Understanding antibiotic use in *Staphylococcus* sepsis

Short Course in Critical Infection
06/11/2023

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Conflict of interest

- Nil to declare

Outline

Introduction	Epidemiology
	Relation between carriage and infection
Treatment:	PSSA
	MSSA
	MRSA

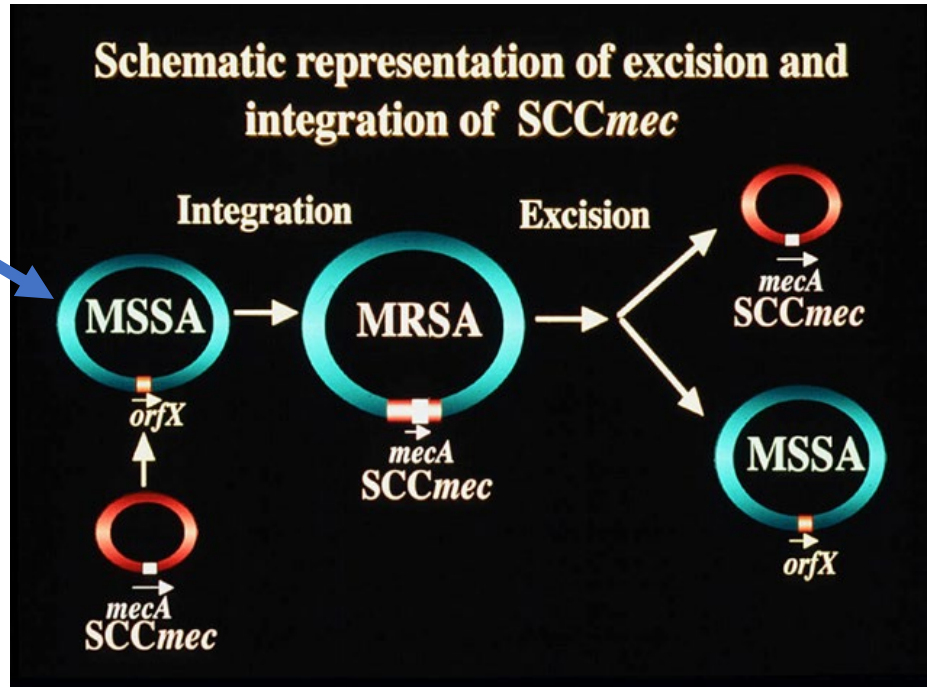
Staphylococcus toxic shock syndrome

Staphylococci

- ***S. aureus***
  - Penicillin-susceptible *S. aureus* (PSSA)
  - Methicillin-susceptible *S. aureus* (MSSA)
  - Methicillin-resistant *S. aureus* (MRSA)
- **Coagulase-negative Staphylococcus**
  - *S. lugdunensis*
    - Behaves like and treated like MSSA
  - Others, such as *S. epidermidis*
    - Some (some strains of CoNS) remain susceptible to flucloxacillin/cefazolin.
    - Rarely susceptible to penicillin
- **Diseases**
  - Bacteraemia
  - Toxic shock syndrome (*S. aureus*)

PSSA

blaZ gene



(IWG-SCC). Source: https://www.sccmec.org/index.php/en/

Infants (age <1 year)
Peak colonisation at
1 month (50-60%)

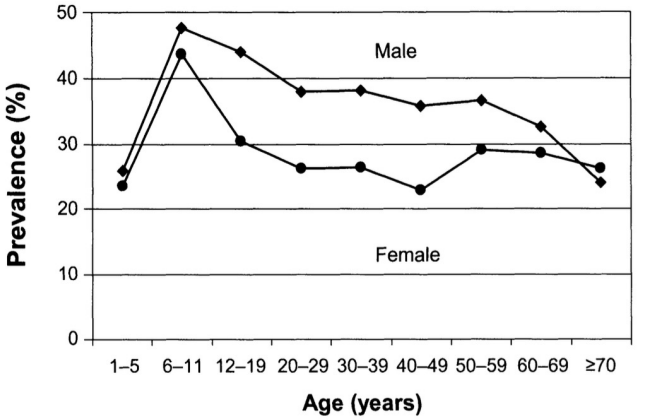
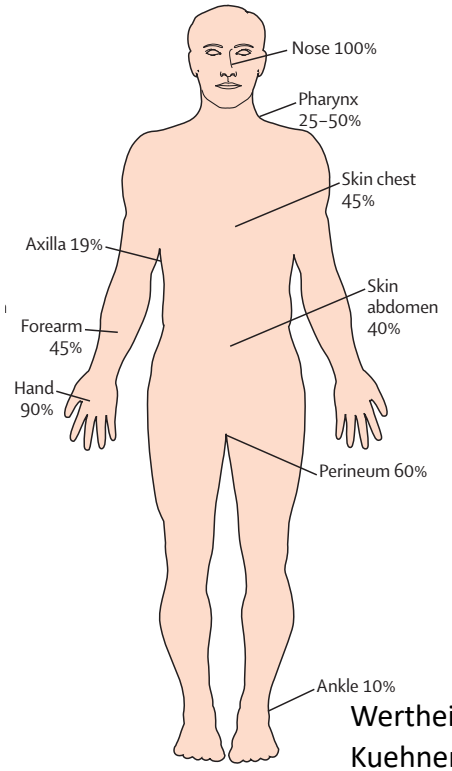


Figure 1. Prevalence of *Staphylococcus aureus* nasal colonization, by age and sex—National Health and Nutrition Examination Survey, 2001–2002.

