peltola et al, CID 2011;53:97-8)**

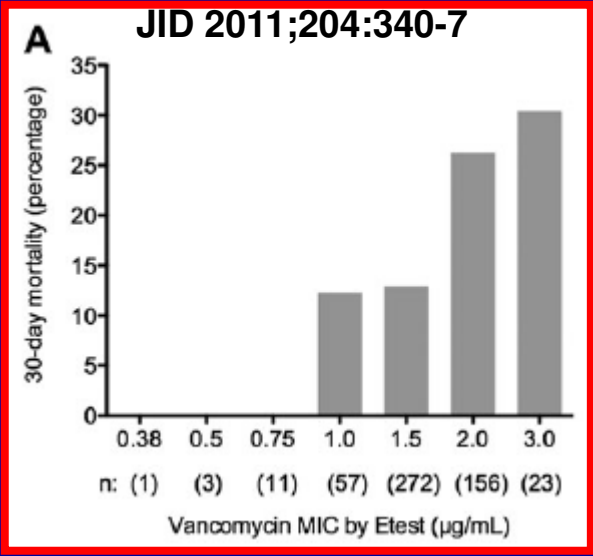
Vancomycin is the mainstay of MRSA treatment

…but antibiotic resistance is a moving target

encoded altered peptidoglycans

- ♥ **VISA**: MIC 4-8 µg/ml, rare, cell wall thickening
- ♥ **"Creep":** The reported trend of increased vancomycin MIC of susceptible MRSA isolates. Affects outcome





- ♥ Debate: no proven "creep" in children (PIDJ 2010;29:882-4) heteroresistance?

Vancomycin dosage for MRSA

CID 2011;52:285, PIDJ 2013;32:32

- In seriously ill patients with suspected MRSA infections, a loading vancomycin dose of 25-30 mg/kg may be considered (C3)
- AE
- For serious infections, vancomycin trough concentrations of 15-20 µg/ml are recommended, which correlates with AUC/MIC >400, PD predicting efficacy (B2)
- Data are limited to guide vancomycin dosing in children. IV vancomycin 60 mg/kg is recommended in children with serious or invasive disease (B3)

Alternative agents

- Teicoplanin (UK, SSTIs, bacteremia)
- Quinupristin-dalfopristin (synercid)
- Tigecycline
- Linezolid
- Daptomycin
- Ceftaroline
- Delafloxacin

JAC 2012;67:2182-90
EJCP 2010;66:919-27
(off-label use in Europe)

Clinical Experience with linezolid in children

- New class (oxazolidinone)
- Broad activity against G(+), including MRSA, MRSE, VRE, PRSP
- 4 uncontrolled and 7 RCTs in children
- Linezolid is safe and efficacious in children with serious G(+) infections
- The recommended dosage: IV/PO 10mg/kg, tid in children <11y, bid in older (C3)
- "…reserved for children who are intolerant to or fail conventional agents…monitor haematological …and neurological complications" (time-related)

Daptomycin use in children

PIDJ 2007;26:1128-32

- A novel cyclic lipopeptide rapidly bactericidal against MRSA and VRE
- Inactivated by alveolar surfactant; should not be used for pneumonia (approved for bacteremia and SSTIs)
- A series of 15 children at Dallas Children's, with invasive SA infections (8 bacteremia, 12 disseminated, 12 thrombosis)
- 14/15 MRSA, 1 MSSA
- Dose 4-6mg/kg/d, duration 6-34d (median 10)
- Good clinical response
- Well tolerated; no CPK elevation

Ceftaroline

PIDJ 4/2011
CID 2011; 55:S173

- A new "5th-G cephalosporin"
- Approved by the FDA in 10/2010
- For adults with cSSTIs and CAP
- The G(-) activity similar to ceftriaxone; designed to have high affinity for PBP2a, thus is active MRSA, PRSP and most VRE
- Common AEs: diarrhea (5%), nausea (4%), rash (3%)
- No real data for children

Delafloxacin

JAC 2013; 2012; 67:2814

- A Gram positive-oriented FQ with distinct chemical structure
- Dual activity against DNA gyrase and topoisomerase 4
- Active against MRSA, with reduced selection of resistance
- Still investigational

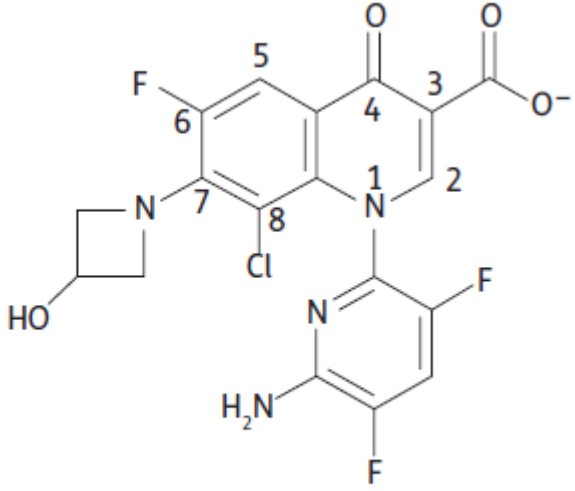
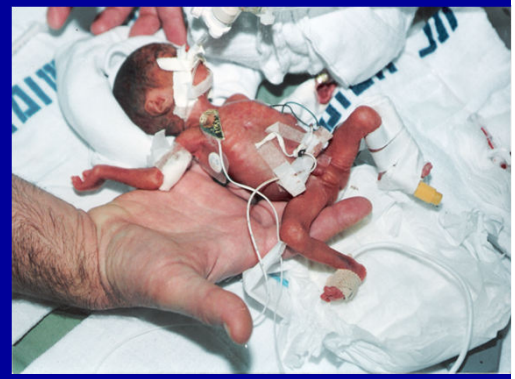


