Must We Change Initial Empiric Antibiotic Treatment?

Skin and Soft Tissue Infections and Osteoarticular Infections

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April 15, 2011
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Secretaria: Dr. Pablo Tregnaghi

The Issue: *Staphylococcus aureus*

- Prior to 2002, virtually all community strains were methicillin-susceptible
- Increasing incidence of MRSA in all invasive staphylococcal infections, currently at ~ 40% of all staphylococcal isolates, but has not increased further during the past 3 years

The Issue: *Staphylococcus aureus*

- Empiric therapy needs to take into consideration that *S. aureus* might be resistant to methicillin
- Each region has different susceptibility data that accurately inform the decision on empiric therapy
- How high of a “target attainment” is required for each individual patient with skin or osteoarticular infection?
  80%? 90%? 95%? 99%?

The Issue: *Staphylococcus aureus*

Rady Children's Hospital-San Diego
ANTIBIOGRAM
July 2009 to June 2010

Definitions:

1) BACTERIAL ISOLATES: Include organisms isolated from Blood/CSF/Soft Tissues/Wound/Peritoneum/Trachea/Stool/Urine. This analysis includes isolates from both inpatient and outpatient sources and may include duplicate isolates.
2) PRIMARY SUSCEPTIBILITY METHOD: Broth microdilution.
3) SUSCEPTIBLE (S): Infecting organism is inhibited by antimicrobial levels attained in the BLOOD at USUAL dosages.
4) RESISTANT (R): Resistant to usually achievable blood concentrations of the drug under consideration.
5) Between (S) & (R), there is a range of INTERMEDIATE (I) which can generally be achieved only by maximum dosages of the antibiotic under consideration. The table below presents data for susceptible (S) isolates only.
6) MIC INTERPRETIVE STANDARDS: Based on (CLSI)/NCCLS, Clinical Laboratory Standards Institute for Blood, 2010.

PERCENT OF ISOLATES SUSCEPTIBLE BY INHIBITION

ORGANISMS	ISOLATES	PENICILLIN	AMPICILLIN	ANTI-STAPH PENICILLIN (NAFCILLIN)	VANCOMYCIN	CLINDAMYCIN(b)	ERYTHROMYCIN	CEFAZOLIN (e)	CEFUROXIME (e) 2nd Gen	CEFOTAXIME (e) 3rd Gen	CEFTAZIDIME (e) 3rd Gen	CEFTRIAXONE (e) 3rd Gen	CEFEPIME 4th Gen	TMP/SMX	GENTAMICIN	TOBRAMYCIN	RIFAMPIN	MEROPENEM (a)
Staphylococcus aureus	2088	13		62	100	92	49	62(b)				62(b)		100	97		99	
Coag negative Staph	360	14		39	100	66	34	39(c)				39(c)		64	65		96	
Enterococcus faecalis	195	100(d)	100(d)		100													
Enterococcus faecium	26	23(d)	23(d)		46													
Strep pneumoniae	117	40(f)			100	74	58			90(g)		90(g)						
Escherichia coli	2548		50					90	97	98	98	98	98	68	95	95		100
Enterobacter spp	168							14	68	90	90	89	100	96	100	100		99
Klebsiella spp	237							85	94	96	96	96	97	86	97	96		100
Pseudomonas aeruginosa	480										88		85		80	89		88
Proteus mirabilis	236		90					96	100	100	100	100	100		93	95		100
Serratia spp	114							0	0	88	96	96	99	96	99	93		100
Citrobacter spp	65		22					45	78	92	89	92	100	88	94	94		100
Acinetobacter spp	63									63	83	86	83	92	97	97		100
Salmonella spp	61		90							97	97	97		98				
Shigella spp	29		62							100	100	100		28				
Steno maltophilia	89													99		47		4
INTERPRETIVE STANDARDS (mcg/ml)	(S)	See	See	See	≤4	≤0.5	≤0.5	≤8	≤8	≤8	≤8	≤8	≤8	≤2/38	≤4	≤4	≤1	≤4
	(R)	Below	Below	Below	≥32	≥4	≥8	≥32	≥32	≥64	≥32	≥64	≥32	≥4/76	≥16	≥16	≥4	≥16