S. aureus colonisation

- Anterior nares (most common site of colonisation)
  - Exclusive throat or rectal carriage can also occur
- Three carrier types
  - **Persistent** carriers (20% adult population)
  - **Intermittent** carriers (30%)
  - **Non-carriers** (50%)
- Most are colonised with MSSA
  - 30% MSSA, 0.8% MRSA (2001/02, USA gen. pop.)



Wertheim et al, Lancet ID 2005 (PMID: 16310147)
Kuehnert et al, JID 2006 (PMID: 16362880)

There is a direct correlation between *S. aureus* colonisation and infection

- Colonisation ==> infection
  - ~90% isolates match
  - MSSA ≥ 3-fold risk vs. non-carrier
  - MRSA ~20-fold risk vs. non-carrier

Von Eiff et al, NEJM 2001 (PMID: 11136954)
Wertheim et al, Lancet 2005 (PMID: 15325835)
Marzec et al, AJIC 2016 (PMID: 27038392)

- **Not colonized ≠ infection**

- MSSA colonized –> MSSA infection
- MRSA colonized –> MRSA infection

- **Chance of MRSA infection is unlikely if the MRSA screening was negative during the index hospitalization**

Epidemiology

S. aureus is the most common cause of bacteraemia

<u>% MRSA amongst *S. aureus* in blood culture varies by region/countries</u>

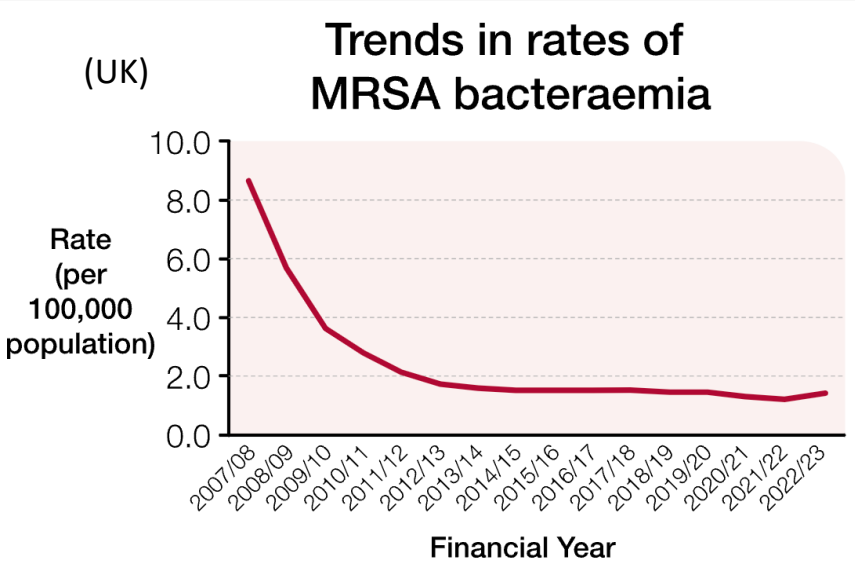
In Australian in 2021: MRSA (17%)

Greece, Romania = MRSA (40%)

Norway, Netherlands, Iceland = MRSA (1-2%)

TABLE 3 Rank order of pathogens causing bloodstream infection worldwide submitted to the SENTRY Program, 1997–2016, by age group

	Pathogen (%) for patients aged:					
Rank	<1 yr	1–5 yrs	6–18 yrs	19–49 yrs	50–64 yrs	>64 yrs
1	*S. aureus* (16.4)	*S. aureus* (15.9)	*S. aureus* (26.4)	*S. aureus* (24.9)	*S. aureus* (23.1)	*E. coli* (26.6)
2	*E. coli* (13.7)	*S. pneumoniae* (11.4)	*E. coli* (12.6)	*E. coli* (18.1)	*E. coli* (19.9)	*S. aureus* (20.1)
3	*K. pneumoniae* (8.6)	*E. coli* (9.2)	*P. aeruginosa* (6.6)	*K. pneumoniae* (7.3)	*K. pneumoniae* (8.6)	*K. pneumoniae* (8.0)
4	*E. faecalis* (6.9)	*K. pneumoniae* (7.9)	*K. pneumoniae* (6.5)	*P. aeruginosa* (5.4)	*P. aeruginosa* (5.9)	*E. faecalis* (5.9)
5	*S. epidermidis* (6.3)	*P. aeruginosa* (5.7)	*S. epidermidis* (5.1)	*E. faecalis* (4.8)	*E. faecalis* (5.3)	*P. aeruginosa* (5.4)



PSSA

Pre-penicillin: 100% *S. aureus* were PSSA

By 1960's: most *S. aureus* were penicillin-resistant (~10% remained susceptible to penicillin)

Since ~2015: PSSA has increased, **now 20-25% *S. aureus* are PSSA**

SENTRY (1997-2016) data: AAC 2019 (PMID: 31010862)
Coombs et al, CDI 2022 (PMID: 36529133)
UK Health Security Agency, 2022/23 data
Rountree et al, MJA 1978 (PMID: 152838)
Coombs et al, Microorganisms 2022 (PMID: 36014068)

S. aureus – a deadly bacteria

- Bundaberg tragedy (27 Jan 1928)
  - 18 out of 21 children became seriously ill within 7 hours following diphtheria immunisation with fever, vomiting, diarrhoea, seizure, loss of consciousness
  - **12 children died within 24 hours (aged 2 -7 years)**
  - ***S aureus* sepsis (toxic shock syndrome) due to contaminated diphtheria toxin-antitoxin vials**
  - **Penicillin discovered 1929; clinical use 1945**

DIPHTHERIA INOCULATION RESULTS IN TWELVE DEATHS.

