

(all lectures based on clinical cases with questions for the panel and audience)



# Treating MDR Gram positive endocarditis

**Prof. Pierre Tattevin**

Infectious Diseases & ICU

Pontchaillou Univ. Hosp. , Rennes, France

# Disclosures (2017-2022)

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## Scientific advisor

- MSD
- Pfizer
- Eumédica
- Correvio/Cardiome
- Shionogi
- Gilead

# Medical history #1

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## Day 1

- 63-year old man
- Type 1 diabetes, BMI  $28 \text{ kg/m}^2$
- Admitted for a 3-day course of fever and SOB
- On admission
  - ✓  $T^\circ 39.3^\circ\text{C}$ , chills
  - ✓ Blood pressure 120/70 mm Hg,  $\text{SaO}_2$  95%
  - ✓ New murmur (mitral regurgitation)
  - ✓ Crackles on lower lungs



# Medical history #1

- blood cultures (6 bottles)
- echocardiography tomorrow
- amoxicillin 12 g/d + cloxacillin 12 g/d + gentamicin 3 mg/kg/d

**Table 20** Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)<sup>a</sup>

Antibiotic	Dosage and route	Class <sup>b</sup>	Level <sup>c</sup>	Comments
<b>Community-acquired native valves or late prosthetic valves (<math>\geq 12</math> months post surgery) endocarditis</b>				
Ampicillin with (Flu)cloxacillin or oxacillin with Gentamicin <sup>d</sup>	12 g/day i.v. in 4–6 doses  12 g/day i.v. in 4–6 doses  3 mg/kg/day i.v. or i.m. in 1 dose	IIa	C	Patients with BCNIE should be treated in consultation with an ID specialist.

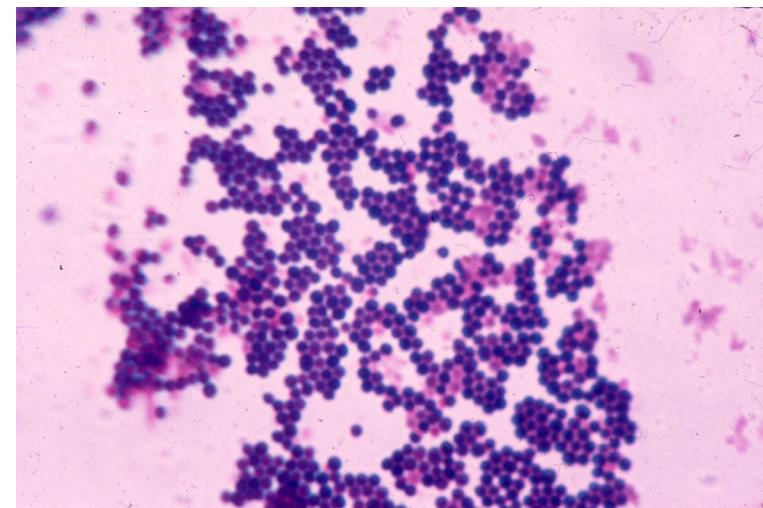
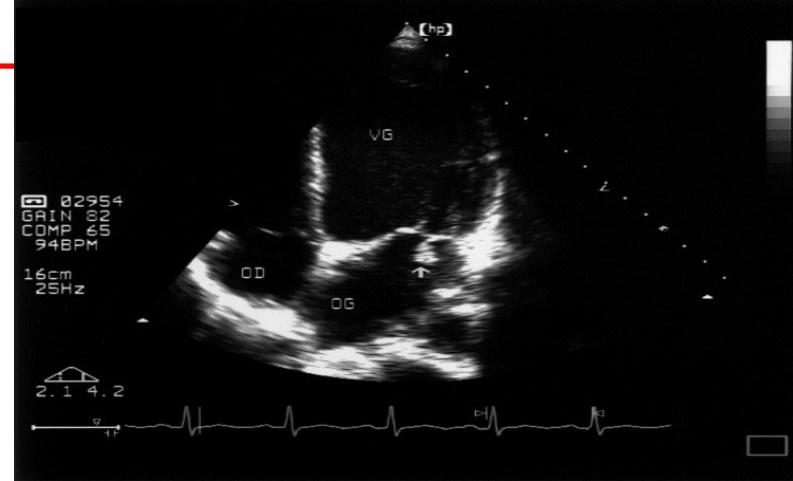
Habib G. et al Eur Heart J 2015