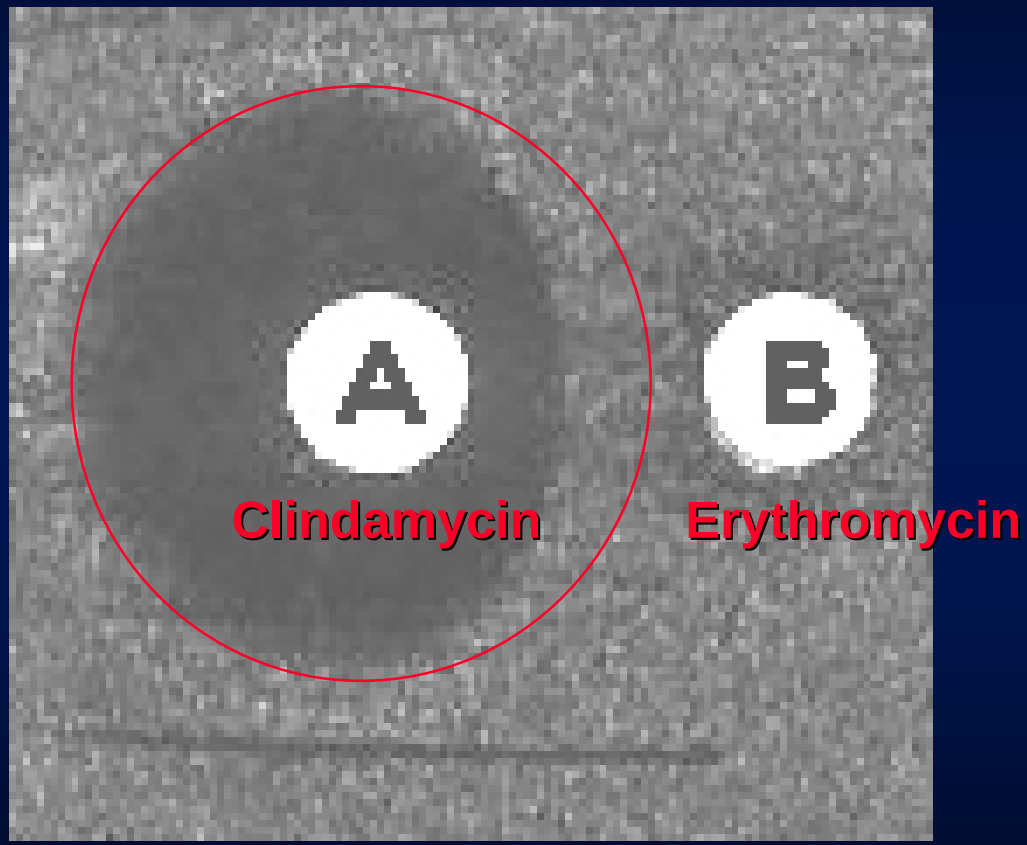
The Issue: *Staphylococcus aureus*

PERCENT OF ISOLATES SUSCEPTIBLE BY INHIBITION

ORGANISMS	ISOLATES	PENICILLIN	AMPICILLIN	ANTI-STAPH PENICILLIN (NAFCILLIN)	VANCOMYCIN	CLINDAMYCIN(h)	ERYTHROMYCIN	CEFAZOLIN (e)	CEFUROXIME (e) 2nd Gen	CEFOTAXIME (e) 3rd Gen	CEFTAZIDIME (e) 3rd Gen	CEFTRIAXONE (e) 3rd Gen	CEFEPIME 4th Gen	TMP/SMX	GENTAMICIN	TOBRAMYCIN	RIFAMPIN	MEROPENEM (a)
Staphylococcus aureus	2088	13		62	100	92	49	62(b)				62(b)		100	97		99	

- Vancomycin: uniformly active against MRSA (except hVISA), not rapidly cidal; nephro/ototoxicities
- Clindamycin: less bactericidal than vancomycin; variable resistance rates; diarrhea; poor tasting oral suspension
- TMP-SMX: active *in vitro*, but no prospective studies!
- Rifampin: gets into tissues well, but may be antagonistic for some strains, not synergistic; development of resistance if only rifampin present at site of infection
- Aminoglycosides: poorly active in low pH pus

"D Test"
For Inducible Clindamycin Resistance



D-test positive organisms that do NOT constitutively produce methylase, but are "inducible" may still be treatable with clindamycin (eg, in low pathogen-load infections)