BUNDABERG TRAGEDY.

FATAL INJECTIONS.

TERRIBLE BLOW TO PARENTS.

AGONISING SCENES.

ANGUISH OF BEREAVED PARENTS.

WHOLE FAMILY WIPED OUT.

TRAGIC LOSS.

AWFUL BLOW.

WHOLE FAMILY LOST.

PARENTS' ORDEAL.

UNFORGETTABLE SCENES.

THE CAUSE.

SEVERAL POSSIBILITIES.

DOCTOR'S STORY.

NO CHANGE IN METHOD.

DUE TO POISON.

STATEMENT BY DR. SCHMIDT.

NOT WRONG SERUM.

"ABNORMAL."

OFFICIAL STATEMENT.

3 DEAD.

SEVEN ILL.

TRAGEDY AT TORRENS CREEK.

BURNT OUT.

THREE BUSINESS HOUSES

FORTY KILLED.

TRAIN PLUNGES INTO RIVER.

SNOW STORM.

SEVERAL DEATHS.

A HOT WEEKEND.

THE REWARD.

EMPIRE PROSPERITY.

NEW ERA OPENING.

JOB CONTROL.

MURADA HELD UP.

BERRIMA DELAYED.

CHILD KILLED.

PLAGUE.

AT HYDERABAD.

100 DEATHS A DAY.

TO ENGLAND.

AFRICAN CONTRACT.

ANZAC MOUNTED.

THE DESERT CAMPAIGN.

MAN KILLED.

SIX PERSONS INJURED.

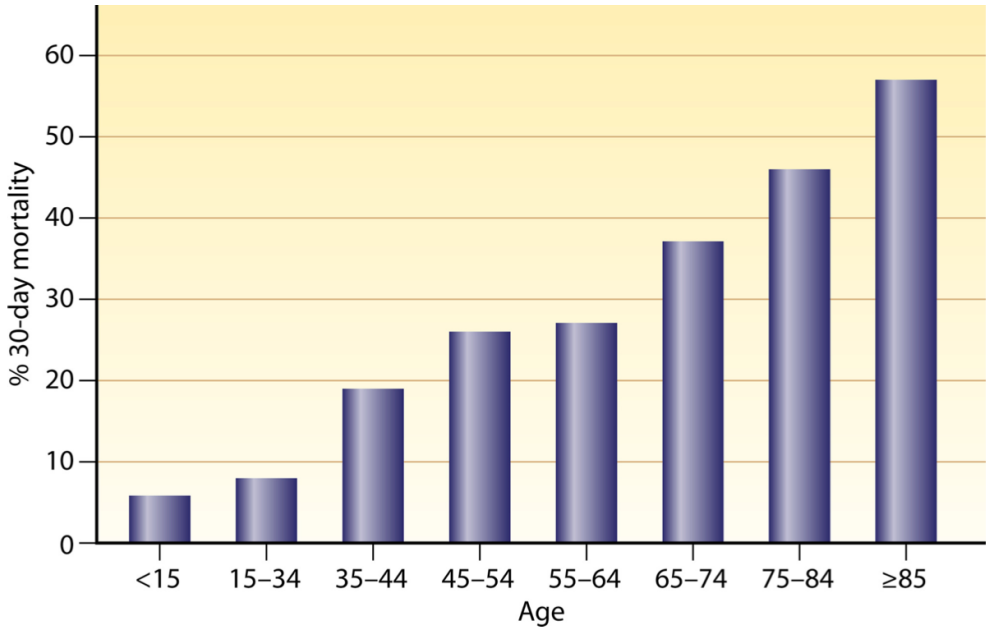
Brisbane Courier (1928)

Rountree, MJA1978 (PMID: 152838)

S. aureus bacteraemia is almost always fatal without an antibiotic treatment

Antibiotic	Mortality	Ref
Pre-penicillin	80-90%	Lancet 1960 (PMID: 13831996)
Penicillin	~25%	AMA AIM 1954 (PMID: 13180039)
1950's (erythromycin, chloramphenicol, tetracycline, streptomycin)	40-60%	AJM 1957 (PMID: 13402795); Lancet 1959 (PMID: 13631970)
Methicillin	~25%	NEJM 1962 (PMID: 13860546)
Vanomcycin	~25%	NEJM 1960 (PMID: 14409280); CMI 2022 ((PMID: 35339678)

Higher mortality with increasing age (despite tx)



Van Hal, CMR 2012 (PMID: 22491776)

