# Skin & soft tissue infections caused by MDR strains

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# Perspectives

Systematic/taxonomic
Burden – organism-specific
Burden – clinical, difficult-to-treat

# Organisms (selected)

*S. aureus*/MRSA

*Streptococcus pyogenes*
other streptococci

Diphtheroids (*Corynebacterium minutissimum* e.g.)

*Bacillus anthracis*

*Erysipelothrix rhusiopathiae*

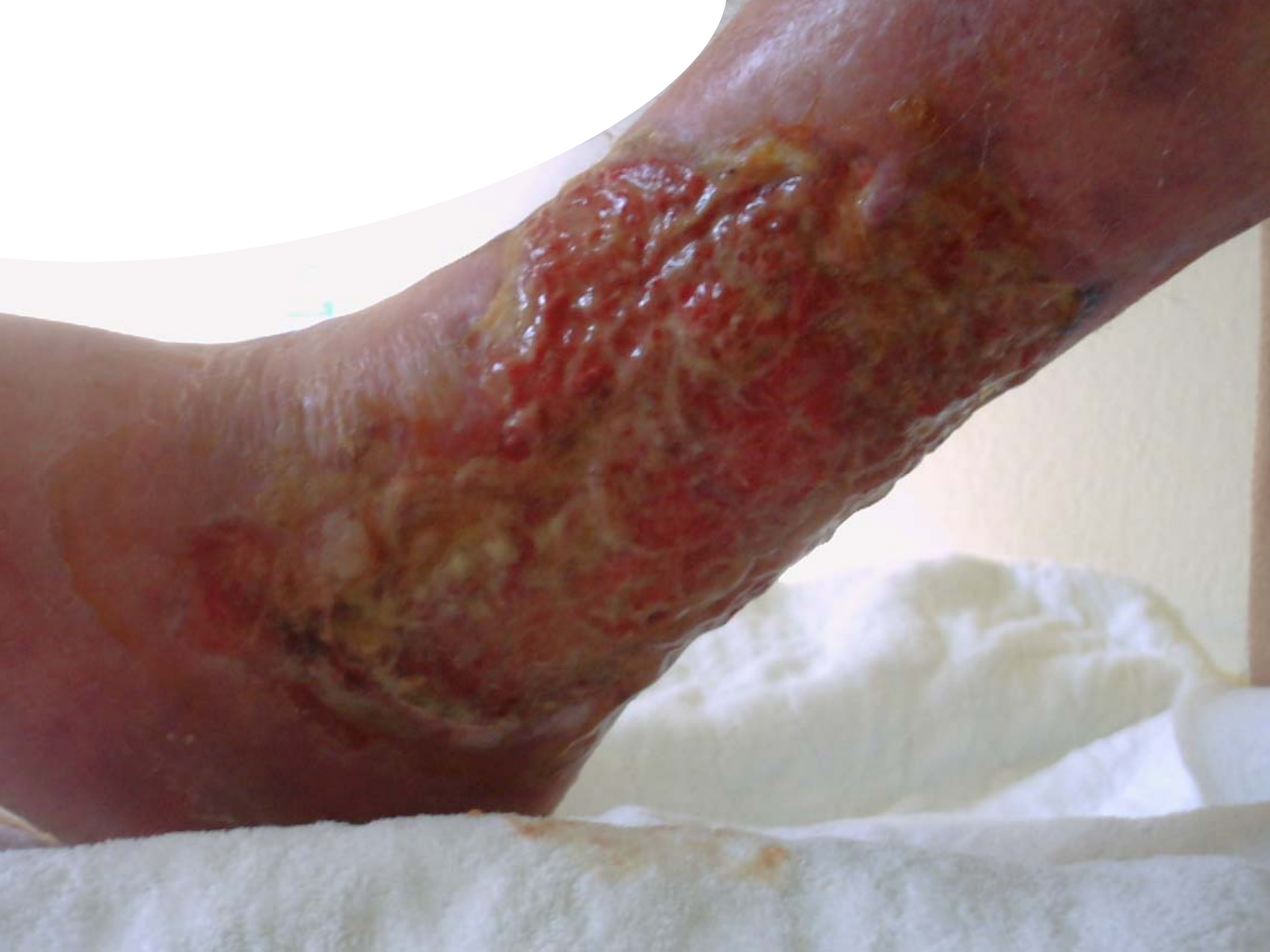
*Nocardia* spp.