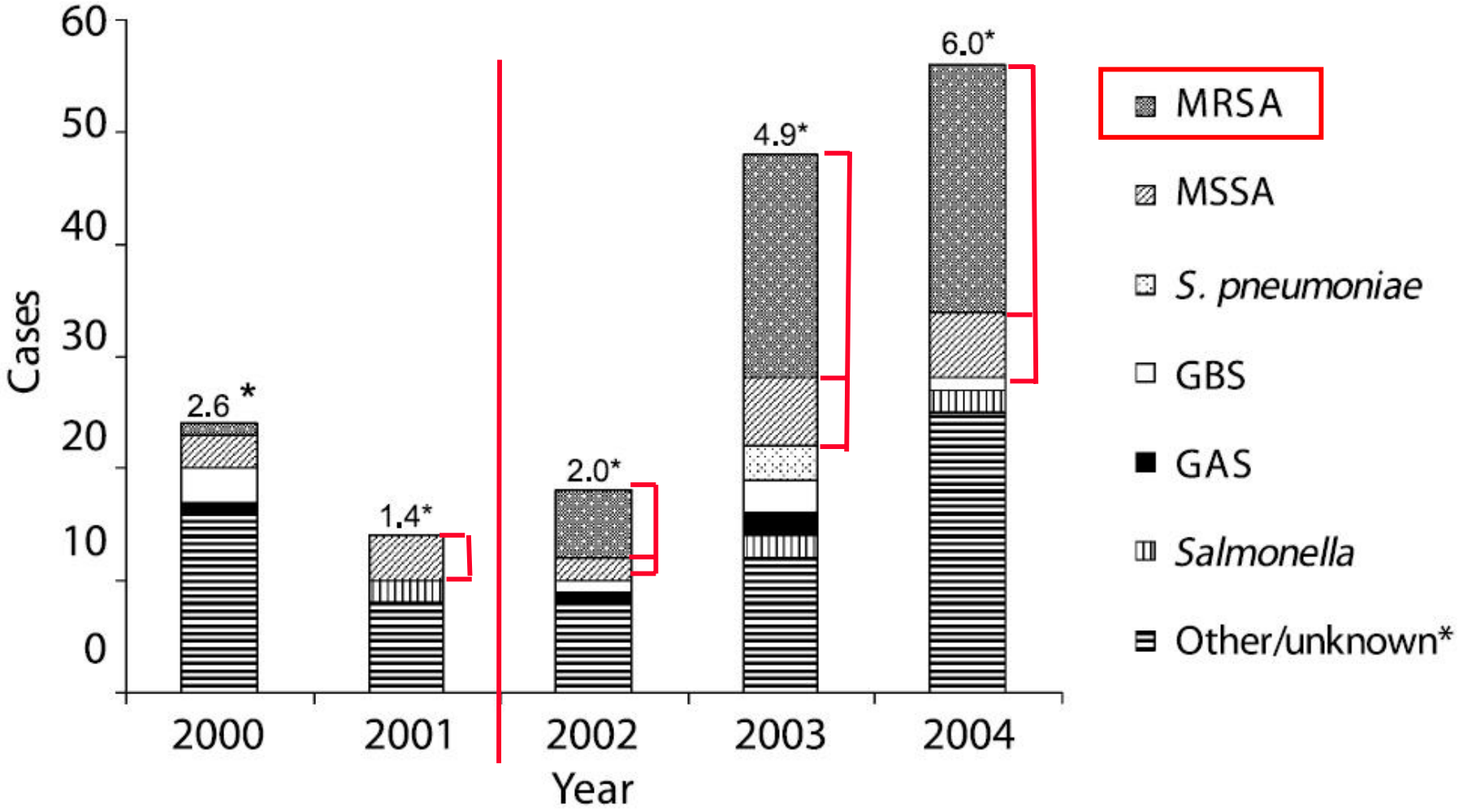


FIGURE 1. Etiology of acute osteoarticular infection 2000–2004.

Arnold SR et al. 2006 J Pediatr Orthop. Le Bonheur Children's, Memphis, TN

Osteo in the CA-MRSA Era

Table 1 Acute haematogenous osteomyelitis: Comparison of isolated organisms

Isolated organism	Current study no. (%) **2005**	Nade study no. (%) **1974**
S. aureus	34 (76%)	42 (75%)
Methicillin-resistant S. aureus	4 (9%)	0
S. pneumoniae	2 (4%)	3 (5%)
S. pyogenes	2 (4%)	6 (11%)
Group B *Streptococcus*	2 (4%)	0
Yersinia entercolitica	1 (2%)	0
H. influenzae	0	2 (4%)
S. haemolyticus	0	1 (2%)
E. coli	0	1 (2%)
Bacillus proteus	0	1 (2%)

Goergens ED et al. 2005 J Paediatr Child Health. **Osteo in Australia**

Why are we concerned?