Figure 1. Delafloxacin.

A premature infant with an infection



- AL is 26w, 890 gm neonate
- 2 courses of antibiotics
  - D1 – ampicillin and gentamicin (RD)
  - D17 – pip/tazo and amikacin (NEC)
- D32 – hypothermia, APBs, reduced perfusion, thrombocytopenia
- Vancomycin and meropenem started

A premature infant with an infection

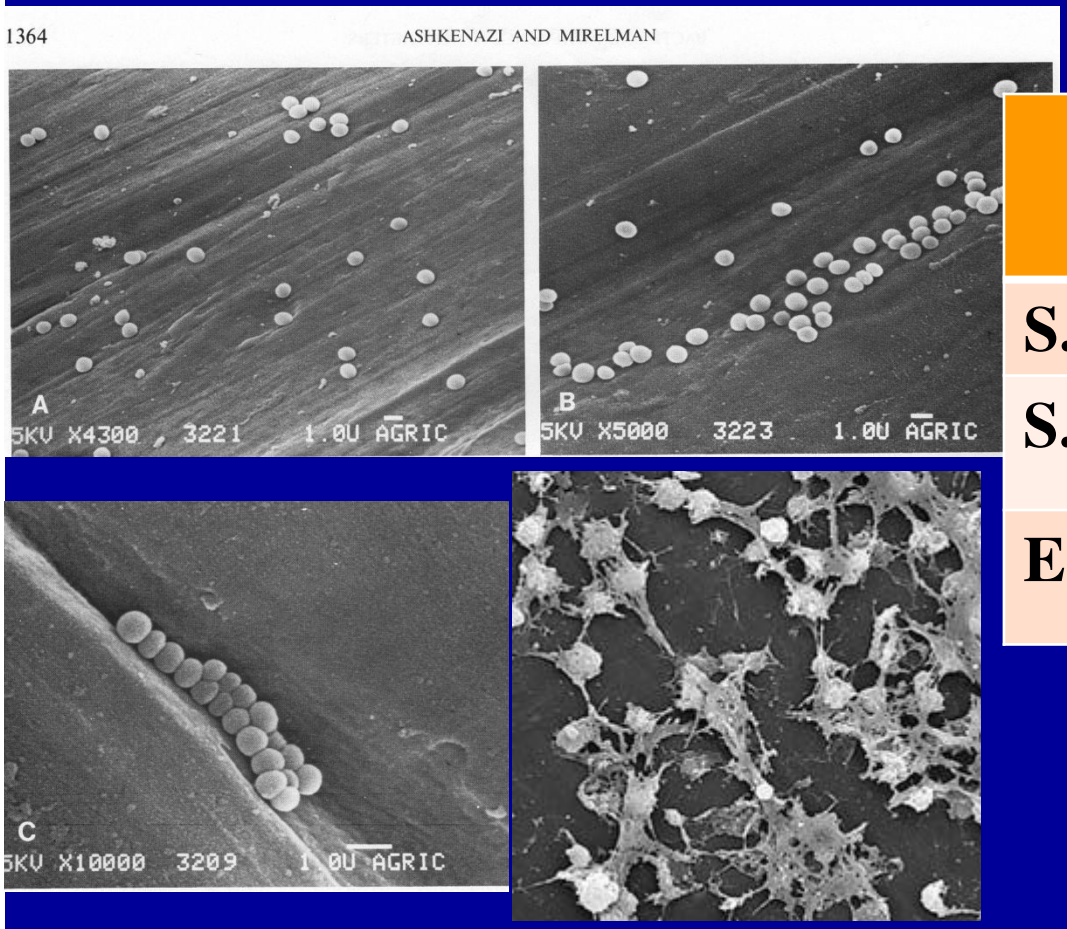
- **D32 – 2 blood cultures: *CoNS***

Penicillin –	**R**	**Vancomycin -**	**S**
Oxacillin –	**R**	**Rifampicin -**	**S**
Trime/sulfa –	**R**		
Amox/clav –	**R**		
Ciprofloxacin –	**R**		
Ofloxacin –	**R**		
Gentamicin –	**R**		
Amikacin -	**R**		
Piperac/tazo -	**R**		