Clostridia

# *Nocardia* SSTI and MDR

| | | | | | |
|---|---|---|---|---|---|
| *N. abscessus* | | | | ClariR, CipR, | ImiR |
| *N. nova* complex | | Amoxi/ClavR | | | |
| *N. farcinica* | AmpR, | | CefR, ClariR | | |
| *N. cyriacigeorgica* | | Amoxi/ClavR, | | ClariR, CipR | |
| *N. brasiliensis* | AmpR, | | CefR, ClariR, | | ImiR |
| *N. otitidiscaviarum* | AmpR, | Amoxi/ClavR, | CefR, ClariR, | | ImiR |

Brown-Elliott et al. *Clin Microbiol Rev* 2006; 19: 259-82
Schlaberg et al. *J Clin Microbiol* 2008; 46: 265-73
Glupcynski et al. *Clin Microbiol Infect* 2006; 12: 905-12



# *Nocardia* SSTI and MDR

TABLE 2. Activities of antimicrobial agents against 51 clinical isolates of *Nocardia* spp.[a]

| Antimicrobial agent | No. of isolates for which the MIC (mg/liter) was: | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ≤0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 |
| Tigecycline | 7 | 5 | 4 | 6 | 6 | 10 | 11 | 2 | | | | |
| Minocycline | 6 | | 1 | 6 | 14 | 24 | | | | | | |
| Linezolid | 5 | 7 | 7 | 7 | 22 | 3 | | | | | | |
| Moxifloxacin | 6 | 2 | 2 | 9 | 11 | 19 | | 1 | | | | 1 |
| Ertapenem | | | 2 | 2 | 4 | 8 | 17 | 4 | 3 | 6 | 2 | 3 |
| Imipenem | 3 | 3 | 2 | 7 | 22 | 10 | | 1 | 1 | | | 2 |
| Meropenem | 1 | 1 | 2 | 3 | 9 | 9 | 16 | 5 | 1 | 1 | | 3 |
| Amikacin | 2 | 2 | 8 | 12 | 22 | 4 | | | | 1 | | |

[a] The values for trimethoprim-sulfamethoxazole are as follows: MIC of 0.5/9.5 mg/liter, $n = 45$; MIC of 1/19 mg/liter, $n = 2$; MIC of >2/38 mg/liter, $n = 4$.

Cervenado et al. *Antimicrob Agents Chemother* 2007; 51: 1102-4

*S. aureus*/MRSA

*Streptococcus pyogenes*
other streptococci

Diphtheroids (*Corynebacterium minutissimum* e.g.)

*Bacillus anthracis*

*Erysipelothrix rhusiopathiae*

*Nocardia* spp.✓

Clostridia

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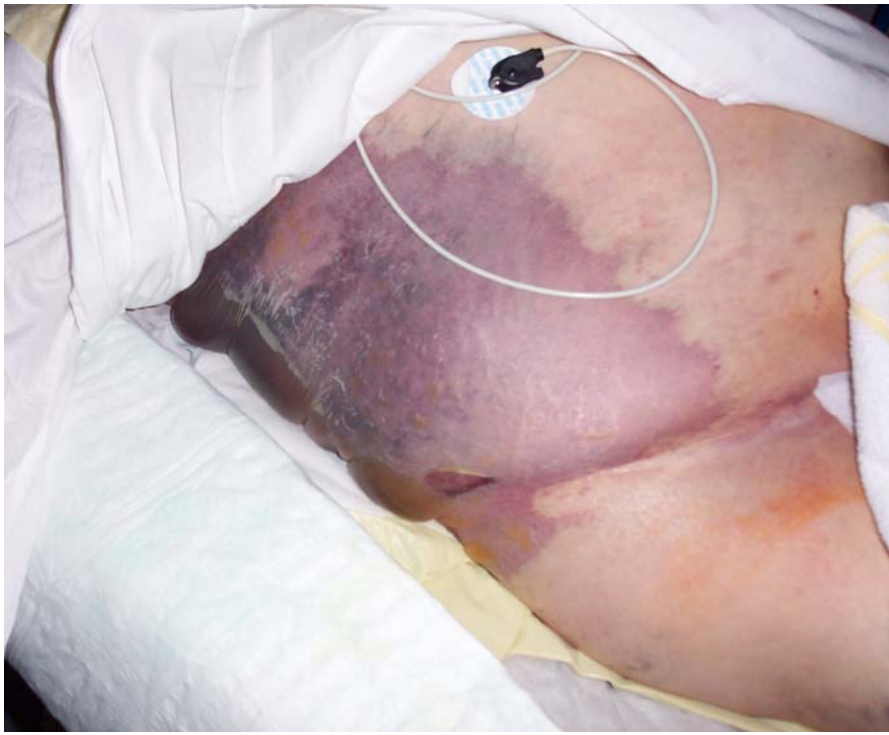
Clostridia