# Medical history #1

## Day 2

- Mitral regurgitation (moderate)
  - Left ventricular ejection fraction 50%
  - Vegetation 10 mm
- 
- BC positive (time-to-positivity, 14 h), GPC
  - PCR MecA positive

=> Vancomycin (loading dose 30 mg/kg then continuous infusion 60 mg/kg/d)



# Medical history #1

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## Day 8

- Looks slightly better, no signs of metastatic infections, but
- Persistent fever 38-38.5°C
- Day 7 BC still positive (time-to-positivity, 14 h)
- Vancomycin steady state plasma concentrations 30 mg/L
- Control TTE = no major change (TOE planned for tomorrow)

## Antibiogramme 1 SIR

Espece étudiée	Staphylococcus aureus
OXACILLINE	Résistant
ERYTHROMYCINE	Résistant
PRISTINAMYCINE	Sensible
LINEZOLIDE	Sensible
CLINDAMYCINE	Sensible
AMIKACINE	Résistant
KANAMYCINE	Résistant
TOBRAMYCINE	Sensible
GENTAMICINE	Sensible
NETILMICINE	Sensible
TETRACYCLINE	Sensible
CIPROFLOXACINE	Résistant
FOSFOMYCINE	Sensible
COTRIMOXAZOLE	Sensible
AC FUSIDIQUE	Sensible

## HEMOCULTURE

nat. du prélèvement	Sang périphérique
Flacon H	H1
Date du PVT	03/02/2017
Heure du PVT	23h30
Code à barres aéro	449293535956
Code à barres ana	446580848417
Culture aérobie	positive
Heure incubation AE	14

## CMI ATB

bactérie AE étudiée

ATB n°1 :

CMI n°1

Sensible selon CASFM 2016.

ATB n°2 :

CMI n°2

Sensible selon CASFM 2016.

ATB n°3 :

CMI n°3

Sensible selon CASFM 2016.

Staphylococcus aureus

Vancomycine

0,750

Teicoplanine

0,500

Daptomycine

0,250

## CMI ATB

bactérie AE étudiée

ATB n°1 :

CMI n°1

Sensible selon EUCAST-CASFM 2016.

ATB n°2 :

CMI n°2

Sensible selon EUCAST-CASFM 2016.

