Initial Management of Infections in the Era of Enhanced Antimicrobial Resistance

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Staphylococcus aureus Infections

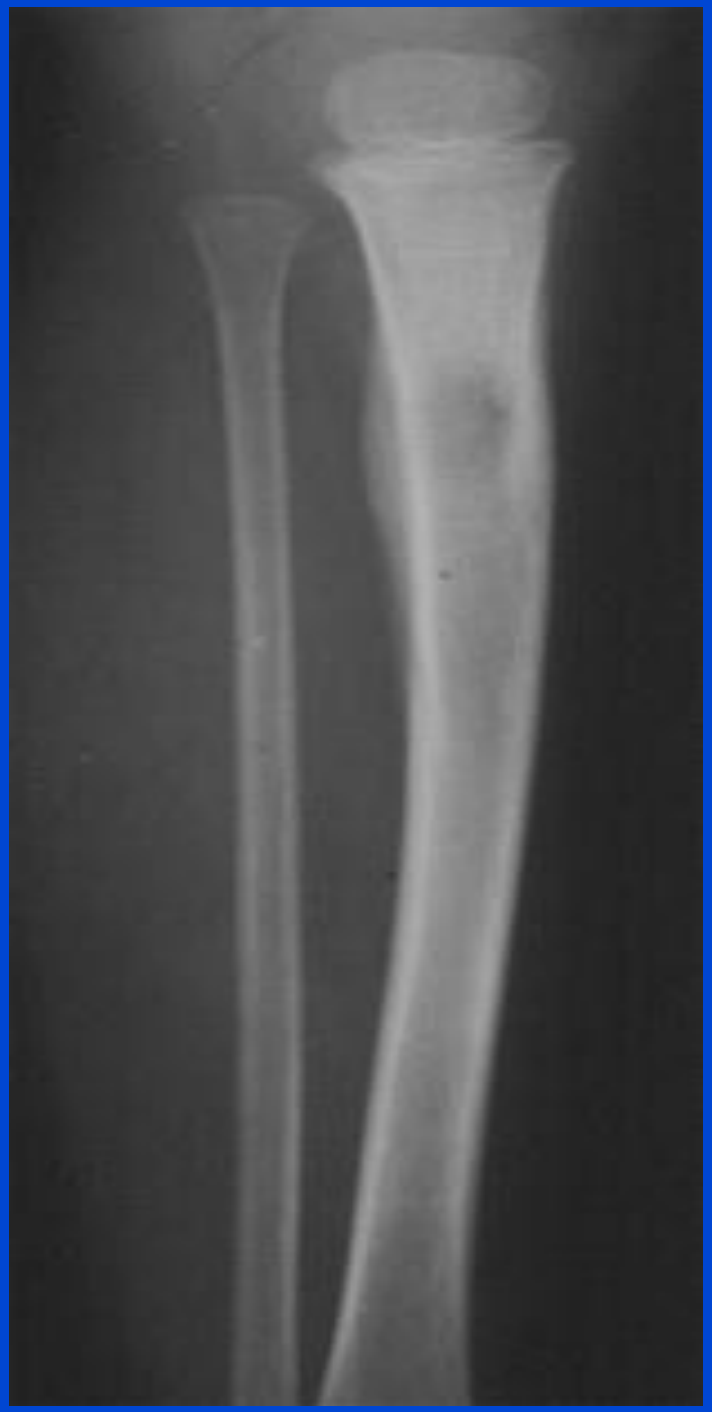
- A 8 YO boy develops fever, bone pain and a limping gait for 10 days. He was struck in the shin by a baseball two days before onset of the pain. A plain radiograph is suggestive of osteomyelitis.
- The best choice of an antibiotic is :