# Clostridial SSTI and MDR

- No resistance to penicillin, clindamycin, metronidazole in virtually all strains except
- *C. tertium* (100% PenR, but susceptible to Amoxi/Clav, Imi and Metro, variable susceptibility to clindamycin)

Roberts et al. *J Antimicrob Chemother* 2006; 57: 992-8

Table 2. Percentage of susceptible isolates for each antimicrobial agent tested during the three surveys: comparison of results from this study with previous surveys[3,4]

| | Penicillin | | | Amoxicillin/ clavulanate | | | Clindamycin | | | Metronidazole | | | Chloramphenicol | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Organisms | 1987 | 1993–94 | 2004 | 1987 | 1993–94 | 2004 | 1987 | 1993–94 | 2004 | 1987 | 1993–94 | 2004 | 1987 | 1993–94 | 2004 |
| *Bacteroides fragilis* group | 2 | 2 | 1 | 96 | 93 | 86 | 83 | 66 | 48 | 100 | 98 | 99 | 99 | 100 | 99 |
| *B. fragilis* | 0 | 2 | 1 | 97 | 95 | 92 | 90 | 85 | 60 | 100 | 100 | 99 | 99 | 100 | 100 |
| *B. fragilis* group without *B. fragilis* | 4 | 3 | 1 | 94 | 89 | 78 | 75 | 37 | 33 | 100 | 95 | 99 | 100 | 100 | 98 |
| *Fusobacterium* spp. | 70 | 88 | 100 | 100 | 100 | 100 | 90 | 69 | 90 | 100 | 100 | 100 | 100 | 100 | 100 |
| *Prevotella* species and other Gram-negative bacilli | 64 | 48 | 26 | 95 | 100 | 100 | 90 | 91 | 82 | 100 | 96 | 100 | 100 | 100 | 100 |
| *Clostridium* spp. | 91 | 90 | 83 | 100 | 100 | 97 | 82 | 74 | 63 | 100 | 100 | 98 | 96 | 100 | 95 |
| Non-spore-forming Gram-positive bacilli | 93 | 77 | 81 | 100 | 100 | 100 | 93 | 82 | 90 | 36 | 36 | 35 | 100 | 100 | 97 |
| Anaerobic cocci | 92 | 81 | 84 | 98 | 96 | 100 | 94 | 89 | 89 | 94 | 95 | 100 | 98 | 100 | 97 |
| Total | 46 | 38 | 34 | 97 | 96 | 92 | 83 | 72 | 63 | 95 | 94 | 95 | 97 | 99 | 98 |

Wybo et al. *J Antimicrob Chemother* 2007; 59: 132-9

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*Nocardia* spp.✓

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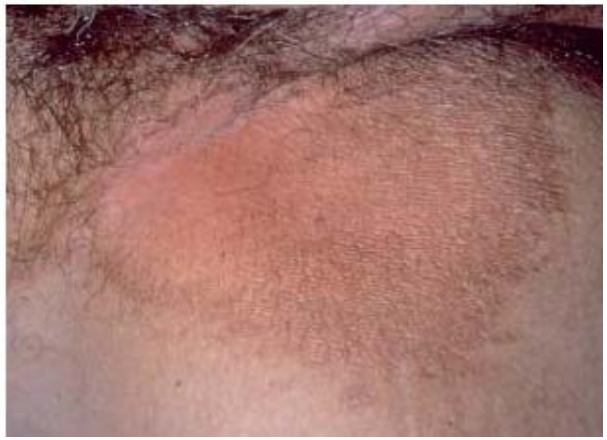
# *Corynebacterium* SSTI and MDR