Dallas, Tx

TABLE 2. Comparison of MRSA Versus Other Acute Osteomyelitis

Characteristics	Group 1 MSSA (n = 72)	Group 2 MRSA (n = 36)	Group 3 Non–*S. aureus* With Positive Culture (n = 57)	Group 4 Culture Negative (n = 125)	*P**
Male, %	61	72	54	58	NS
Black, %	14	44	26	36	2 vs 1: 0.001
White, %	36	31	26	42	NS
Hispanic, %	47	22	46	28	2 vs 1: 0.021; 2 vs 3: 0.039
Age of ≥5 y, %	75	78	52	36	2 vs 3: 0.004; 2 vs 4: <0.001
Trauma, %	43	50	30	28	2 vs 3: 0.082; 2 vs 4: 0.024
Open wound, %	25	11.1	23	12	NS
Antibiotics before admission, %	31	42	44	28	NS
Days of symptoms before admission	5 (3–7)	6 (3–7)	6 (3–13)	7 (3–12)	NS
Fever at presentation, %	78	83	63	54	2 vs 3: 0.064; 2 vs 4: 0.003
* CRP of >4 mg/dL, %	58	86	42	34	2 vs 1: 0.007; 2 vs 3: <0.001; 2 vs 4: <0.001
* ESR of >40 mm/h, %	60	83	56	57	2 vs 1: 0.013; 2 vs 3: 0.007; 2 vs 4: 0.003
Anemia at presentation, %	31	61	35	20	2 vs 1: 0.005; 2 vs 3: 0.012; 2 vs 4: <0.001
* Arthritis, %	14	33	25	12	2 vs 1: 0.035
Multiple bones involved, %	21	19	14	1	NS
* Days of positive blood culture†	1 (0–1)	2 (0–3.25)	—‡	—	2 vs 1: 0.008
* Days to defervescence	1 (0–4)	5 (2–10)	1 (0–3)	0 (0–1)	2 vs others: <0.05
* Any complication, %	49	86	49	11	2 vs others: <0.001
* Abscess, %	26	69	39	11	2 vs 1: <0.001; 2 vs 3: 0.07; 2 vs 4: <0.001
* Need for surgery, %	49	78	68	20	2 vs 1: 0.007; 2 vs 4: <0.001
* Days to normal CRP	8 (5–14)	25 (14–52)	11 (6–16)	6 (3–11)	2 vs others: <0.05
* Days to normal ESR	21 (13–26)	53 (30–120)	30 (19–62)	15 (8–31)	2 vs 1 and 4: <0.05
* Days on intravenous antibiotics	7 (4–12)	22 (10–33)	8 (8–23)	4.5 (3–6)	2 vs others: <0.05
* Total days on antibiotics	29 (23–40)	42 (28–69)	36 (26.5–50)	25 (21–32.5)	2 vs 1 and 4: <0.05
Days of hospitalization	7 (5–10)	15 (10–25)	9 (5–14)	5 (4–7)	2 vs others: <0.05
Relapse or sequelae, %	17	29	19	11	2 vs 4: 0.029

*Only significant *P* values are shown. Only shown MRSA versus others.

Saavedra-Lozano J et al. 2008 J Pediatr Orthop

Clinical disease caused by CA-MRSA

- More inflammation by CRP, ESR
- Longer positive blood cultures
- More abscess formation
- More complications
- More surgeries
- Slower decrease in fever
- Longer IV antibiotic therapy

Why are we concerned?