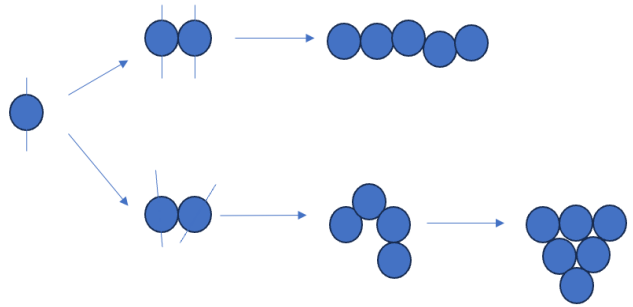
Even today: Mortality is 16-20% at one month, and 22- 33% at three months

Bai et al, CMI 2022 (PMID: 35339678)
Includes studies published since 2011

Treatment: *Staphylococcus aureus* bacteraemia

Lab notification of a positive blood culture result

- Gram-positive cocci in clusters --> *Staphylococcus* species
- Approach
  - Assess patient – is the clinical picture consistent with an infection?
    - NO: **wait** for further identification
    - YES: repeat blood culture and start anti-staphylococcal antibiotic
    - If already known bacteraemia: How many days since the effective antibiotic? –> identify and treat source
- Which antibiotic?
  - 17% *S. aureus* are MRSA
    - Recent negative MRSA screening swab makes MRSA infection unlikely
    - Nil MRSA risk factors (if swab not available) – less likely MRSA
  - Coagulase-negative Staphylococci – a common contaminant!



- Usually within 3-4 hours, micro lab can provide a definitive answer

mec gene	*fem/nuc* gene	Staphylococci
Negative	Positive	MSSA/PSSA
Positive	Positive	MRSA
Positive	Negative	Coag. neg *Staphylococcus*

- Further confirmation and antimicrobial susceptibility expected within 24-48 hours
- If automated system reports penicillin-resistant, taken as “Penicillin-resistant”
- If reports penicillin-susceptible, further testing is done to confirm this, i.e., “truly penicillin-susceptible” (Henderson et al, JAC 2023, PMID: 37071589)

Penicillin-susceptible: PSSA bacteraemia –> treatment

Staphylococcus aureus	
Penicillin	S
Flucloxacillin	S
Cefazolin	S
Vancomycin	S

- Treatment options:
  - Benzylpenicillin 1.8g q4h
  - Flucloxacillin 2g q6h
  - Cefazolin 2g q8h

- If penicillin susceptible, why not use penicillin?
  - Potential advantages of penicillin
    - Lower MIC distribution for penicillin compared with other active β-lactam agents
    - Higher free non-protein bound plasma drug concentration

Henderson et al, IJAA 2019 (PMID: 31181352)

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Benzylpenicillin versus flucloxacillin for penicillin-susceptible *Staphylococcus aureus* bloodstream infections from a large retrospective cohort study

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Table 1
Comparison of variables for patients treated with benzylpenicillin compared with flucloxacillin[a]

Variable	Benzylpenicillin ($N = 315$)	Flucloxacillin ($N = 600$)	*P*-value
Outcomes			
Median LOS (days)	23	23	0.59
7-day mortality	5 (1.6)	41 (6.8)	<0.001
30-day mortality	33 (10.5)	85 (14.2)	0.11

Table 3
Propensity-score-adjusted analysis of 30-day mortality

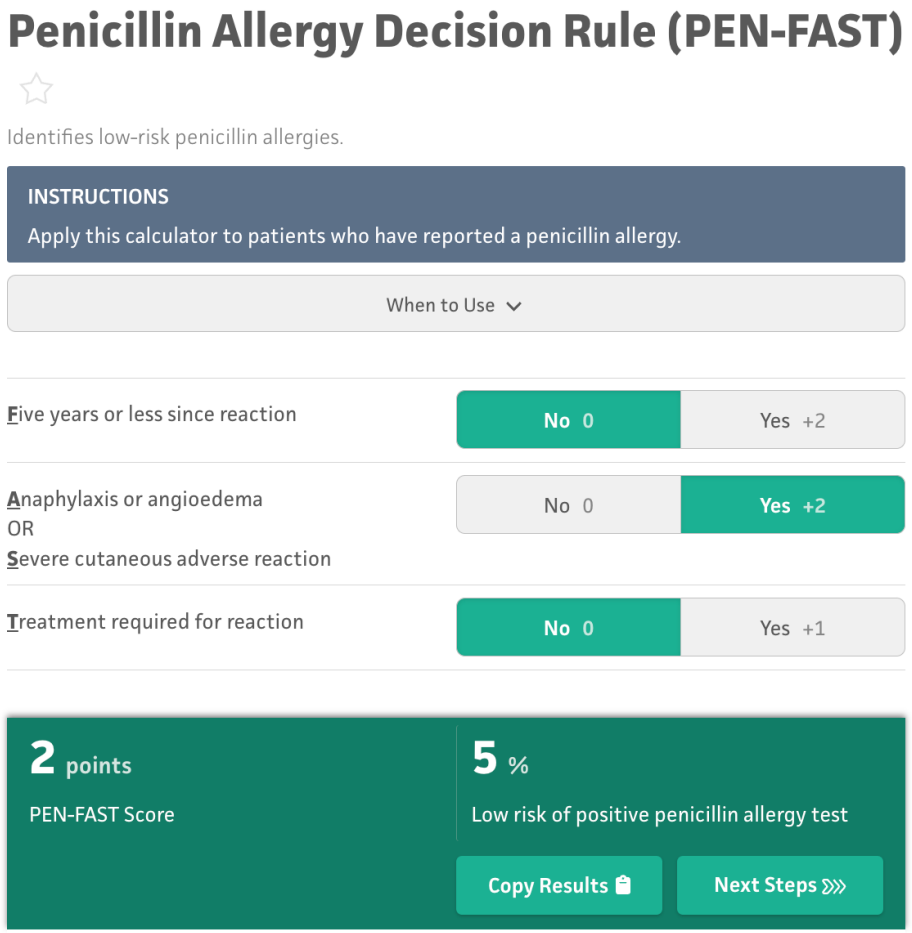
Variable	OR (95% CI)	*P*-value
Treatment with flucloxacillin	1.06 (1.01–1.1)	0.03