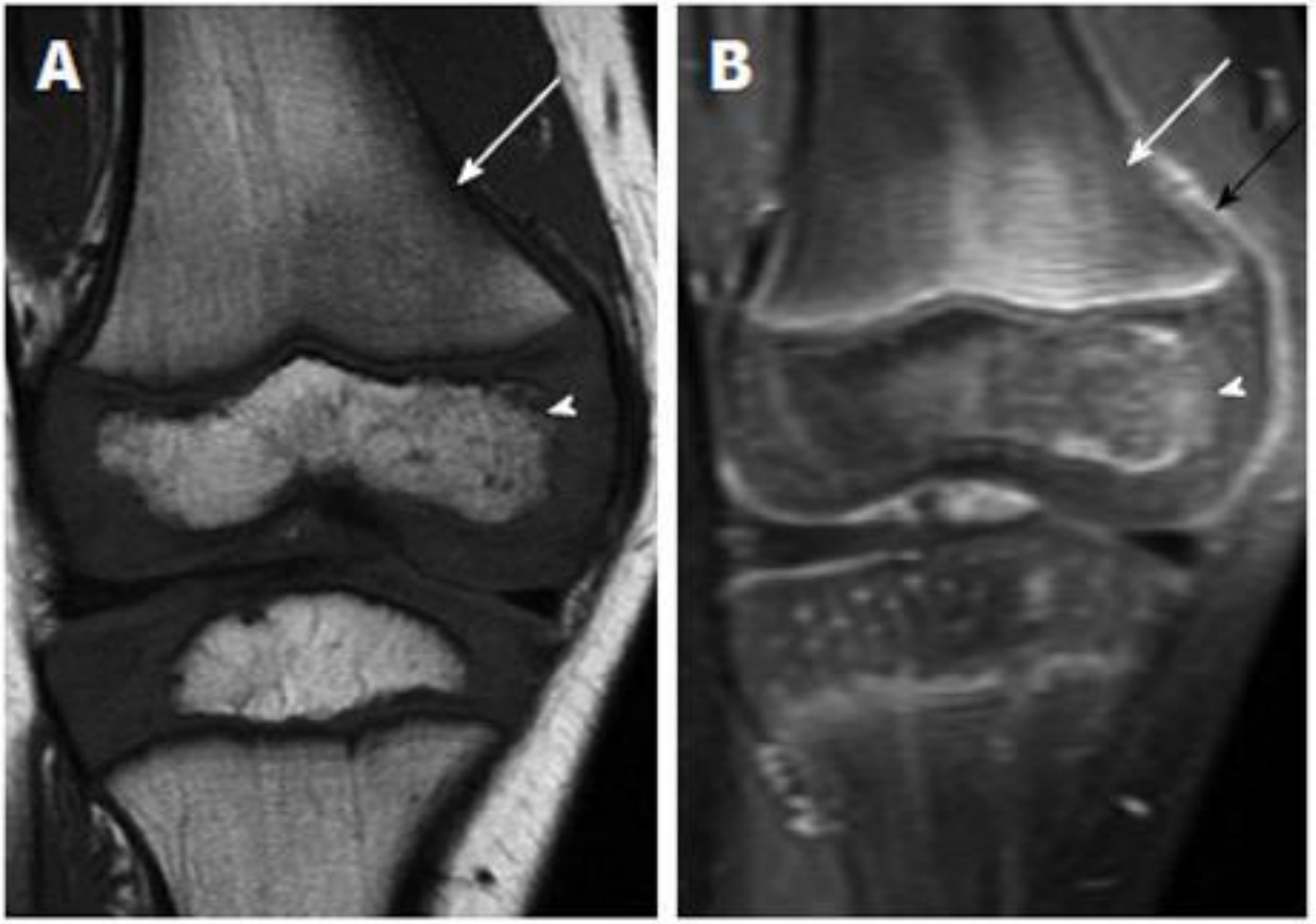
  A: Cefazolin

  B: Clindamycin

  C: Vancomycin

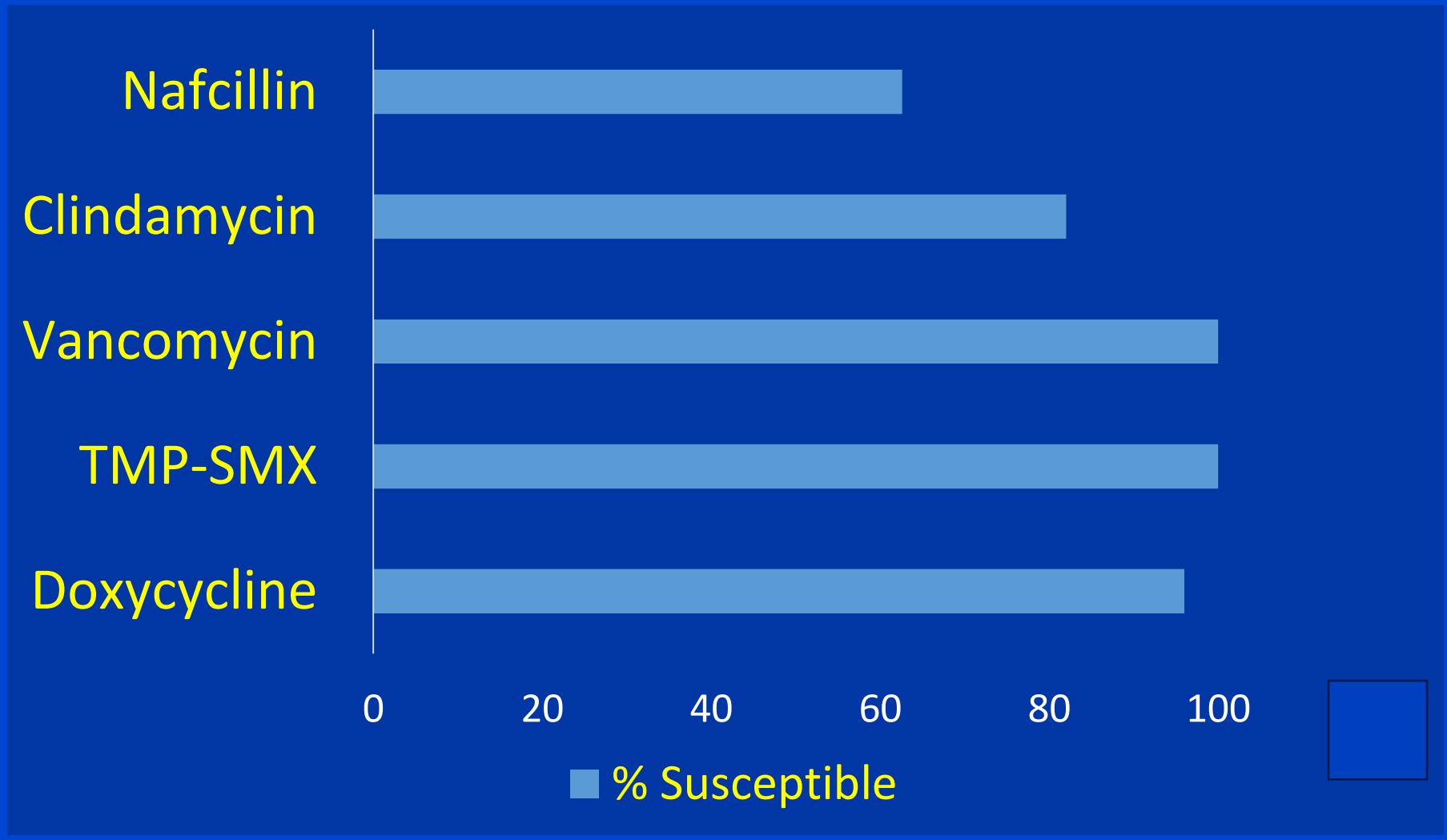
  D : Ceftriaxone





World J Radiol. Aug 28, 2014; 6(8): 530-537