Bocchini CE et al. 2006 Pediatr

Series from Baylor, Tx

TABLE 3 Clinical, Laboratory, and Radiographic Features of Children With *pvl*+ and *pvl*− Acute *S aureus* Osteomyelitis

Characteristic	*pvl*+ (*n* = 59)	*pvl*− (*n* = 26)	*P*
Single site of infection, *n* (%)	50 (84.7)	25 (96.2)	.17
Multiple sites of infection, *n* (%)	9 (15.3)	1 (3.8)	
Location of single-site osteomyelitis, *n* (%)[a]			NS
Femur	15 (25.4)	6 (23.1)	
Tibia/fibula	20 (33.9)	10 (38.5)	
Other[b]	15 (25.4)	9 (34.6)	
Antibiotics prior to diagnosis, *n* (%)	18 (30.5)	6 (23.1)	NS
Duration of symptoms prior to diagnosis, d	6.0	6.1	NS
Surgical intervention, *n* (%)	54 (91.5)	22 (84.6)	NS
ICU treatment, *n* (%)	11 (18.6)	1 (3.8)	.01
ESR at presentation			.0008
n	56	25	
Mean ± SD, mm/h	80 ± 28.7	60 ± 21.8	
Median (range), mm/h	88 (4–140)	62 (15–97)	
Maximum ESR			<.0000001
n	59	26	
Mean ± SD, mm/h	104 ± 27.8	68 ± 26.5	
Median (range), mm/h	112 (4–140)	70 (15–140)	
CRP level at presentation			.000002
n	49	20	
Mean ± SD, mg/dL	23.1 ± 18.1	7.1 ± 7.1	
Median (range), mg/dL	20 (0.7–79.4)	5.7 (1.1–35.2)	
Maximum CRP level			<.0000001
n	53	23	
Mean ± SD, mg/dL	24.6 ± 16.8	7.5 ± 6.7	
Median (range), mg/dL	23.8 (0.8–79.4)	6.4 (1.1–35.2)	
WBC count at presentation			.03
n	59	26	
Mean ± SD, cells × 10^3/mm^3	15.1 ± 6.6	11.6 ± 6.4	
Median (range)	13.8 (4.07–39.82)	9.5 (5.25–32.27)	
ANC at presentation			.002
n	59	26	
Mean ± SD, cells × 10^3/mm^3	12.1 ± 6.4	7.5 ± 4.9	
Median (range)	10.9 (2.89–37.43)	5.2 (1.82–21.3)	
Blood culture positive for *S aureus* isolates, *n*/*N* (%)	39/58 (67.2)	5/26 (19.2)	.0001
Surrounding myositis/pyomyositis on MRI, *n*/*N* (%)	28/45 (62.2)	6/19 (31.6)	.05
Subperiosteal/intraosseal abscess on MRI, *n*/*N* (%)	34/45 (75.6)	9/19 (47.4)	.06

Clinical disease: pvl+ CA-MRSA

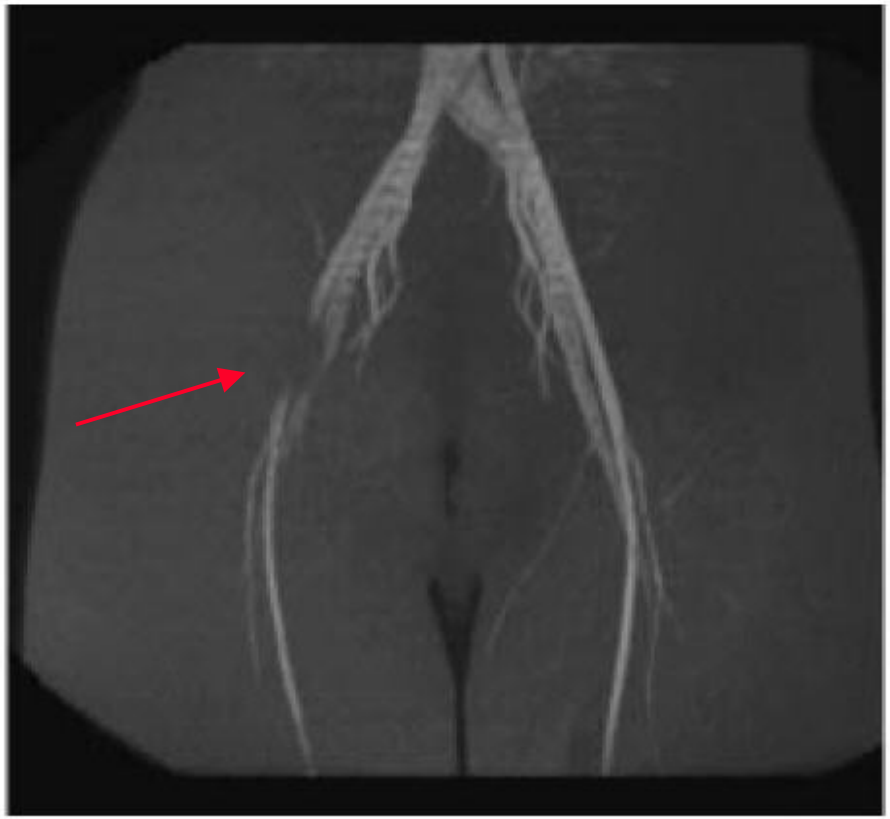
- More inflammation by CRP, ESR
- More likely to be in the PICU
- More likely to have + blood cult
- More likely to have surrounding pyomyositis
- Trend toward more abscess formation (p=0.06)