A large RCT is currently actively recruiting (SNAP trial)

“Penicillin allergy”

- Up to 10% of patients report allergy to penicillin
  - 95% do not have a true allergy

- <u>PEN-FAST score of 2 or less</u>
  - Safe to proceed with direct oral challenge (equivalent to skin testing)
  - PO 250mg amoxicillin
  - Monitor for 2 hour (rash, urticaria, diffuse erythema, angioedema, decreased SpO2, or anaphylaxis)
  - If nil adverse reaction, directly de-label penicillin allergy



MD calculator (Trubiano et al)

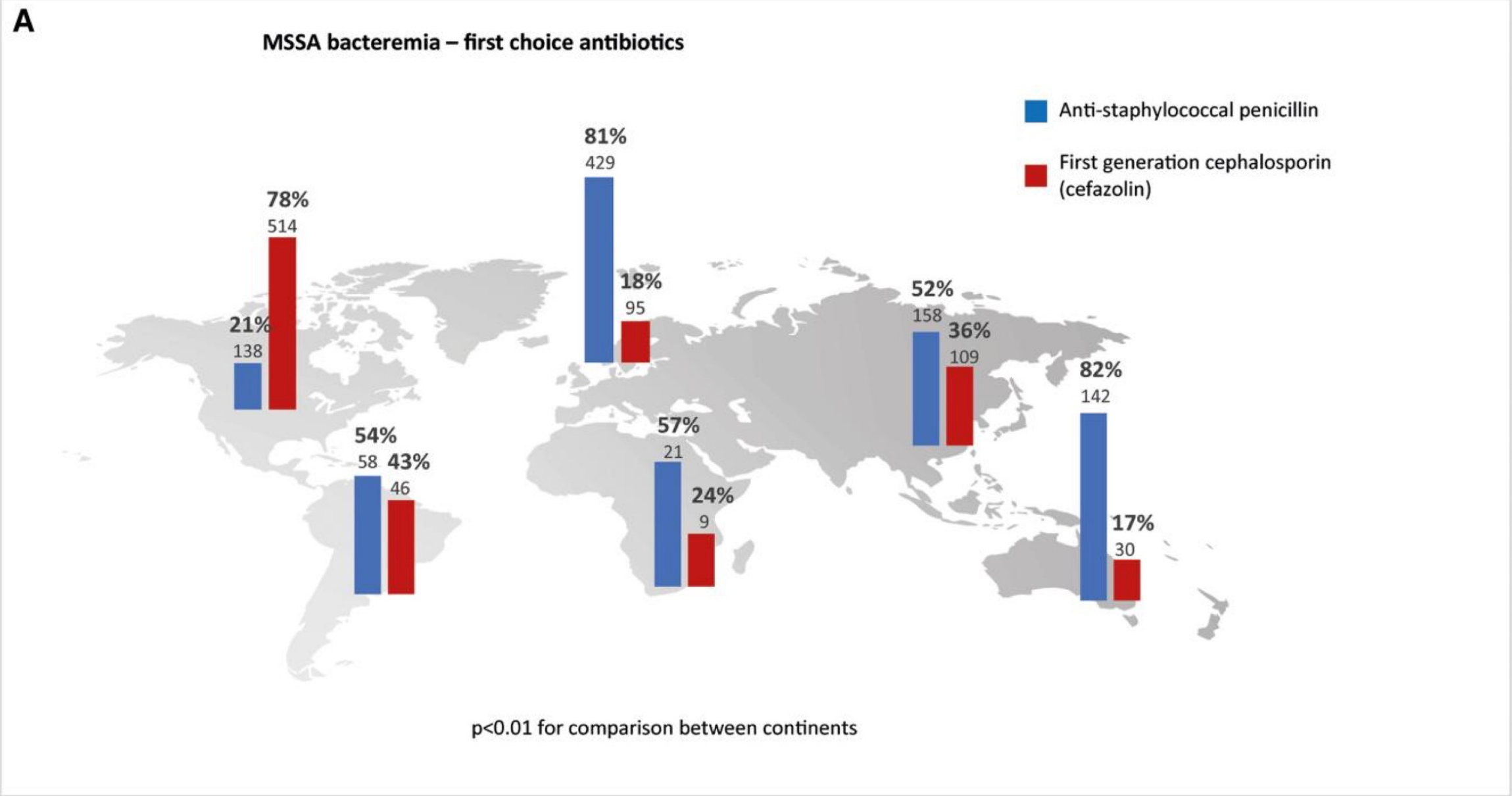
Copaescu and Trubiano et al, JAMA int med 2023 (PMID: 37459086)