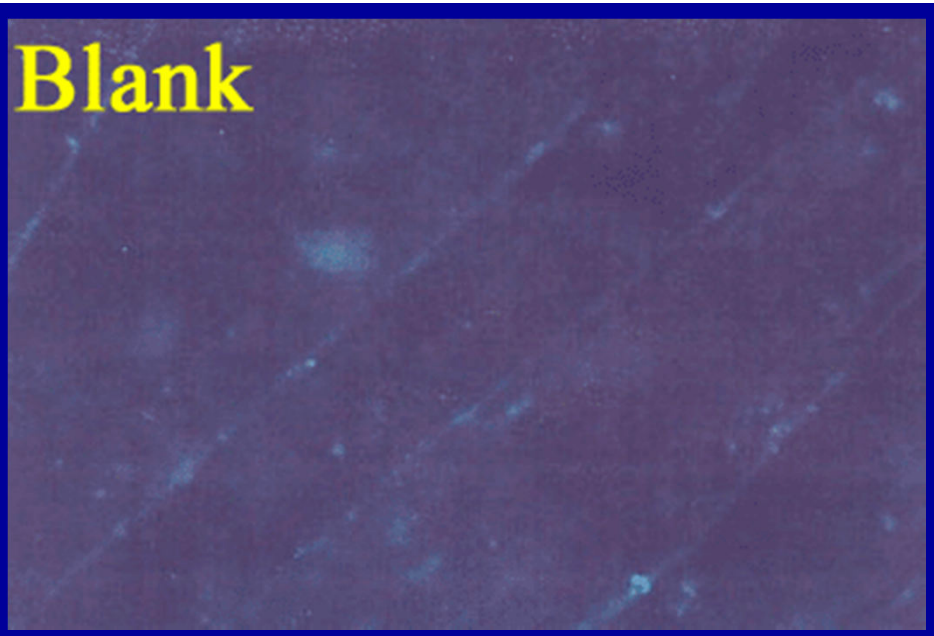
Staphylococcus epidermidis

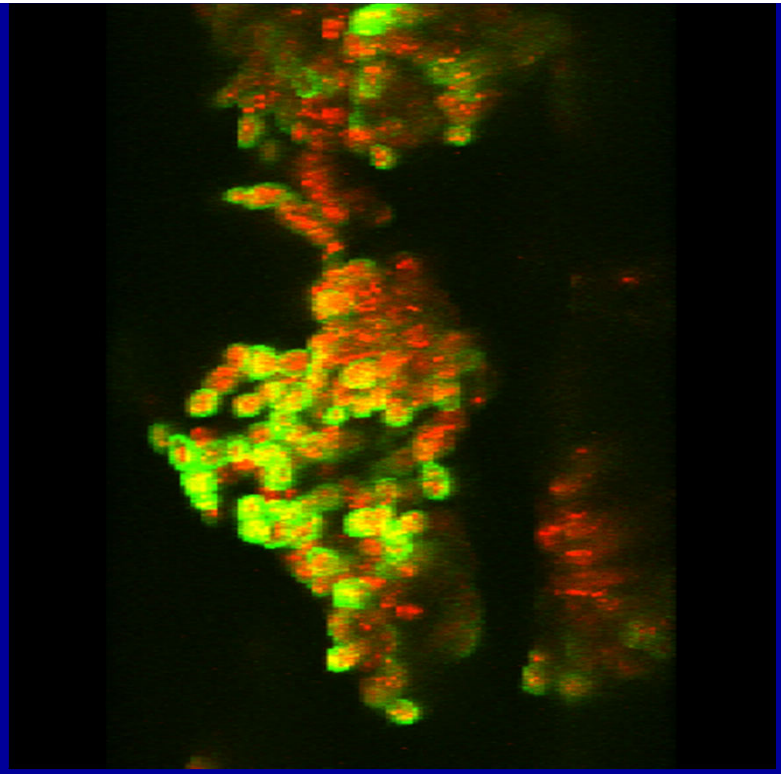
- The main CoNS causing human disease
- Converted from symbiont to a human pathogen, causing clinically-significant infections
- Related mainly to indwelling medical devices, causing hard-to-treat infections: pathogen of modern medicine
- In US: 1M indwelling devices-related nosocomial infections/year

S. epidermidis infections
CVC-related infections



Bacteria	Adherence ($x10^5/cm^2$)
S. epidermidis	62.4+/-5.9
S. aureus	38.2+/-4.3
E. coli	3.7+/-0.4





A biofilm is an aggregate of microorganisms which adhere to each other on a surface, embedded within a self-produced matrix of extracellular polymeric substance (slime).