Staphylococcus aureus

Ceftaroline

0,500

Céftobiprole

0,750

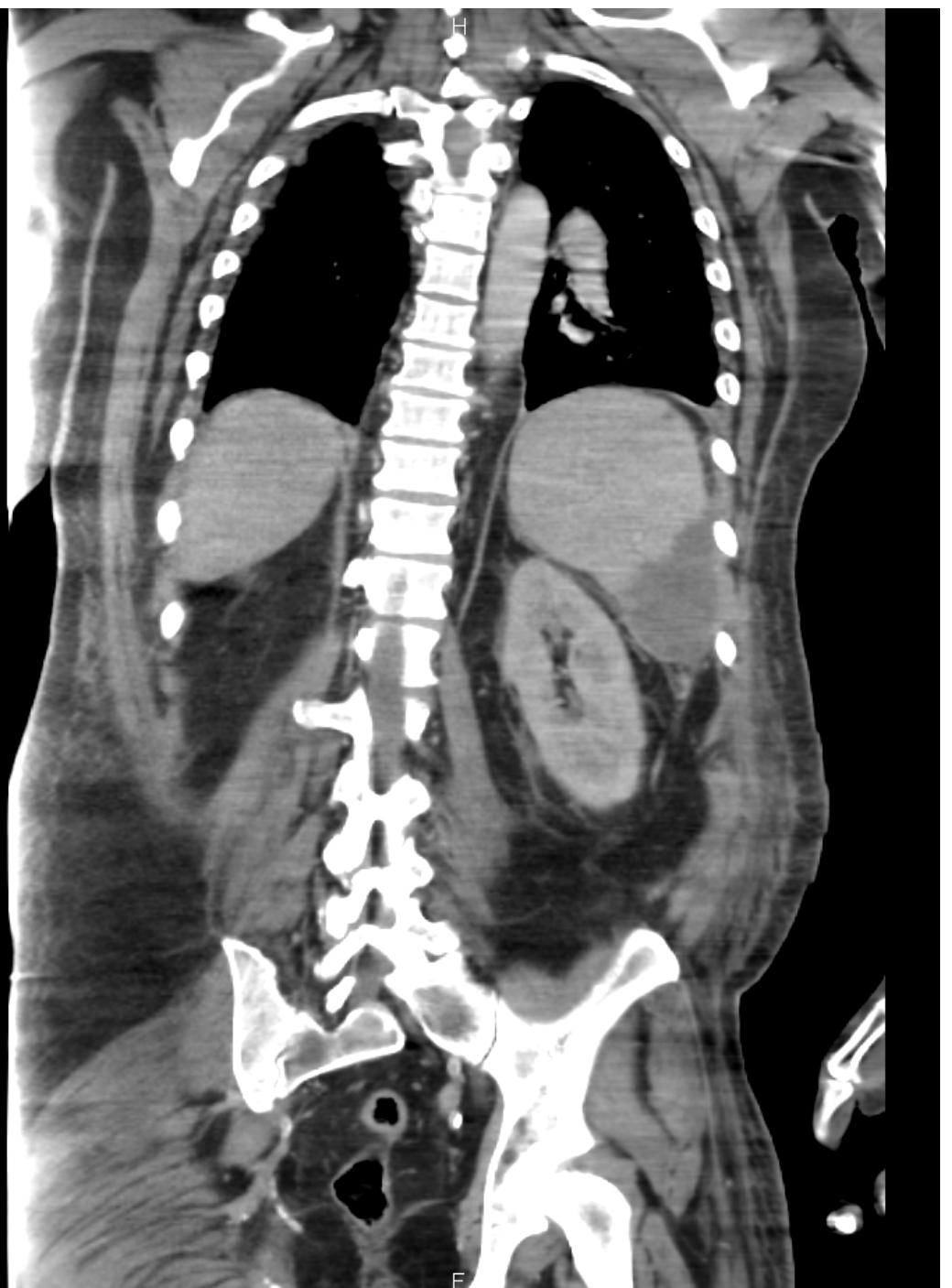
# Question #1

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What would you do ?

- Add gentamicin +/- rifampicin
- Switch to HD daptomycin + fosfomycin or ceftaroline
- Abdomen CT scan (despite no abdominal complaint)
- Call José (Europe), Vance (America), or Eugene (Australia)





# Why abdomen CT scan was the best answer ?

Clinical Infectious Diseases

EDITORIAL COMMENTARY



IDSA  
Infectious Diseases Society of America



## Combination Therapy for Methicillin-resistant *Staphylococcus aureus* (MRSA) Bacteremia: Beauty Remains in the Eye of the Beholder

Adolf W. Karchmer

Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

### RCTs on combination therapy for *S. aureus* BSI

- Daptomycin + fosfomycin
- Daptomycin + betalactams
- Anti-staphylococcal penicillin (ASP) + vancomycin
- SOC + rifampin