Empiric Therapy of Osteomyelitis

Venous Thrombosis Associated With Staphylococcal Osteomyelitis in Children

Blanca E. Gonzalez, MD[a,c], Jun Teruya, MD, DSc[a,b,c], Donald H. Mahoney, Jr, MD[a,c], Kristina G. Hulten, PhD[a,c], Rachael Edwards, BS[b,c], Linda B. Lamberth[a,c], Wendy A. Hammerman, RN[a,c], Edward O. Mason, Jr, PhD[a,c], Sheldon L. Kaplan, MD[a,c]

Departments of [a]Pediatrics and [b]Pathology, Baylor College of Medicine, Houston, Texas; [c]Texas Children's Hospital, Houston, Texas



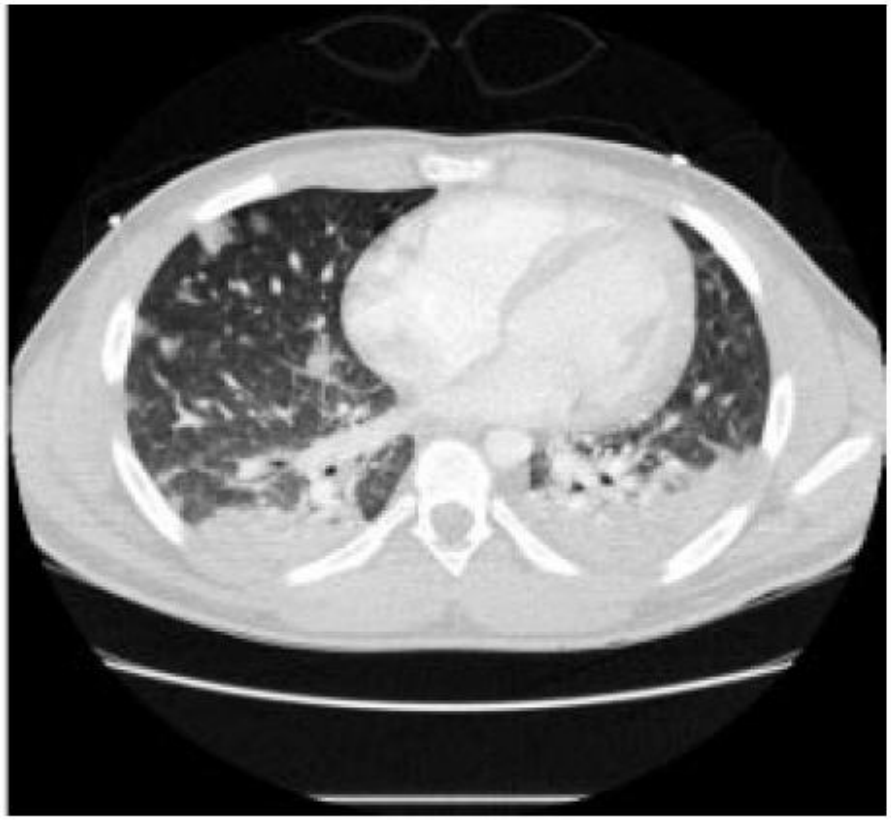
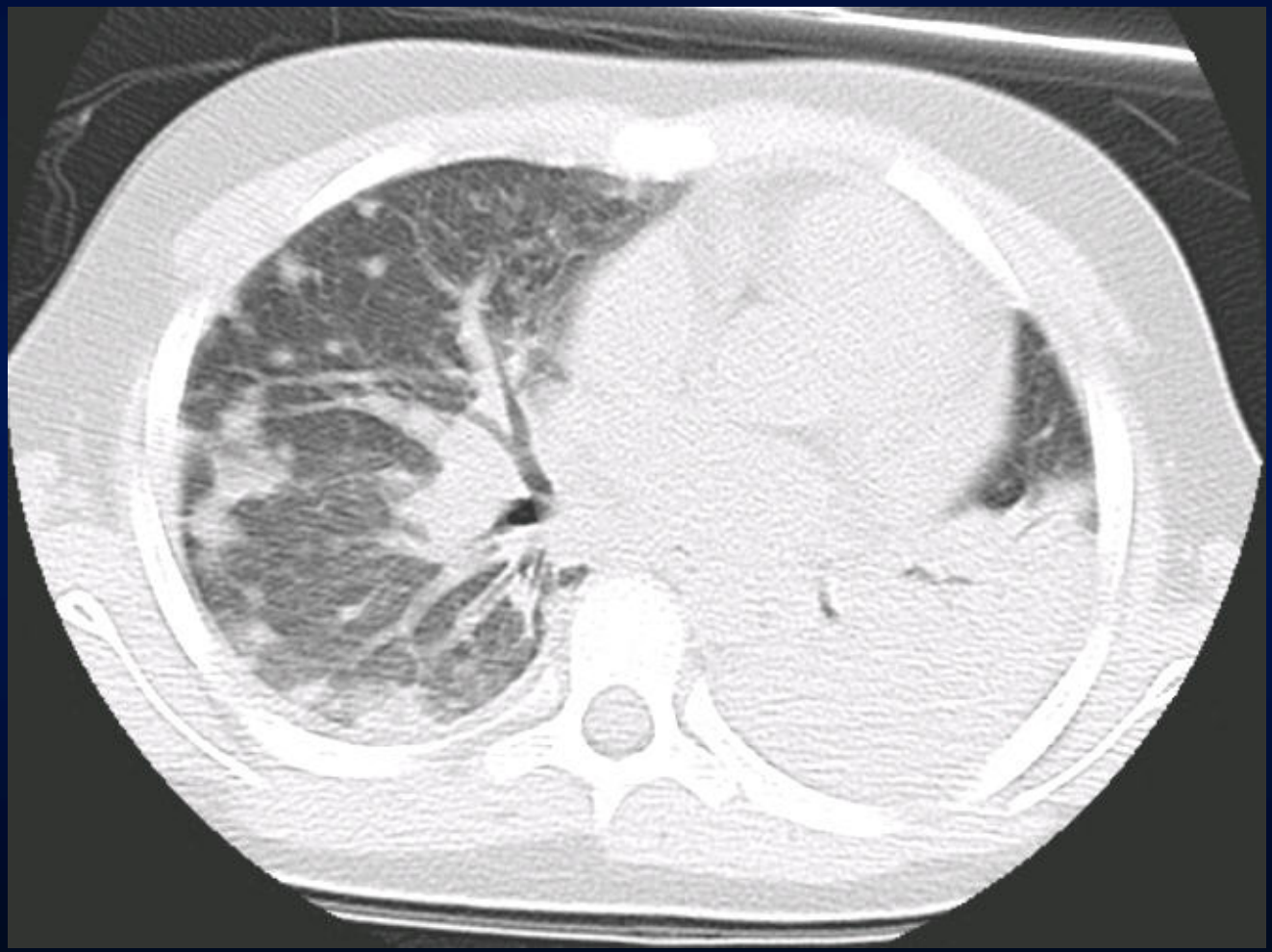


FIGURE 1

Magnetic resonance venography and computed tomography of the chest in a patient with *S aureus* osteomyelitis and VT. Image shows interruption of flow in the right femoral vein. This patient had a femoral-popliteal thrombosis and multiple septic emboli shown on the computed tomography scan. He required the insertion of an inferior vena cava filter.