Quorum sensing: bacterial density-coordinated gene expression, affecting virulence and protective factors

S. epidermidis infections

VP shunt infections

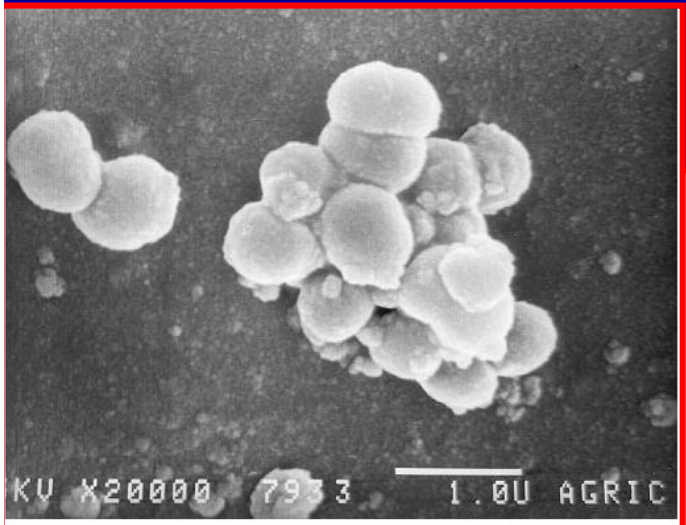


Fig. 2. Adherence of *S. epidermidis* to the surface of a VP shunt as demonstrated by scanning electron microscopy, with formation of a microcolony. ×27,000.

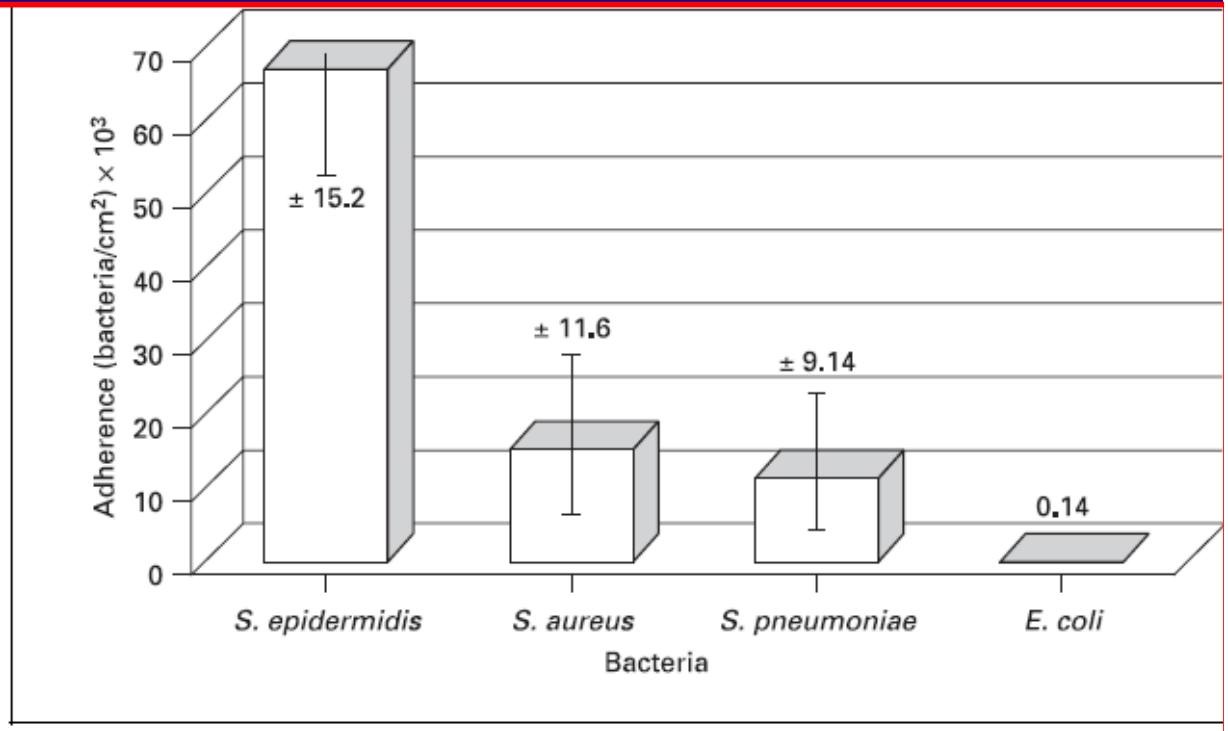


Fig. 3. Association between type of bacteria and adherence to VP shunts. Adherence was examined with a bacterial concentration of 10^7/ml and incubation time of 20 min at 37°C. Data presented as mean ± standard deviation of three determinations.

S. epidermidis infections

VP shunt infections

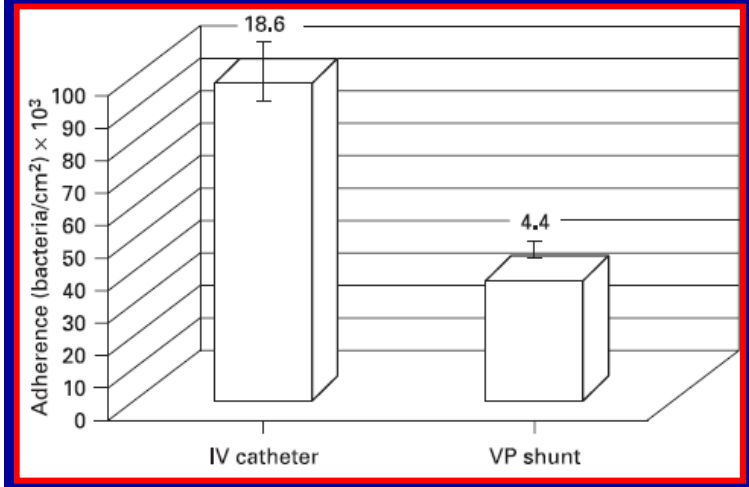


Table 1. Surface hydrophobicity, slime production and adherence of various bacteria to VP shunts in vitro