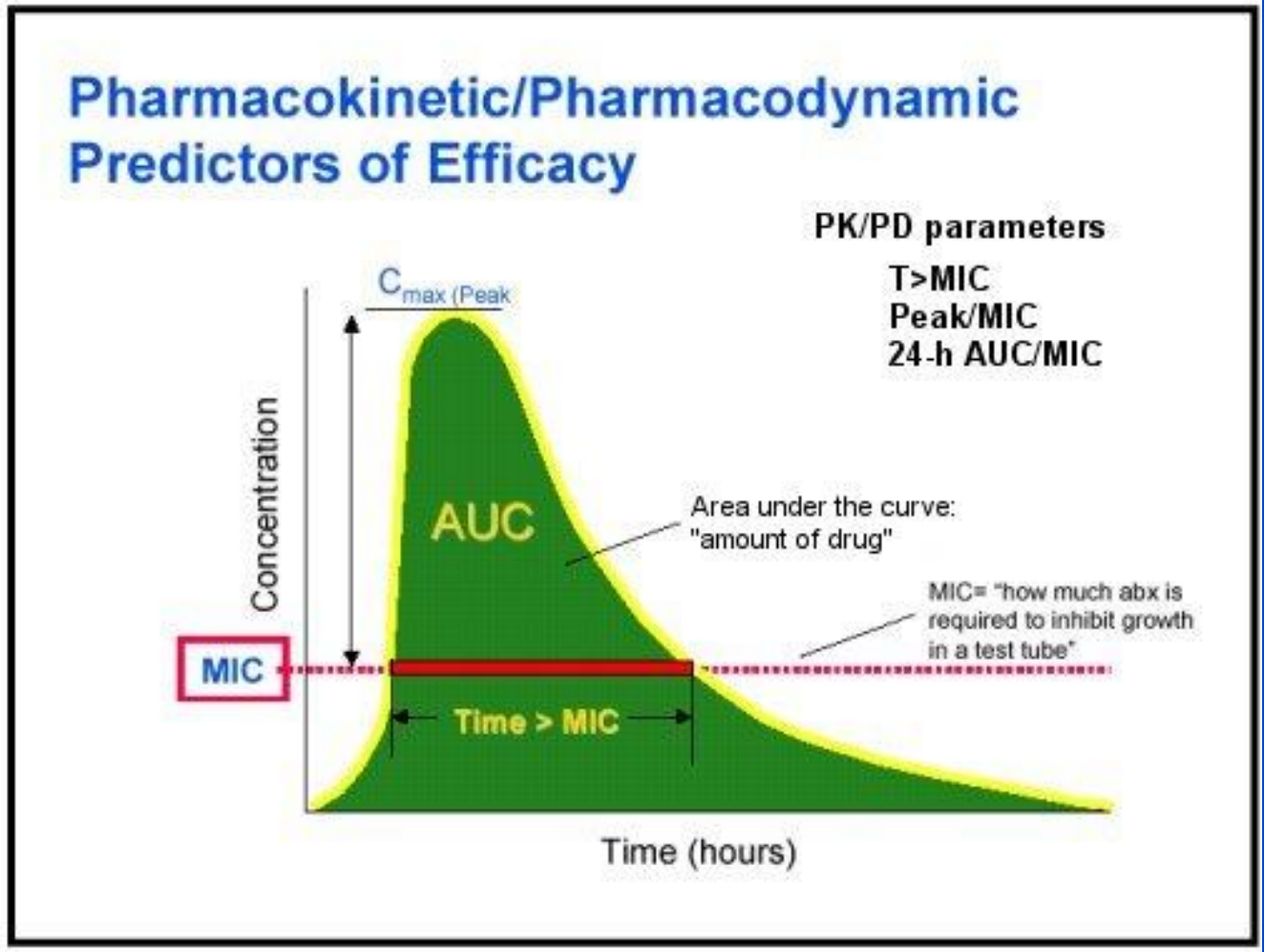
Staphylococcal Antimicrobial Susceptibilities : 2017



326 total isolates

Denise Robison, OUHSC Microbiology

What is an AUC:MIC Ratio?