Methicillin-susceptible: MSSA bacteraemia –> treatment

Staphylococcus aureus	
Penicillin	R
Flucloxacillin	S
Cefazolin	S
Vancomycin	S

- Treatment options:
  - Flucloxacillin 2g q6h
  - Cefazolin 2g q8h

- Which is better? Flucloxacillin or cephazolin
  - Flucloxacillin -> higher odds of nephrotoxicity, liver toxicity, and allergic reactions
  - Cefazolin -> Inoculum effect, hence potential treatment failure
    - A significant increase in the minimal inhibitory concentration of an antibiotic when the number of organisms inoculated is increased (PMID: 25000230, PMID: 29977970)

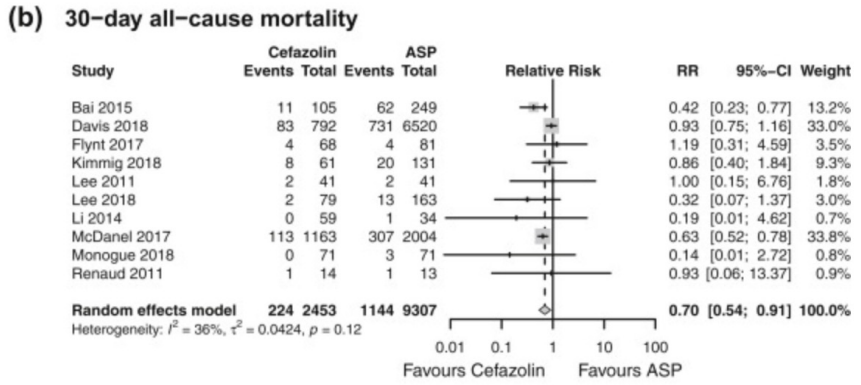


Survey: 2031 physicians from 71 different countries on 6 continents

Westgeest et al, CID 2023 (PMID: 37310693)

MSSA bacteraemia –> treatment

- Flucloxacillin or cefazolin?
  - No difference in 30-day mortality (large Australian retrospective cohort study, 7312 episodes of SAB, fluclox (90%), cefazolin (10%) - PMID: 29499317
  - **2019 systematic review - PMID: 30928559**
    - **Lower 30-day mortality with cefazolin (RR 0.70 (95% CI 0.54 - 0.91)) and less nephrotoxicity (RR 0.36 (95% CI 0.21 - 0.59))**
    - **Low quality evidence: Non-randomised studies**
- What about other β-lactams (non-fluclox/non-cefazolin) in the treatment of MSSA BSI
  - There are no RCTs – observational studies have shown mixed results
    - Used from the start or for completion of treatment after the clearance of BC
    - **Ceftriaxone versus SOC: 30-day mortality: Non-inferior** - PMID: 35326838
      - Systematic review of retrospective cohort studies



Cephazolin vs. flucloxacillin PMID: 30928559

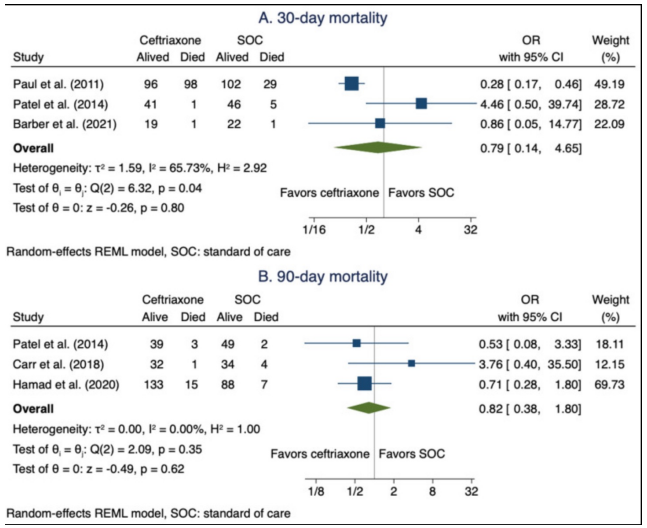


Figure 3 Meta-analysis of 30-day mortality (**A**) and 90-day mortality (**B**).

Ceftriaxone vs. SOC PMID: 35326838

MSSA bacteraemia –> treatment (2nd line, 3rd line…)

Vancomycin: NO NO

- Several cohort studies have reported poor outcomes with vancomycin treatment of MSSA BSI
- Increased mortality, prolonged bacteraemia, higher relapse (2-3 higher risk with vancomycin) - PMID: 22011388, PMID: 17664322, PMID: 23985343
- If penicillin allergic –> PEN-FAST assessment
- Use daptomycin if cannot use flucloxacillin or cefazolin (see below)

Other Antibiotics:

- **Daptomycin**: Non-inferior to SOC (40% MRSA, 60% MSSA): Total 245 patients - NEJM 2006; PMID: 16914701
- **Linezolid:** Non-inferior to vancomycin in catheter related SAB (44% MRSA, 56% MSSA): Total 142 patients - PMID: 19072714
- Newer cephalosporins: **Ceftobiprole** – non-inferior to daptomycin: Total 390 patients (26% MRSA, 74% MSSA) - NEJM 2023, PMID: 37754204