Bacteria	Hydro-phobicity, %	Slime production	Adherence ($\times 10^3/cm^2$)
S. epidermidis	64	+	67.66
S. aureus	90	–	15.26
S. pneumoniae	50	–	11.61
E. coli	0	–	0.29

S. epidermidis infections

The Pediatric Infectious Disease Journal

Wolters Kluwer Health | Lippincott Williams & Wilkins

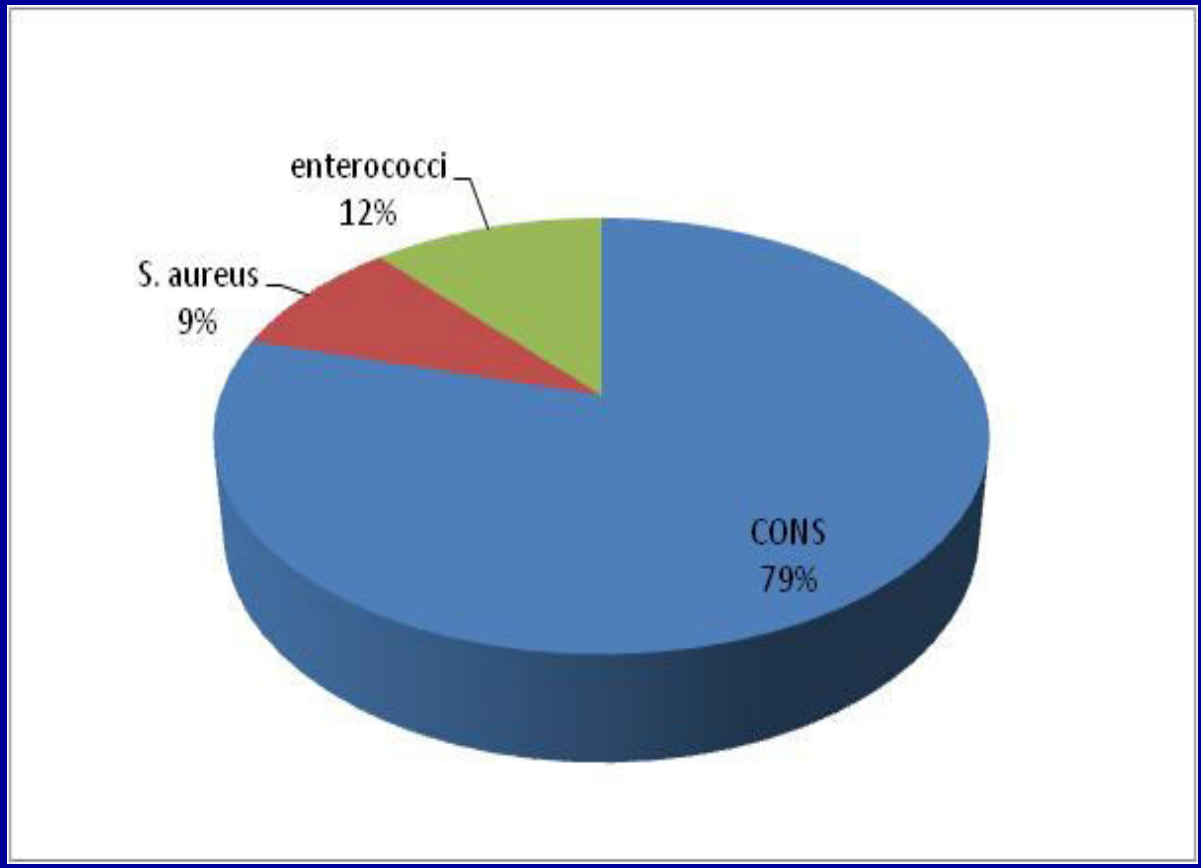
ORIGINAL STUDIES

PIDJ 2011; 30:585-90

Healthcare-associated Versus Community-associated Infective Endocarditis in Children

Bacteria	%
CoNS	27%
S. aureus	18%
K. kingae	14%
Enterococcus sp	10%
K. pneumoniae	9%
P. aeruginosa	9%
Viridans strep	4%
Culture-negative	10%