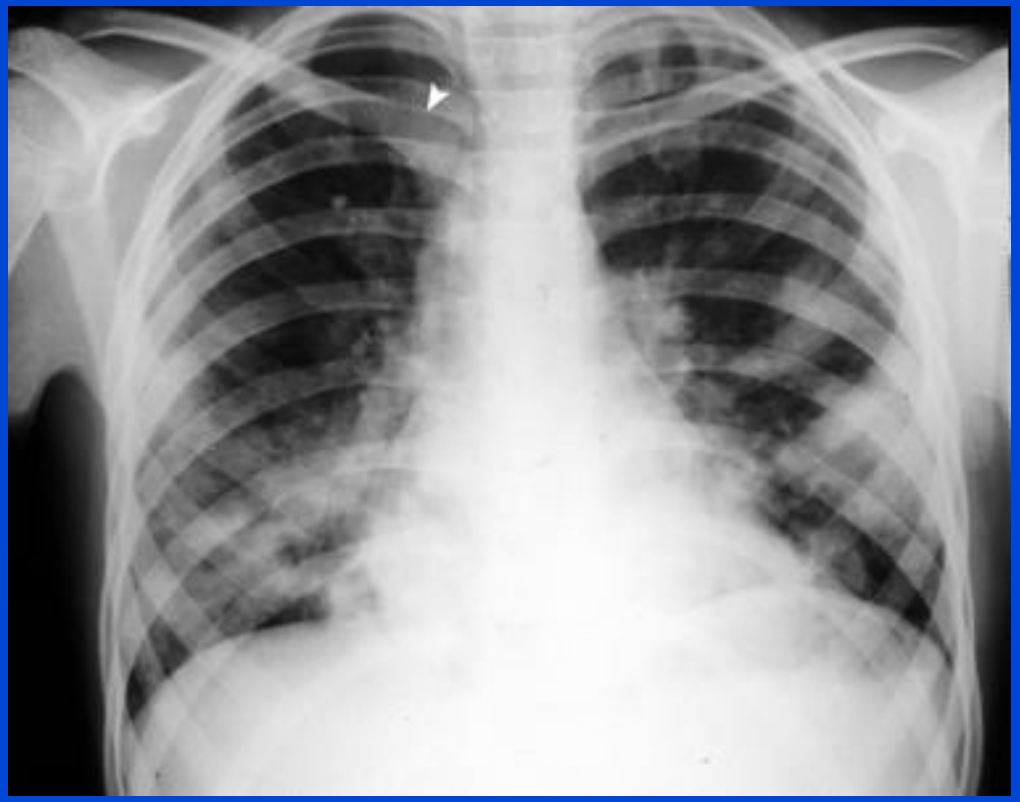
How much is enough?

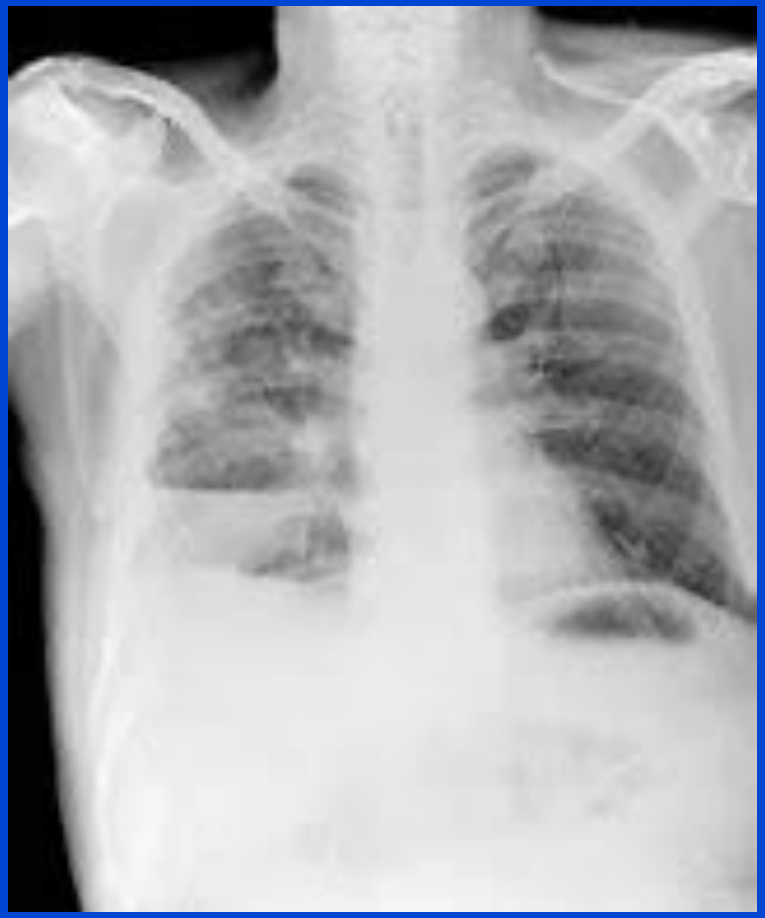
- In ex vivo models, simulated vancomycin peaks of 40, 20, 10 and 5 mg/L showed no difference in killing of Staph
- Irrelevance of peaks suggests killing is not concentration-dependent
- In ventilator-associated staph pneumonia, AUC:MIC ratios of $\geq$ 345 predicted good clinical outcomes, and ratios > 850 with good microbiological outcomes
- AUC:MIC ratios are not easily calculated
- Trough vancomycin levels predict AUC:MIC, and correlate somewhat with outcome (needs to be studied in children)
- Revised monitoring guidelines for children should appear later in 2018