Salvage treatment for persistent bacteraemia (>3-4 days of bacteraemia despite source control or occult source)

- Daptomycin + ceftaroline combination: PMID: 30858203

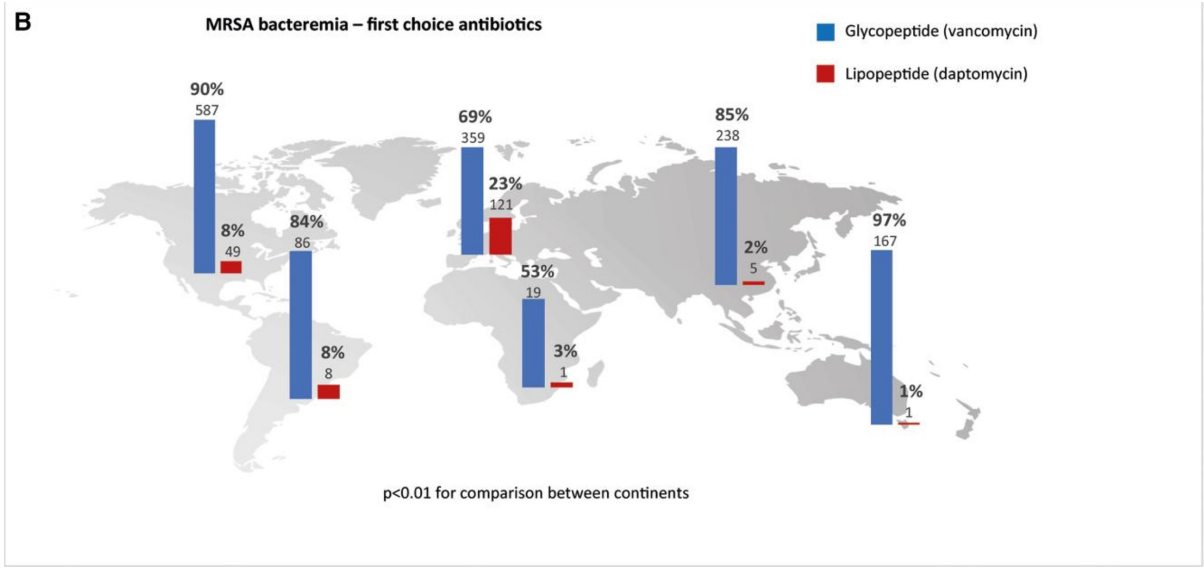
A large RCT is currently underway: flucloxacillin versus cefazolin (SNAP trial)

Methicillin-resistant: MRSA bacteraemia –> treatment

Staphylococcus aureus	
Penicillin	R
Flucloxacillin	R
Cefazolin	R
Vancomycin	S

- Current treatment of choice is **vancomycin**

- But is vancomycin the best antibiotic?
  - Higher failure in MSSA bacteraemia
  - Need drug level monitoring
    - Trough measurement versus AUC/MIC monitoring
  - Newer anti-MRSA therapies are available: Linezolid, daptomycin, ceftaroline, ceftobiprole



Survey: 2031 physicians from 71 different countries on 6 continents

Westgeest et al, CID 2023 (PMID: 37310693)

Vancomycin level monitoring

- Vancomycin has dose-related nephrotoxicity.
  - High trough (>20): Nephrotoxicity
  - Low trough (<15 if serious infections): Treatment failure

- Previously recommended trough target of 15-20mg/**L was never the real target** but a surrogate for true target of AUC/MIC of >400

- More recent evidence suggests many patients can achieve a goal AUC/MIC with troughs less than 15 mg/L.

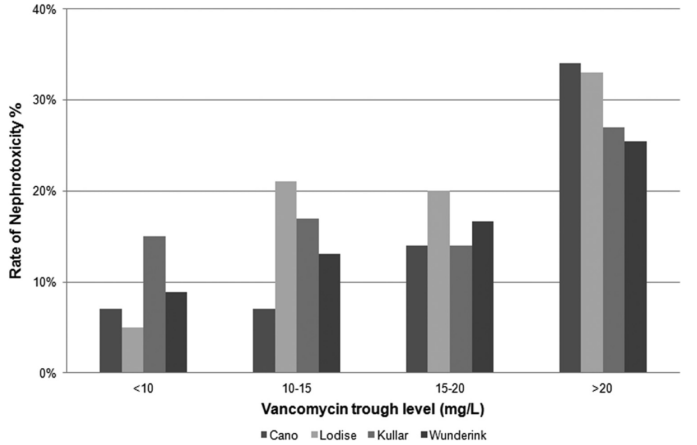


FIG 3 Incidence of vancomycin nephrotoxicity with rising trough levels (8, 22, 36, 50).