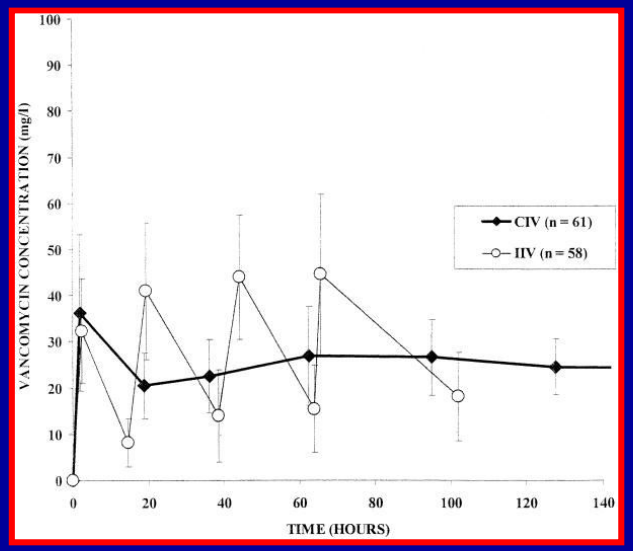
Gram-positive bacteremia at SCMCI, 2012 (N=151)



Vancomycin therapy: thinking outside the box
1. Continuous infusion

Arch Dis Child 2013
JAC 2013;in press

- For bacteria with higher MIC but susceptible.
- Optimize PK/PD, studies in neonates and population PK. Reached target cocent faster with less variability
- A loading dose and CI enable rapid achievement of therapeutic concent
- Optimize bactericidal activity; important in critical patients, clinical outcome studies?



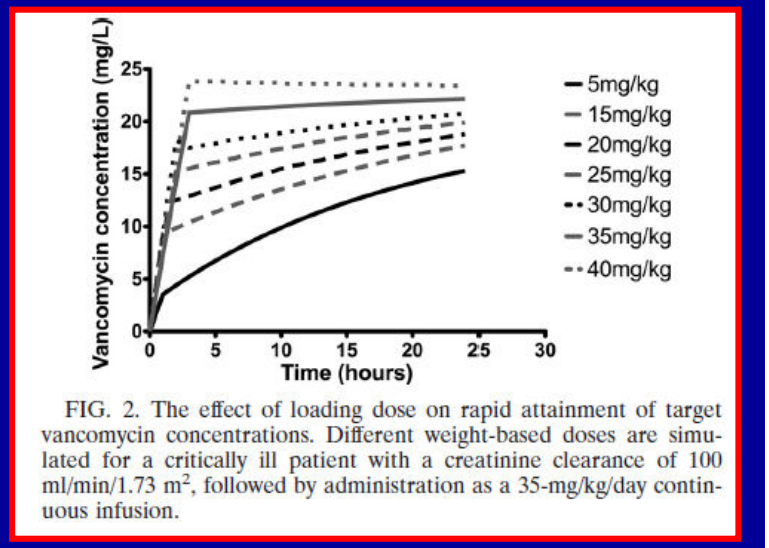
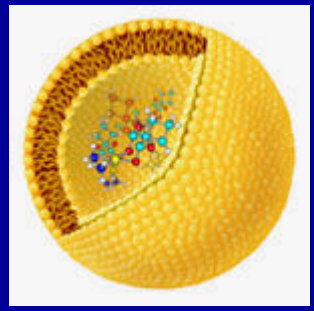


FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m^2, followed by administration as a 35-mg/kg/day continuous infusion.

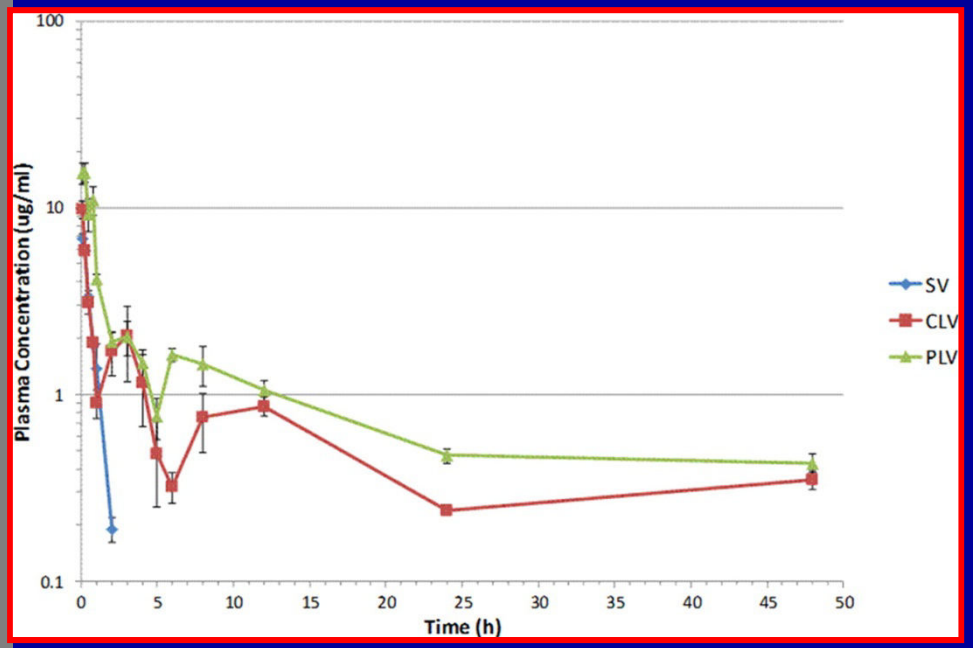
Vancomycin therapy: thinking outside the box