**=> No proven benefit & added toxicity**

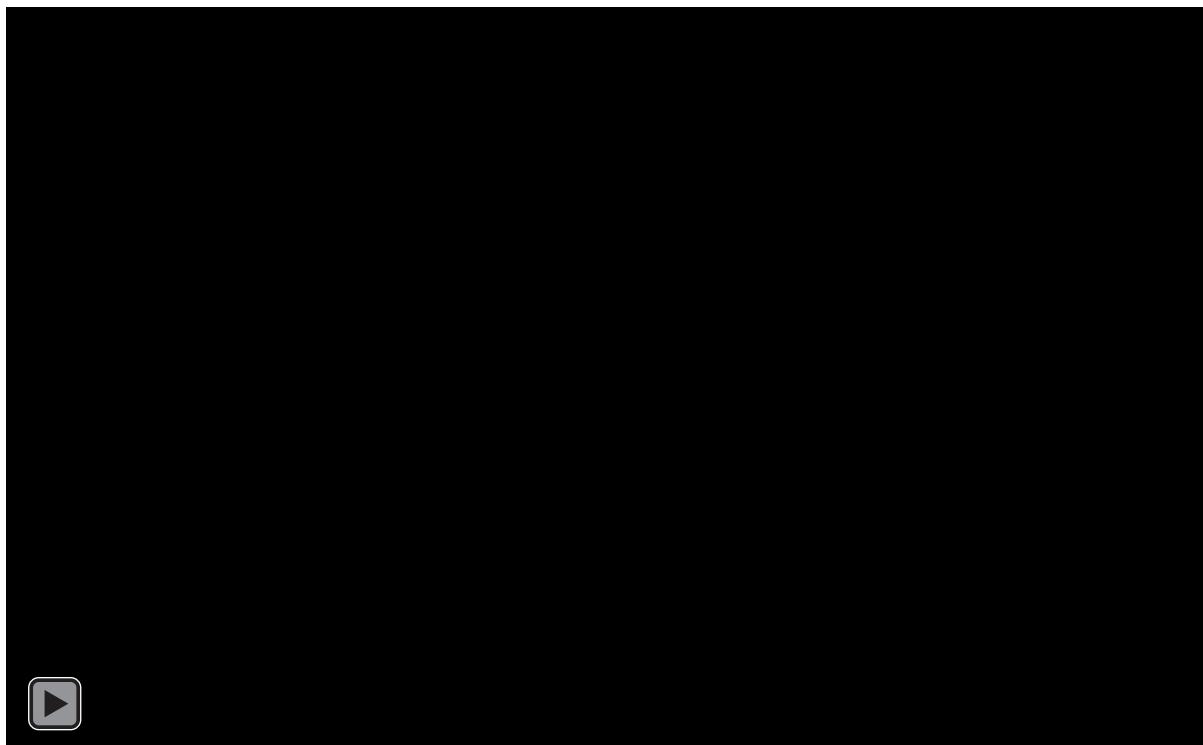
The above studies, plus other retrospective series, leave the clinician with beclouded vision in the effort to perceive beauty—benefit in the pursuit of reduced mortality without increased toxicity—through combination antimicrobial therapy for SAB, particularly MRSAB.

Karchmer AW et al. Clin Infect Dis 2021

# Follow-up history #2

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- **Splenectomy on day 9**
- **TOE (day 10): severe mitral regurgitation (4/4) + vegetation 14 mm**



# Follow-up history #2

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- Cardiac surgery on day 14 (mechanical prosthesis)
- No major complications, but
  - Valve culture positive for MRSA
  - ***BC still positive on day 21*** (day 7 post-surgery)
  - Time-to-positivity, 16 h

## Antibiogramme 1 SIR

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Sensible selon CASFM 2016.

Staphylococcus aureus

Vancomycine

0,750

Teicoplanine

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### CMI ATB

bactérie AE étudiée

ATB n°1 :

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Staphylococcus aureus

Ceftaroline

0,500

Sensible selon EUCAST-CASFM 2016.

ATB n°2 :

CMI n°2

Céftobiprole

0,750

Sensible selon EUCAST-CASFM 2016.