*C. minutissimum (n=20)*

| | | | |
|---|---|---|---|
| Ampicillin | 0.030–32 | 0.250 | 32 |
| Oxacillin | 0.250–>256 | 2 | >256 |
| Cephalothin | 0.060–128 | 0.250 | 128 |
| Cefuroxime | 0.125–64 | 2 | >256 |
| Imipenem | ≤0.003–4 | 0.030 | 4 |
| Tetracycline | 0.125–64 | 4 | 64 |
| Doxycycline | 0.060–1 | 0.250 | 1 |
| Erythromycin | 0.030–>256 | 0.5 | >256 |
| Azithromycin | 0.125–>256 | 0.5 | >256 |
| Clindamycin | 0.250–>256 | 4 | >256 |
| Rifampin | ≤0.003–256 | ≤0.003 | 256 |
| Fusidic acid | ≤0.015–0.250 | 0.030 | 0.060 |
| Ciprofloxacin | 0.030–256 | 0.060 | 16 |
| Gentamicin | 0.030–>256 | 0.060 | >256 |
| Vancomycin | 0.250–0.5 | 0.250 | 0.5 |
| Optochin | 1–256 | 128 | 256 |
| Fosfomycin | >256 | >256 | >256 |
| Nitrofurantoin | 0.5–256 | 16 | 256 |

Soriano et al. *AAC* 1995; 39: 218-14

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other streptococci

Diphtheroids (*Corynebacterium minutissimum* e.g.) ✓

*Bacillus anthracis*

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Clostridia ✓

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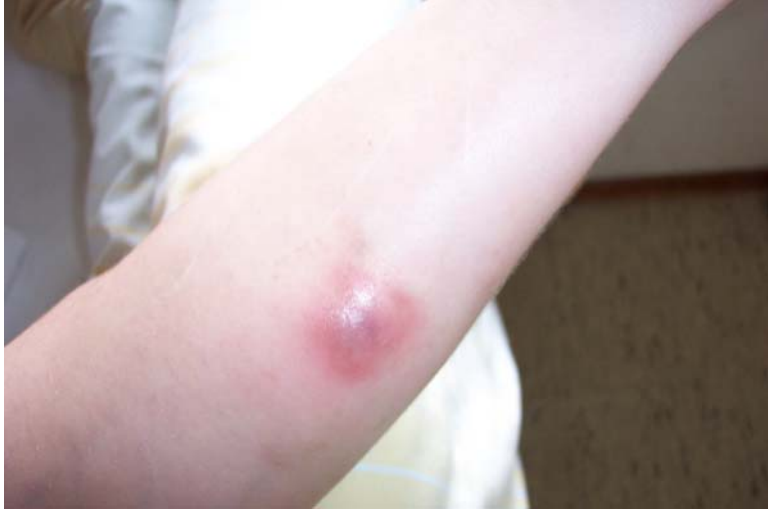


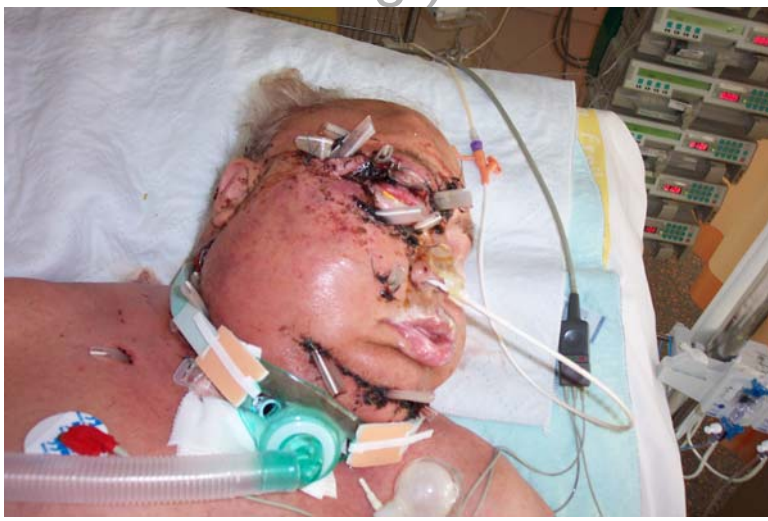
Diphtheroids (*Corynebacterium minutissimum* e.g.) ✓

*Bacillus anthracis* ✓

*Erysipelothrix rhusiopathiae* ✓

*Nocardia* spp.✓

Clostridia ✓



N Engl J Med 2006

# Methicillin-Resistant *S. aureus* Infections among Patients in the Emergency Department

Gregory J. Moran, M.D., Anusha Krishnadasan, Ph.D.,
Rachel J. Gorwitz, M.D., M.P.H., Gregory E. Fosheim, M.P.H.,
Linda K. McDougal, M.S., Roberta B. Carey, Ph.D., and David A. Talan, M.D.,
for the *EMERGE*ncy ID Net Study Group*

**CONCLUSIONS**

MRSA is the most common identifiable cause of skin and soft-tissue infections among patients presenting to emergency departments in 11 U.S. cities. When antimicrobial therapy is indicated for the treatment of skin and soft-tissue infections, clinicians should consider obtaining cultures and modifying empirical therapy to provide MRSA coverage.