How to Monitor

- MRSA strains seem to be gaining resistance slowly
- Low trough levels (< 10) are associated with treatment failure, and probably emergence of resistance
- Trough levels of 10-15 mg/L seem adequate for MSSA infections, non-serious MRSA infections
- Serious, MRSA infections require higher levels, probably 15-20 mg/L
- These higher levels are sometimes associated with nephrotoxicity
- NSAIDs, diuretics, CT contrast, dehydration, age, illness increase nephrotoxicity

Staphylococcal Pneumonia





Negative NP Swabs Accurately Rule Out Staphylococcal Pneumonia*

Test Characteristic	Result	95% CI
Sensitivity	88.0%	67.6% - 96.9%
Specificity	90.1%	86.6% - 92.8%
Positive Predictive Value	35.4%	24.0% - 48.7%
Negative Predictive Value	99.2%	97.4% - 99.8%
Positive Likelihood Ratio	8.9	6.4 - 12.3
Negative Likelihood Ratio	0.1	0.05 - 0.39

*Diagnosis based on recovery of staph in sputum, tracheal aspirates, BAL fluid

Dangerfield, Antimicrob Agents Chemotherapy: 2013

Summary : Staphylococcal Infections

Vancomycin is the recommended initial treatment of serious infections likely caused by staph aureus

Trough levels before 4th dose should be 15-20 mg/L for serious infections likely caused by MRSA

Initial dose (age 1-18 years) should be 20 mg/kg/24 divided Q6H

If the infecting strain is susceptible to clindamycin, most patients should be switched immediately

Adding clindamycin to suppress production of toxins only helps in toxin-mediated diseases

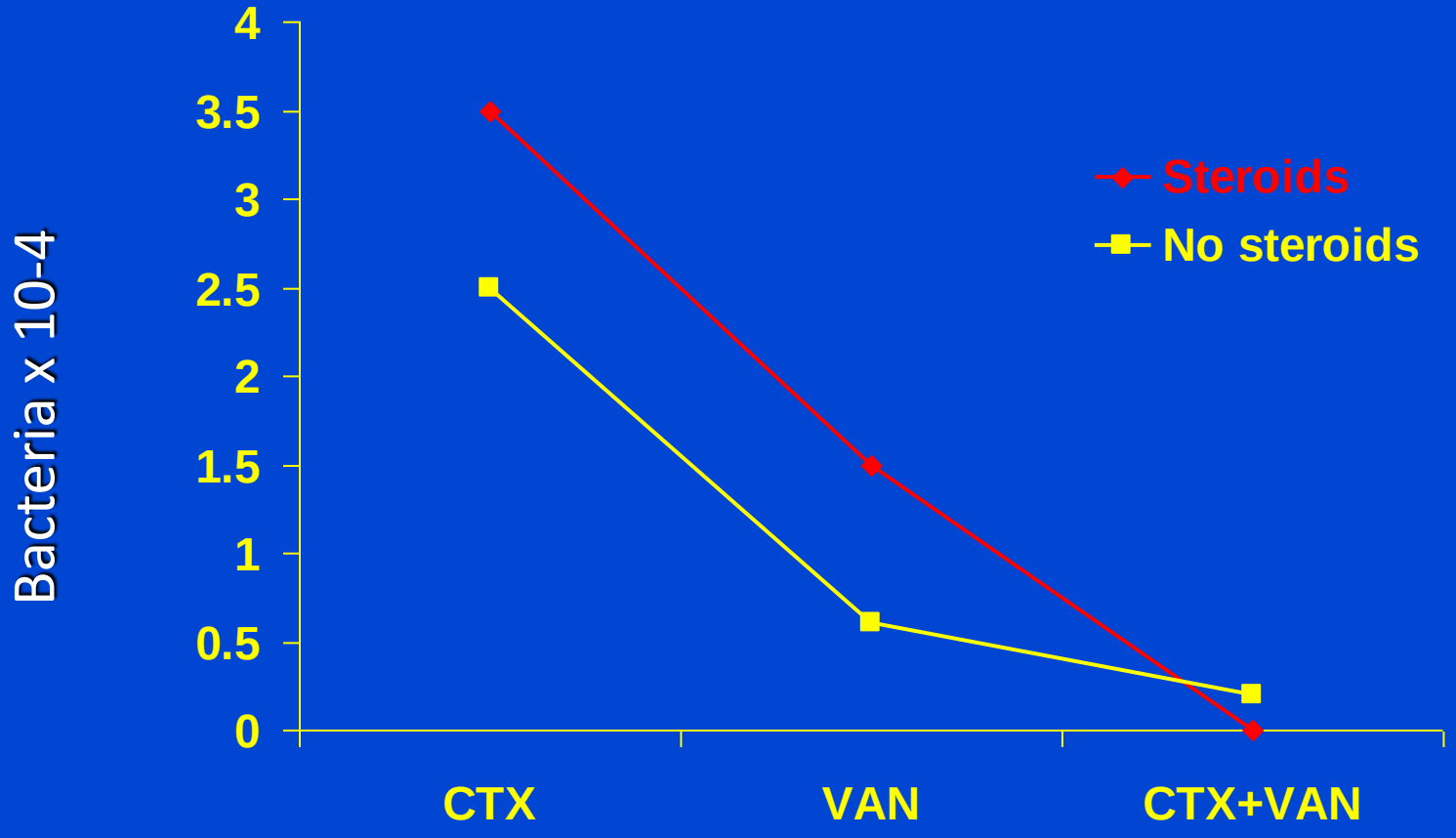
New management guidelines are reportedly forthcoming