# Question #2

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What would you do ?

- HD daptomycin + ceftaroline
- HD daptomycin + fosfomycin
- Dalbavancin
- HD daptomycin + ceftaroline + gentamicin

# Daptomycin + betalactam as salvage treatment

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Use of Antistaphylococcal  $\beta$ -Lactams  
to Increase Daptomycin Activity in  
Eradicating Persistent Bacteremia  
Due to Methicillin-Resistant  
*Staphylococcus aureus*: Role of  
Enhanced Daptomycin Binding

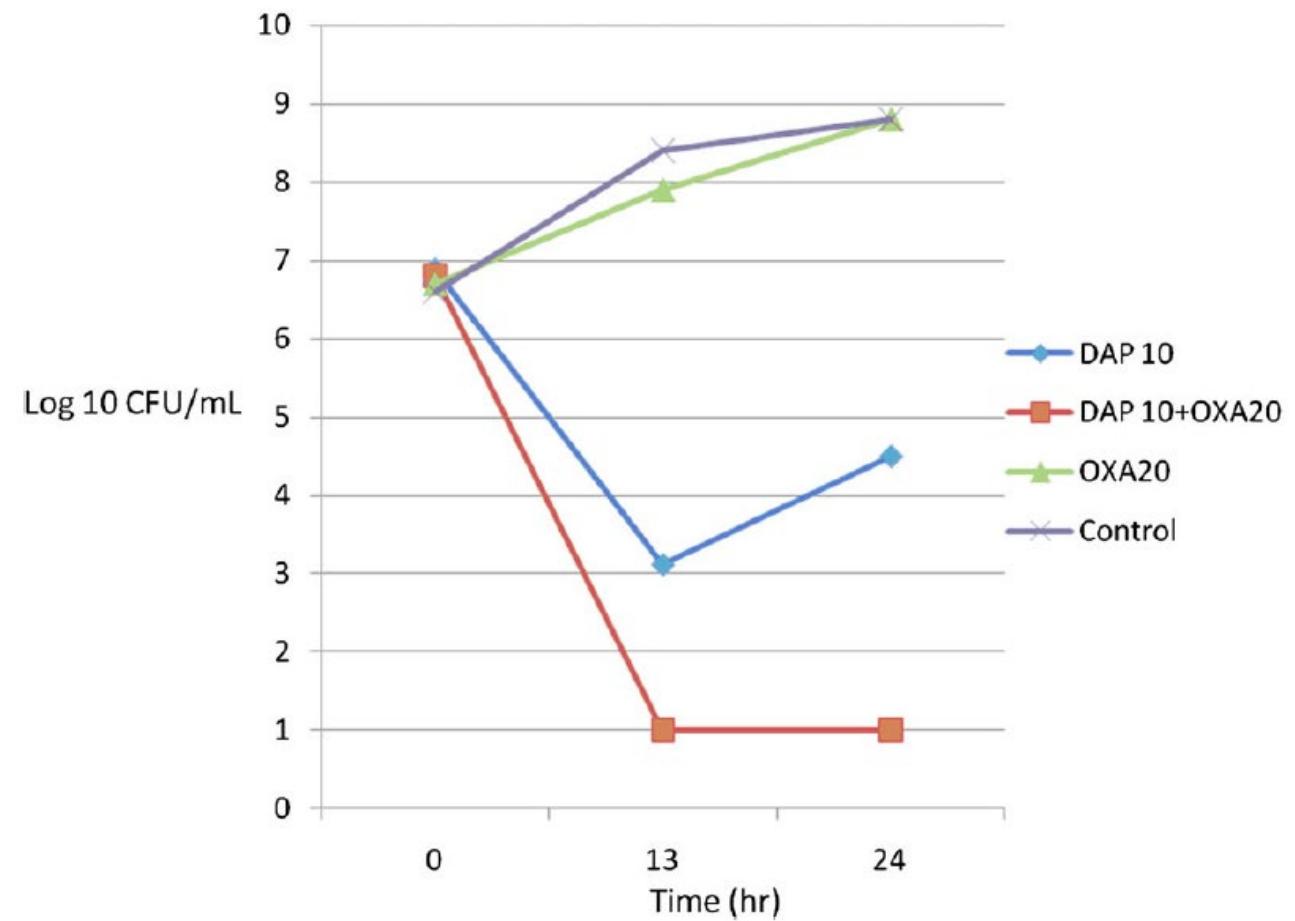
Abhay Dhand,<sup>1</sup> Arnold S. Bayer,<sup>3,4</sup> Joseph Pogliano,<sup>5</sup> Soo-Jin Yang,<sup>3,4</sup>  
Michael Bolaris,<sup>3</sup> Victor Nizet,<sup>5</sup> Guiqing Wang,<sup>2</sup> and George Sakoulas<sup>1,5,6</sup>