2. Liposomal vancomycin

AAC 2011; 55:4537
JAC 2013; in press

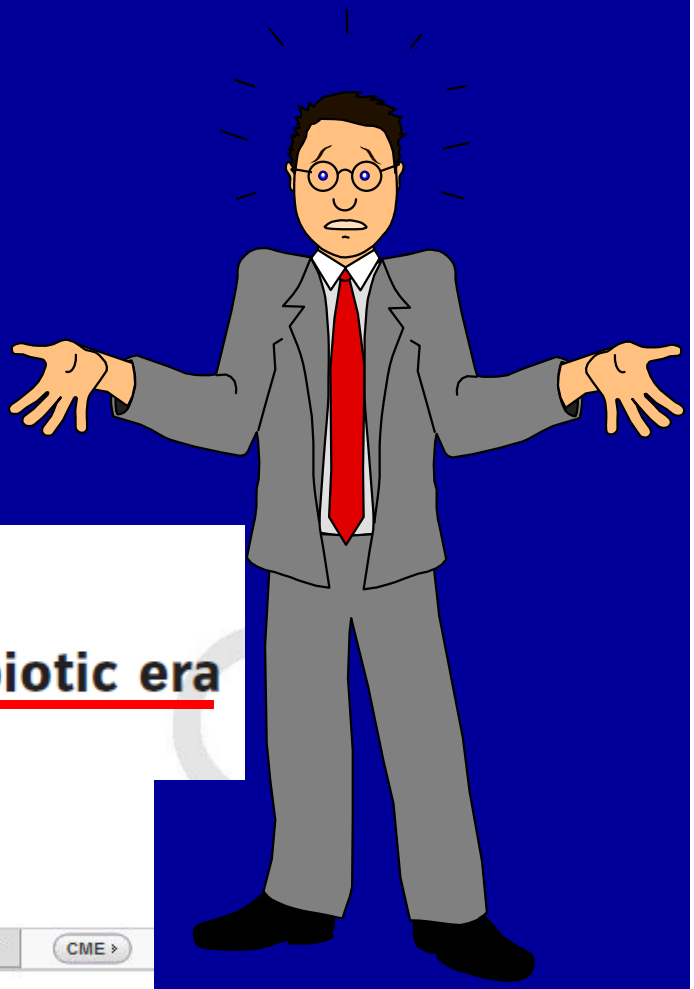


- Decrease vanco MIC of MRSA by 2-fold
- Decrease toxicity
- Increase uptake by tissue macrophages and enhance intracellular killing of MRSA
- Pegylation increases lung, liver spleen concentrations.
- Proof-of-concept in a murine model



Future trends

Prediction is extremely difficult…
especially about the future
N. Bohr



Journal of Paediatrics and Child Health

VIEWPOINT

Beginning and possibly the end of the antibiotic era

Shai Ashkenazi[1,2,3]