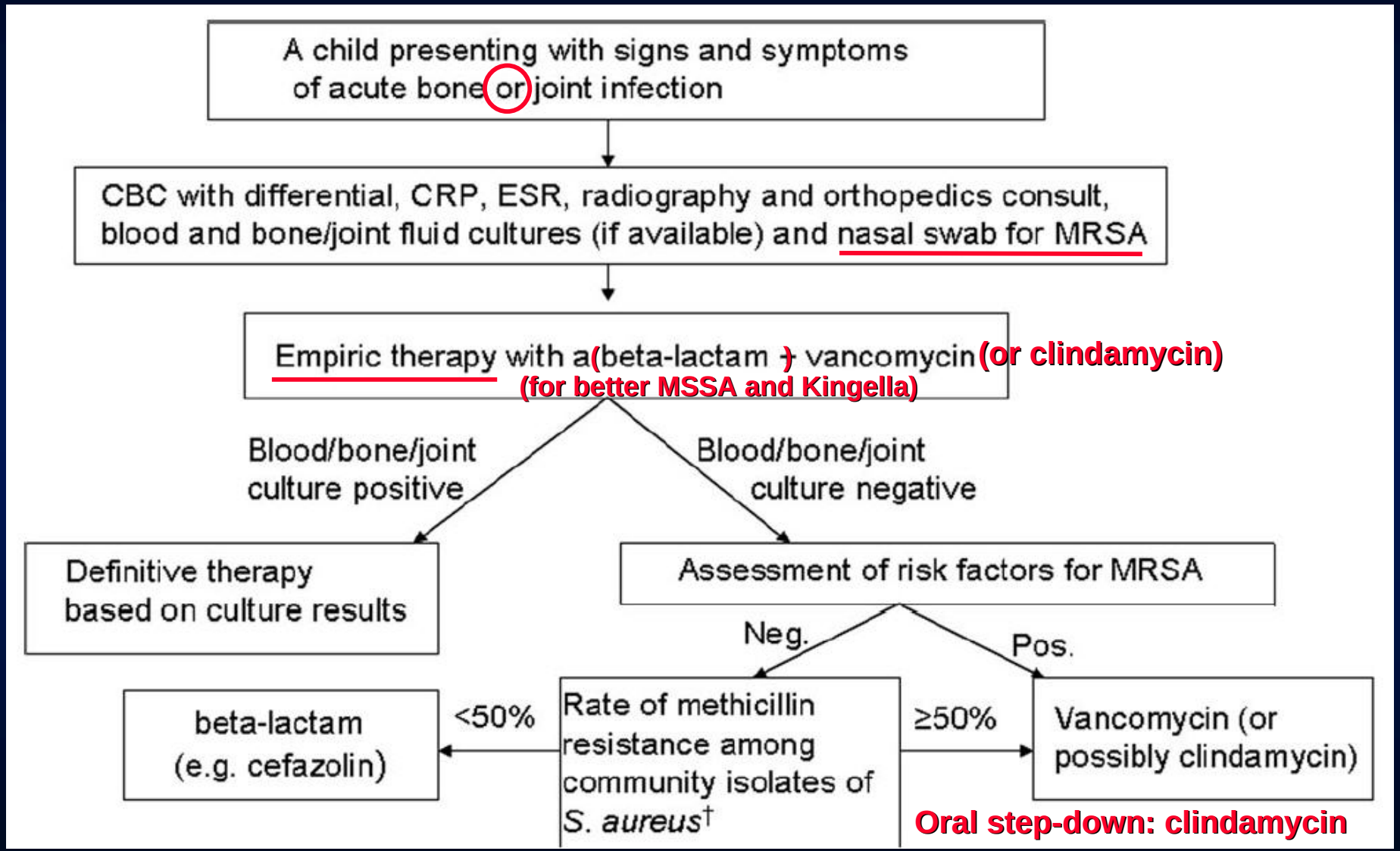
Gonzalez B et al. 2006 Pediatr. Thromboembolic Complications of MRSA

Empiric Therapy:
Consider Thromboembolic Complications of Disseminated CA-MRSA



Rady Children's Hospital, San Diego, CA

Empiric Therapy for Osteoaraticular Infections



Joshi AY et al. PIDJ 2008 Mayo Clinic, MN

The Issue: *Staphylococcus aureus*

- Other empiric therapy options (allergy):
  - Daptomycin is approved for adults for skin/skin structure infxns and bacteremia-endocarditis, but inactivated by lung surfactant, and is CONTRAindicated for pneumonia
  - Linezolid is active, ‘static; but bone marrow toxicity a problem after 14 days of Rx
  - Combination therapy?

Liu C et al. Clinical Practice Guidelines By The Infectious Diseases Society of America for the Treatment of Methicillin-resistant *Staphylococcus aureus* Infections in Adults and Children. Clin Infect Dis. 2011 Feb;52(3):285-92.

Summary

- Vancomycin for severe infection (disseminated infection, hips, spine); or if in a region where susceptible: clindamycin
- Addition of nafcillin/methicillin for severe infection; likely to be more effective if MSSA is the pathogen
- Combination therapy is often used for severe infections:
  - Vancomycin plus clindamycin
  - Vancomycin plus rifampin
  - Triple therapy (concerns for antagonism)