# Epidemiology

| | |
|---|---|
| Community-onset MRSA disease | |
| in San Francisco: | ~300 per 100,000 |
| in the UK: | ~13 per 100,000 |
| | |
| Invasive Strep A disease | |
| in Europe | ~3 per 100,000 |
| Strep A necrotizing fasciitis | |
| in Ontaria/Canada | <1 per 100,000 |


Liu et al. *Clin Infect Dis* 2008; 46: 1637-4

Delaney et al. *BMC Medicine* 2008; 6:2

Lamagni et al. *J Clin Microbiol* 2008 (e-pub ahead of print)

Kaul et al. *Am J Med* 1997; 103: 18-24

# CA-MRSA

- Prospective study (2003 to 2005)
- CA-MRSA (n = 102 patients) and CA-MSSA (n = 102 patients)
- most common sites of infection:
  - skin/soft tissue 80 and 93%, respectively,
  - respiratory tract 13 and 6%, respectively,
  - blood 4 and 1%, respectively.
- PVL gene: 54 vs 10%

Davis et al. *J Clin Microbiol* 2007; 45:1705-11

# CA-MRSA

- Antibiotics: 80 vs 64%
- Admission: 46 vs 18%
- „Cure“ rate: 61 vs 84%

  [SSTI „cure“ rates higher with adequate therapy (61 vs 38%)]
- One death (CA-MRSA pneumonia)

Davis et al. *J Clin Microbiol* 2007; 45:1705-11

# CA-MRSA

| | CA-MRSA | CA-MSSA |
|---|---|---|
| ▪ EryS | 9% | 69% |
| ▪ ClindaS | 54% | 75% |
| ▪ Co-trimS | 99% | 100% |
| ▪ TetS | 91% | nd |

Davis et al. *J Clin Microbiol* 2007; 45:1705-11

# CA-MRSA SSTI

Treatment and Outcomes of Infections by Methicillin-Resistant *Staphylococcus aureus* at an Ambulatory Clinic[▽]

John D. Szumowski,[1]* Daniel E. Cohen,[2] Fumihide Kanaya,[2] and Kenneth H. Mayer[2,3]

*Harvard Medical School, Boston, Massachusetts[1]; Fenway Community Health, Boston, Massachusetts[2]; and Brown University School of Medicine, Providence, Rhode Island[3]*

- N=339 outpts (many HIV+, 227 MRSA SSTIs)
- retrospective analysis, 1998-2005
- initially usually ß-lactam, recently co-trimoxazol
- „concordant“ antibiotic therapy associated with better resolution (adjusted OR ~6)

*AAC 2007; 51:423-8*

# CA-MRSA SSTI

- Prospective study in children (n=69) with CA-MRSA skin and soft tissue abscesses
- Treatment: drainage 96%, wound packing 65%, antibiotics 100% (initially inadequate 93%, eventually adequate 36%)
- Admission 6%
- Admission predicted by
  - lesion initially >5 cm (P = 0.004)
  - NOT: inadequate antibiotic therapy (P = ns)
- No difference in overall outcomes according to different antibiotic therapies

Lee et al. *Pediatr Infect Dis J* 2004; 23: 123-7

# CA-MRSA SSTI

- Incision & drainage critical
- Admission needed in <10% to ~50%
- In more severe disease (or with underlying disease/comorbidity) concordant therapy associated with better outcome (includes co-trimoxazole); „old“ drugs will do?