The NEW ENGLAND JOURNAL of MEDICINE

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Perspective

The Future of Antibiotics and Resistance

Innovative treatment options of resistant bacteria
Beyond antibiotics…

- C… to
  c… ity

We should be the parents of our future

rather than

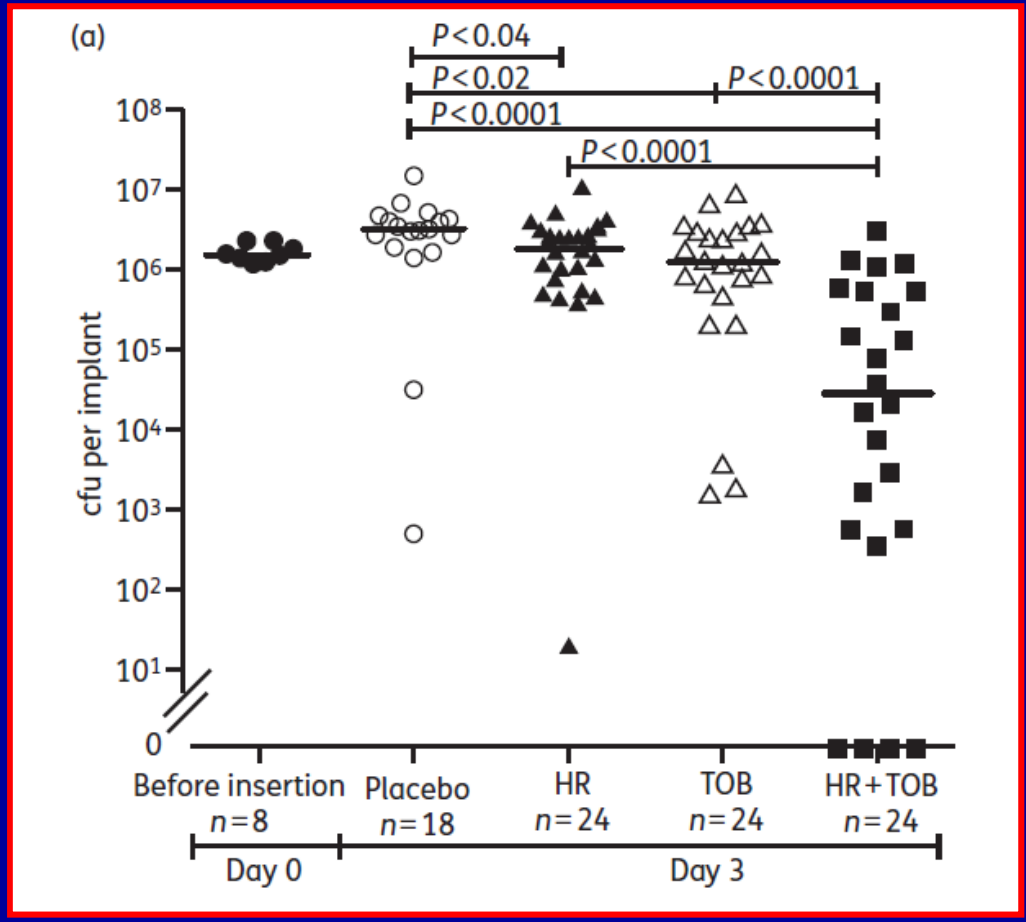
The offspring of our past

Quorum sensing inhibitors: in vivo proof-of-concept

Christensen et al

JAC 2012; 67:1198

A mouse model of intraperitoneal foreign body (biofilm) infection



Innovative treatment options of resistant bacteria
Beyond antibiotics…

- **Quorum sensing inhibitors**
- **Novel immunotherapy: active or passive**

Immunotherapy

1. Active "niche" vaccines

J Bact 2006; 188:8421

- Complicated; SA infection doesn't confer protection against subsequent infections
- Multiple approaches (redundant virulence factors)
- The promising CP5 and 8 conjugated to rEPA (StaphVAX) failed in efficacy study among hemodialysis patients and was halted.

❖ Staph aureus vaccine: two steps forward and one back..

Immunotherapy

2. Passive therapy - in vivo proof-of-concept

- Broad anti-sera were used before the antibiotic era
- Targeted Mabs are currently explored
- poly-N-acetylglucosamine (PNAG): surface PS on MRSA, MRSE, CRE, a major component of biofilms
- Natural abs to PNAG are not protective
- Human Mabs to deacetylated PNAG (F598) mediate opsonic killing
- Protected mice
- A human phase 2 study

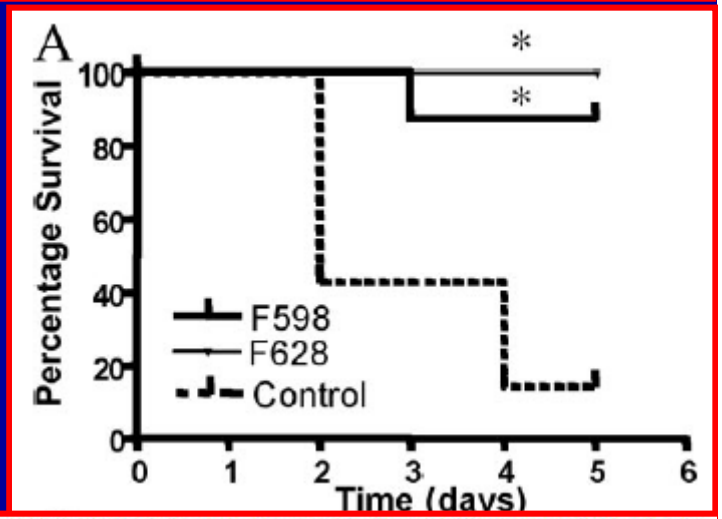


FIG. 6. Protection against *S. aureus* strain Reynolds with IgG1 MAbs

Innovative treatment options of resistant bacteria
Beyond antibiotics…

- Quorum sensing inhibitors
- Novel immunotherapy
- Novel immunomodulators (cytokine agonists or antagonists)
- Inhibit toxin production
- Inhibit bacterial adherence
- Targeted bacteriophages
- Translation interference
- Synthetic biology with engineered bacteria

Thank You
for the attention

Shai Ashkenazi

Antibiotic resistance is a moving target: new resistance mechanism of MRSA?

Journal of Antimicrobial Chemotherapy

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Oxford Journals › Medicine › Journal of Antimicrobial Chemotherapy › Advance Access › 10.1093/jac/dks522

Cell wall thickening is associated with adaptive resistance to amikacin in methicillin-resistant *Staphylococcus aureus* clinical isolates

This Article

J. Antimicrob. Chemother. (2013) doi: 10.1093/jac/dks522

First published online: January 15, 2013

- 2 MRSA isolates from a 12-yo child with osteomyelitis
- Both PVL+, SCCmec type 4, identical on PFGE
- Similar antibiograms, except for amikacin (MIC 64 vs 8 mcg/ml)
- Developed adaptive resistance with altered growth curve and thicker cell wall (36 vs 18 nm).
- Induced in vitro by amikacin