Drug-Resistant *Streptococcus Pneumoniae*

Case

- A 2 YO child develops 40^{o}C fever and cough.
- A chest radiograph shows a dense lobar infiltrate, with no suggestion of a lung abscess or pleural effusion.
- A blood culture grows *S. pneumoniae*.
- The lab reports an MIC of 4 mcg/mL to both penicillin and ceftriaxone.
- The best choice of antibiotics is probably:
  - Ampicillin/amoxicillin
  - Unasyn/augmentin
  - Ceftriaxone/cefdinir
  - Vancomycin

Viable Bacteria in CSF After Antibiotics



Summary : Pneumococcal Infections

- Prevalence of pneumococcal resistance to PCN and ceftriaxone is 0-3% for most body sites
- Resistance can be overcome by use of higher drug dose (90 mg/kg/24 for otitis)
- Resistance is mediated by alterations of PCN-binding proteins, not beta-lactamases
- Pneumococci are resistant to PCN (31%) and ceftriaxone (17%) at concentrations achievable in the CNS
- Use of vancomycin/ceftriaxone overcomes resistance in CNS

Extended Spectrum ß-Lactamases

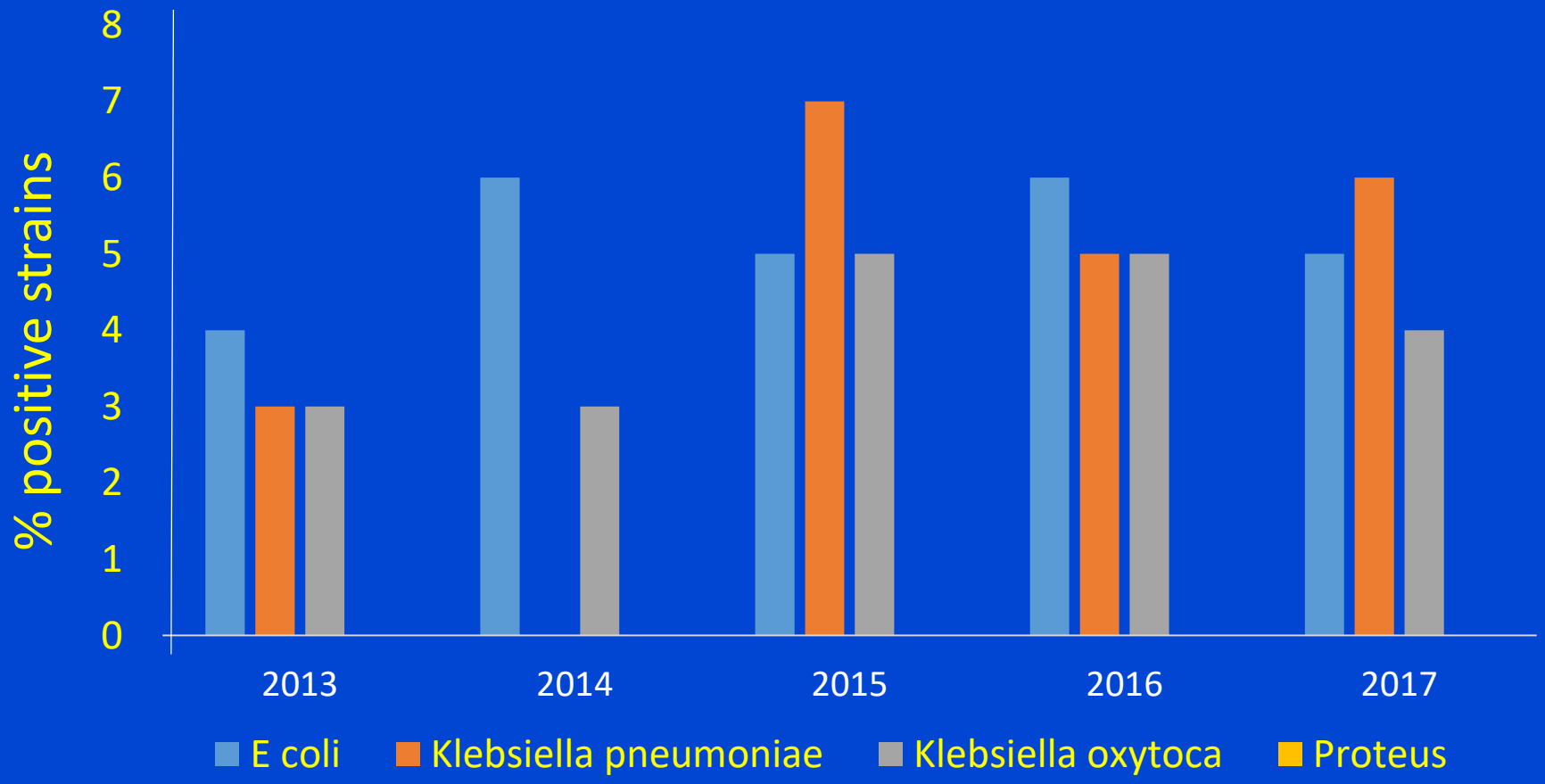
Creation of an OUHSC "Superbug"