# Minocyclin-, Doxycylin-Therapie

| Reference | No. of participating patients | Age, mean years (range) | Strain isolated | Type of infection, no. (%) of infected patients | Type of tetracycline | No. (%) of patients with cure |
|---|---|---|---|---|---|---|
| [12] | 25 | 62 (18–88) | MRSA | Pneumonia, 9 (36)<br>Osteomyelitis, 4 (16)<br>SSSI, 4 (16)<br>Other, 8 (32)[a] | Minocycline plus rifampin | 19 (76) |
| [13] | 1 | 45 | MRSA | Prosthetic aortic valve endocarditis, 1 (100) | Minocycline | 1 (100) |
| [14] | 15 | 61 (25–74) | MSSA | SSSI, 10 (67)<br>Pneumonia, 5 (33) | Minocycline | 12 (80) |
| [15] | 10 | Unknown | MSSA | SSSI, 10 (100) | Minocycline | 8 (80) |
| [16] | 15 | 56 (22–83) | MSSA | SSSI, 15 (100) | Minocycline | 15 (100) |
| [17] | 2 | 69 (54–84) | MSSA | Pneumonia, 2 (100)<br>SSSI, 1 (50) | Minocycline | 2 (100) |
| [18] | 1 | 33 | MSSA | Osteomyelitis, 1 (100) | Minocycline | 1 (100) |
| [19] | 13 | 35 (22–48) | MSSA | SSSI, 13 (100) | Doxycycline | 13 (100) |
| [20] | 3 | unknown | MSSA | Osteomyelitis, 3 (100) | Doxycycline plus rifampin | 1 (33) |

Ruhe JJ et al. *Clin Infect Dis* 2005

# Cotrimoxazole for „severe“ *S. aureus* infection

| | Response |
|---|---|
| Vanco | 57/58 (98%)* |
| Cotrimoxazole | 37/42 (88%)* |

*Failures associated with endocarditis

Markowitz et al. *Ann Intern Med* 1992

# Cotrimoxazole: what´s the concern?

- experimentally not convincing in deep-seated infection
- dosing not clear
- the deeper the infection, the sicker the patient, the poorer the response – why?

  → thymidine (from necrotic tissue) taken up by *Staph* cells (SCV?) antagonizes cotrimoxazole action

reviewed by RA Proctor, *CID 2008*

# MRSA SSTI therapy

Prospective Randomized Trial of Empiric Therapy with Trimethoprim-Sulfamethoxazole or Doxycycline for Outpatient Skin and Soft Tissue Infections in an Area of High Prevalence of Methicillin-Resistant *Staphylococcus aureus*[▽]

Mary Jo Cenizal,[1] Daniel Skiest,[1] Samuel Luber,[1] Roger Bedimo,[1,2] Pat Davis,[1] Patrick Fox,[1] Kathleen Delaney,[1] and R. Doug Hardy[1]*

*University of Texas Southwestern Medical Center[1] and VA North Texas Health Care System,[2] Dallas, Texas*

- N=34 pts with SSTI needing incision & drainage (MRSA, 68%)
- Cotrim 2x960 mg vs Doxy 2x100 mg for 7 days
- Failures: 21% vs 0%

*AAC 2007; 51:2628-30*

# MRSA SSTI therapy ?

Randomized, Double-Blind, Placebo-Controlled Trial of Cephalexin for Treatment of Uncomplicated Skin Abscesses in a Population at Risk for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infection[▽]

Priya M. Rajendran,[1] David Young,[2]* Toby Maurer,[1] Henry Chambers,[3] Francoise Perdreau-Remington,[3] Peter Ro,[4] and Hobart Harris[2]

*Department of Dermatology,[1] Department of Surgery,[2] and Department of Medicine,[3] University of California San Francisco School of Medicine,[4] San Francisco, California*

- N=166 pts with SSTI needing incision & drainage (MRSA, 54%)
- Cephalexin 4x500 mg vs Placebo for 7 days
- Failures: 10 vs 16%

  (MRSA: 2/42 vs 4/43)

*AAC 2007; 51:4044-8*

# CA-MRSA SSTI

- Incision & drainage critical
- Admission needed in <10% to ~50%
- In more severe disease (or with underlying disease/comorbidity) concordant therapy associated with better outcome (includes co-trimoxazole); „old“ drugs will do?

# Summary/conclusions

- MRSA SSTI is a significant burden
- adequate antibiotic therapy improves the outcome in more severe disease
- there is room for improvement
- many other difficult-to-treat SSTIs

# *S. aureus*: [standards] & needs

SAB - Uncomplicated

- need: drugs to shorten iv administration while keeping relapse rates low

SAB - Complicated

- more aggressive (?combination) therapy, active in tissues/abscesses and against SCV

Generally: better MRSA drugs

Better clinical judgment and risk assessment

Special needs: controlled trials of oral drug(s) for osteoarticular infection & foreign-body infection (SCV-active, biofilm-active)