- **7 patients with persistent MRSA bacteremia (7-22 days)**
    - No issue with source control or foreign devices
    - MIC daptomycin & vancomycin  $\leq 1$  mg/L (6/7)
    - ‘optimal’ antistaphylococcal combinations
- => All successfully controlled with ASP + daptomycin**

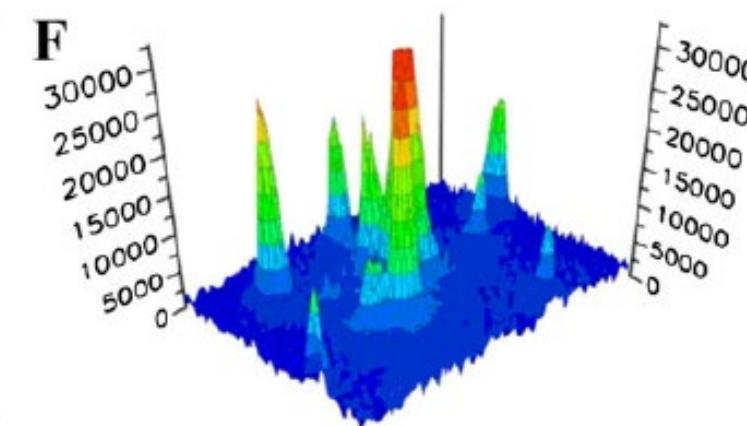
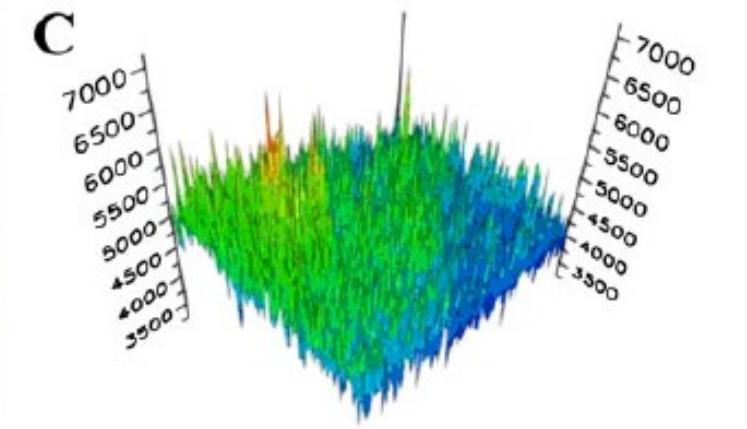
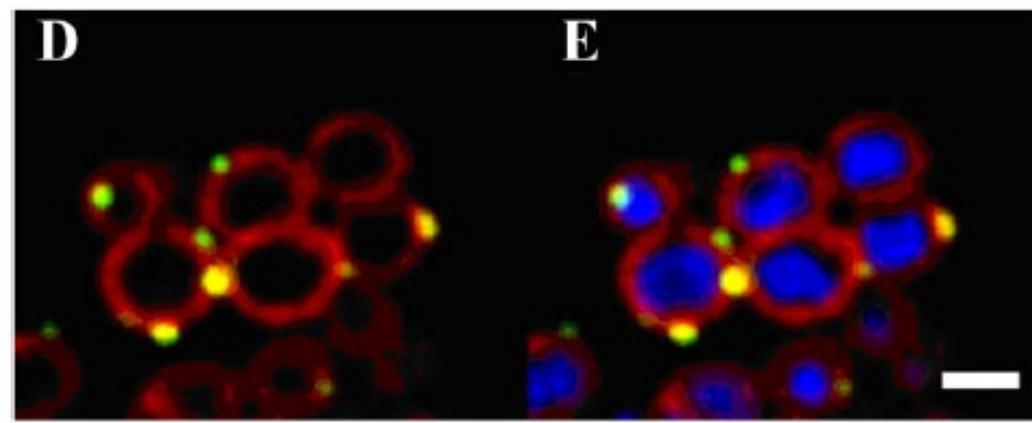
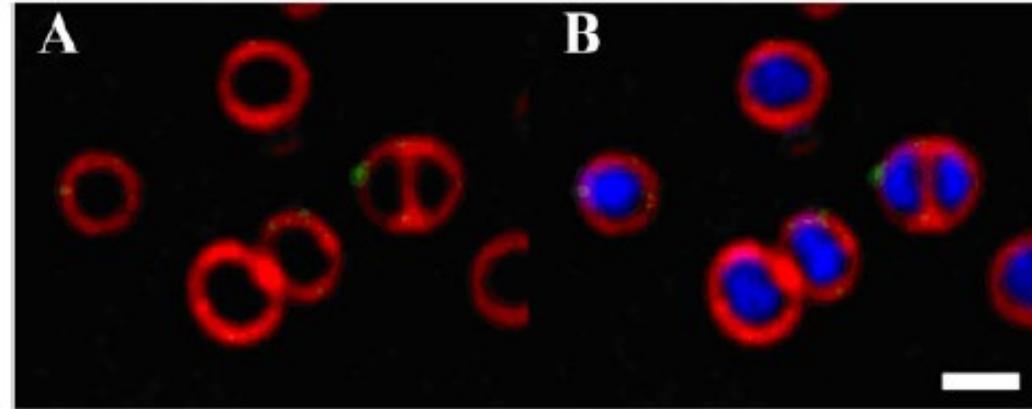
# Daptomycin + betalactam as salvage treatment