- 5 YO girl develops a CNS shunt infection
- Culture persistently grew pseudomonas, susceptible to: cefepime, zosyn, aminoglycosides, meropenem
- Negative cultures with removal of EVD, meropenem
- Tracheal aspirate 19 days later (still on therapy) grew pseudomonas: resistant to cefepime, zosyn, meropenem

ESBL-Producing Bacteria

- Many bacteria (Staph aureus, Hemophilus, Moraxella, Bacteroides, GNR) produce restricted beta-lactamases
- GNR now produce ESBLs, Amp-C, that lyse 3rd generation cephalosporins, code for resistance to other antibiotics
- At Children's Hospital, 6% of E coli, 5-7% of *Klebsiella pneumoniae* produce ESBLs
- ESBL production is induced *while still on therapy*
- Treatment failure occurs in approximately 10% of cases

Extended Spectrum ß-Lactamase Producing Strains : OUHSC, 2013-2017



Risk Factors for Presence of ESBL-Positive Species

Feature	ESBL-positive E coli (%)	ESBL-negative E coli (%)	Probability
Health-care acquired	51.9	19.4	< .001
Male	35.2	20.4	.015
Cephalosporins	16.7	3.7	.002
PCN derivatives	7.4	0.9	.017
Fluoroquinolones	18.5	1.9	< .001

Age, co-morbidities, underlying medical conditions, illness severity were not associated factors

Kang J Clin Micro 2012 (published online)

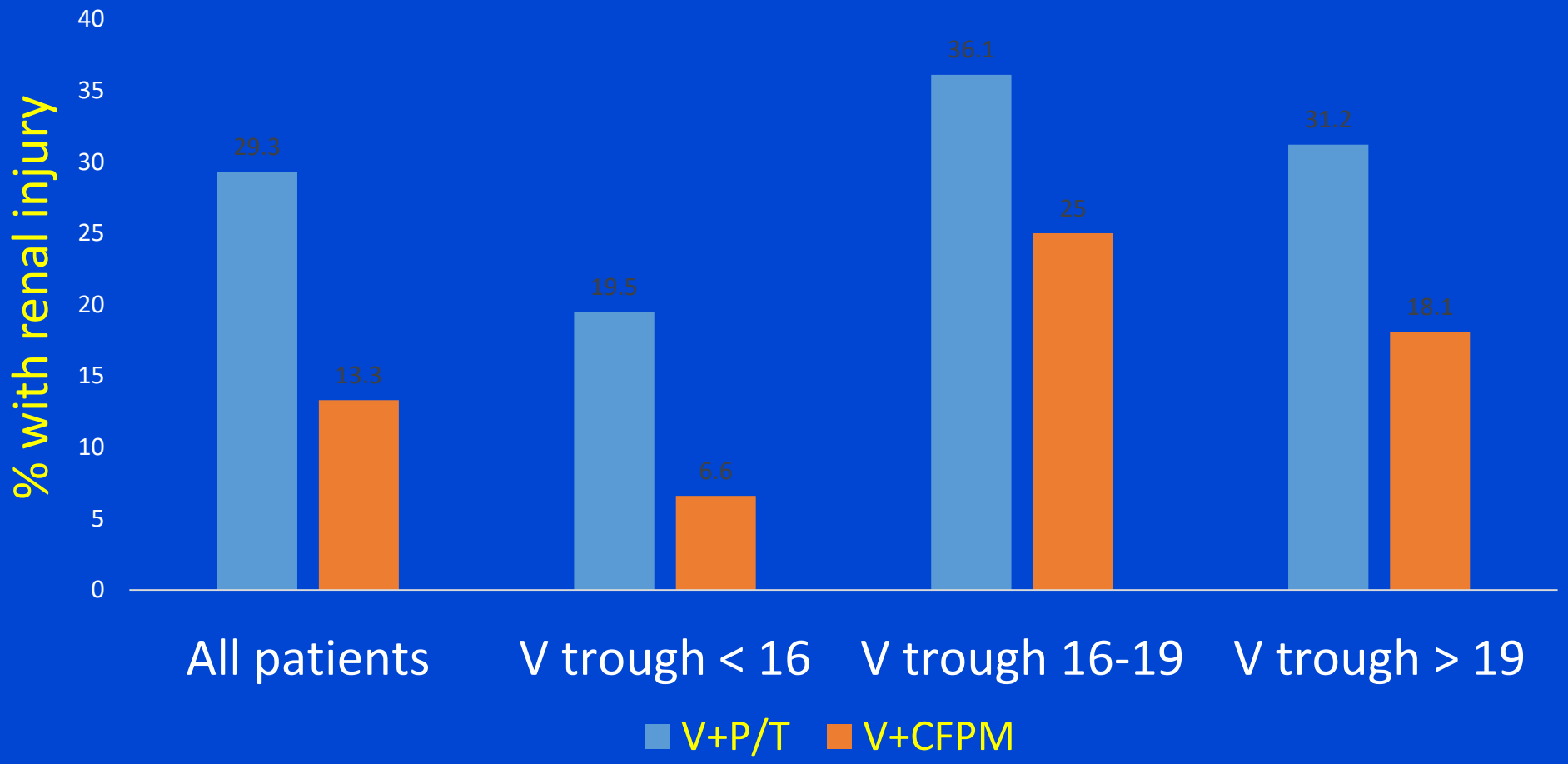
Clinical Score Predicting ESBL Infection