Van hal et al AAC 2013, PMID: 23165462

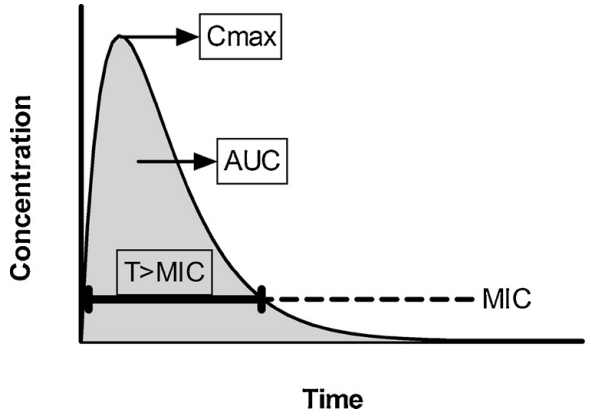


Fig. 2. Concentration-time curve showing the pharmacokinetic parameters C_{max} (maximal concentration) and AUC (shaded area) and the PK/PD index Time > MIC.

Pharma Research 2018 (PMID: 30033398)

Rybak et al, AJHP 2020 (PMID: 32191793)
Tsutsuura et al, BMC 2021 (PMID: 33549035)

Vancomycin level monitoring

- **AUC/MIC** target: **400-600** μg x hr/mL or mg x hr/L
  - Lower risk of nephrotoxicity
  - Statistical trend towards better treatment success
- Can collect a random level –> software programs use Bayesian modelling to determine AUC/MIC and provide recommendation for subsequent dosing
- AUC/MIC recommended in serious MRSA infections, critically ill patients, with underlying renal impairment, or at risk of nephrotoxicity
- Limitations:
  - Difficult to attain the target AUC/MIC if vancomycin MIC is >1
  - Needs some expertise/experience to perform the calculations
  - Use in dialysis patients

Rybak et al, AJHP 2020 (PMID: 32191793)

MRSA bacteraemia –> treatment

- Newer antibiotics:
  - **Linezolid:** non-inferior to vancomycin in catheter-associated MRSA BSI (63 patients with MRSA) – **earlier slide**
  - **Daptomycin: n**on-inferior to vancomycin (89 patients with MRSA) – **earlier slide**
  - **Ceftobiprole**: non-inferior to daptomycin (101 patients with MRSA) – **earlier slide**

- Salvage therapy for persistent MRSA bacteraemia – like in MSSA
  - Daptomycin plus ceftaroline combination

- Other considerations: β-lactams plus vancomycin. CAMERA-2 RCT (Tong et al, JAMA 2020 PMID: 32044943)
  - Flucloxacillin +vancomycin: better bacterial clearance but with added nephrotoxicity risks

- A large RCT is currently underway (SNAP trial)
  - Vancomycin+cefazolin versus vancomycin alone
  - Vancomycin versus daptomycin (future addition)

Staphylococcal toxic shock syndrome

- Can occur with PSSA, MSSA, or MRSA
  - Bacteraemic or non-bacteraemic infections
  - Well known is infection from tampon use in menstruating women
- Presentation like streptococcal toxic shock syndrome
  - Hypotension with 2 or more of following: renal impairment, coagulopathy, elevated bilirubin, ARDS, generalized rash or skin necrosis.
- **Mx (in addition to standard antibiotics)**
  - **Clindamycin 600mg IV q8h x 3 days**
  - **IVIG 2g/kg if unresponsive to fluid resuscitation**
- A large RCT is currently underway:
  - Clindamycin +/- usual care (SNAP trial)

Some *S. aureus* toxins

Haemolysins
Leucocidins (e.g., PVL)
TSST-1
Exfoliative toxins
Enterotoxins

Evidence

- Based on observational studies
- In vitro data
- Pilot RCT (CASSETTE study):

*31 patients with severe *S. aureus* infections

*Better 90-day survival in those who received clindamycin

Campbell et al JAC AR 2022, PMID: 35237755
Dotel et al, Trials 2019, PMID: 31196132

S. aureus Network Adaptive Platform (SNAP) trial

Currently recruiting (~1600 patients enrolled) – 03/11/2023
(86 active sites in 7 countries)

	Domain		
Silo	**Backbone antibiotic**	**Adjunctive antibiotic**	**Early oral switch**
PSSA	(Flu)cloxacillin vs penicillin	No clindamycin vs clindamycin	Continued IV vs early oral switch at either day 7 (uncomplicated disease) or day 14 (complicated disease)
MSSA	(Flu)cloxacillin vs cefazolin		
MRSA	(Vancomycin/ daptomycin) vs (Vancomycin/ daptomycin) + cefazolin		

MRSA: Vancomycin versus Daptomycin (future addition)

Tong et al, CID 2022 (PMID: 35717634)

Summary

- Carriage and infection
  - Invasive infection due to own carriage isolates
  - True non-carriers at low risk of developing invasive *S. aureus* infections
- PSSA
  - Now accounting for ~25% of *S. aureus* bacteraemia
  - Benzylpenicillin treatment may lead to better outcomes (a/w RCT result)
- MSSA
  - Cefazolin treatment may lead to better outcomes (a/w RCT result)
  - In penicillin-allergic patients: Calculate PEN-FAST score for penicillin allergy assessment
  - Avoid vancomycin in MSSA
- MRSA
  - Vancomycin the current standard therapy but has drawbacks
  - A/w RCT results -> role of additional cefazolin; vancomycin versus daptomycin head-to-head
- Toxic shock:
  - Adjunctive anti-toxin therapy lacks clear evidence
  - A/w RCT results -> role of adjunctive clindamycin