Predictor	OR	Point score
Male gender	1.53	2
Age ≥ 55	1.5	2
Healthcare associated infection	3.21	6
Hospital-acquired infection	2.28	4
Sepsis	1.79	3
Prolonged hospitalization	1.88	3
History of previous ESBL infection	7.88	10
3rd generation cephalosporin within 3 months	12.92	13
Other antibiotics within 3 months	2.14	4

Score ≥ 12 = high risk; ≤ 8 = low risk

Bassetti : Curr Opin Infect Dis 2016

Possible Renal Injury With Vancomycin/Zosyn



Moenster, Clin Micro Infection: 2014

Management : ESBL-producing Bacteria

- ESBL, AmpC hydrolase strains are slowly increasing in frequency here
- In controlled studies, outcomes are slightly better when meropenem is used intially, in comparison to any other antibiotic
- If an infecting species develops resistance to meropenem, there is generally no safe, effective fall back option
- Zosyn is the preferred drug for most infections possibly caused by ESBL+ strains

Management II: ESBL-Producing Bacteria

- Patients in septic shock where survival is questionable may receive meropenem briefly until the infecting organism is identified
- Patients on vancomycin and zosyn combinations should be monitored for renal injury
- Urinary tract infections respond well, because of high antibiotic concentrations
- With the possible exceptions of pneumonia, neutropenia, one drug is as effective as multiple drugs once susceptibilities are known, and patient stabilized

Prospects for ESBL Therapy

- Carbapenems in high doses
- Carbapenem plus aminoglycoside combinations
- Prolonged carapenem infusions (> 50% of time above MIC)
- Double carbapenem
  - One drug binds beta-lactamase
  - One drug kills bacteria
- Ceftazidime/avibactam (lung, abdomen, urinary infections)
- Ceftolazone/tazobactam (abdomen and urinary infections)

Urinary Tract Infections

A 17-year old female outpatient presents with a history of frequency, urgency and dysuria for the past ten days. She is afebrile and has no other symptoms or physical findings. Microscopic examination of the urine reveals many white cells and many rod forms. The most appropriate choice of antibiotics probably would be (more than one answer may be almost correct) :

- Intravenous ampicillin
- Oral TMP-SMX
- Oral nitrofurantoin (furadantin or macrodantin)
- Parenteral gentamicin
- Oral cefdinir

Susceptibilities of 522 Urinary *E coli* Isolates

Antibiotic	% Susceptible
Amikacin	99
Ampicillin, ampicillin/sulbactam	46-53
Cefdinir	91
Ceftriaxone	95
Gentamicin	91
Meropenem	100
Nitrofurantoin	99
Piperacillin/tazobactam	98
TMP/SMX	70

Data from Leigh Peek, PharmD

Summary : UTIs

- Bactrim and cefdinir are the best oral antibiotic choices for outpatient, uncomplicated UTIs
- Success rates with oral antibiotics exceed those predicted by MIC's, because of higher urinary concentrations
- Most patients with pyelonephritis should be hospitalized
- Initial antibiotic therapy of pyelonephritis could be ceftriaxone, unless the patient has had multiple courses of antibiotics and/or multiple pyelonephritis episodes

Fluoroquinolones in 2018

- Quinolones are easy to use, have good activity against Gram-positives (not MRSA), mycoplasma, many Gram-negatives including pseudomonas and some ESBL + strains
- Enter prostatic tissues more readily than other antibiotics
- Quinolones are the only oral drugs effective against pseudomonas
- Initial fears of arthropathy in children are unfounded
- FDA notes increasing reports of tendon injuries, other arthropathies, QT prolongation, psychiatric disturbances, hypoglycemia, aortic aneurysm dissections
- FDA recommends use of quinolones only when no other antibiotic is active