Use of Antistaphylococcal  $\beta$ -Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus*: Role of Enhanced Daptomycin Binding

Abhay Dhand,<sup>1</sup> Arnold S. Bayer,<sup>3,4</sup> Joseph Pogliano,<sup>5</sup> Soo-Jin Yang,<sup>3,4</sup> Michael Bolaris,<sup>3</sup> Victor Nizet,<sup>5</sup> Guiqing Wang,<sup>2</sup> and George Sakoulas<sup>1,5,6</sup>



# Daptomycin + betalactam as salvage treatment



# Daptomycin + betalactam as salvage treatment

## Daptomycin Plus $\beta$ -Lactam Combination Therapy for Methicillin-resistant *Staphylococcus aureus* Bloodstream Infections: A Retrospective, Comparative Cohort Study

Sarah C. J. Jorgensen,<sup>1</sup> Evan J. Zasowski,<sup>1,2</sup> Trang D. Trinh,<sup>1,3</sup> Abdalhamid M. Laghf,<sup>1</sup> Sahil Bhatia,<sup>1</sup> Noor Sabaghah,<sup>1</sup> Jacinda C. Abdul-Mutakabbir,<sup>1</sup> Sara Alosaimy,<sup>1</sup> Ryan P. Mynatt,<sup>4</sup> Susan L. Davis,<sup>1,5</sup> and Michael J. Rybak<sup>1,4,6</sup>

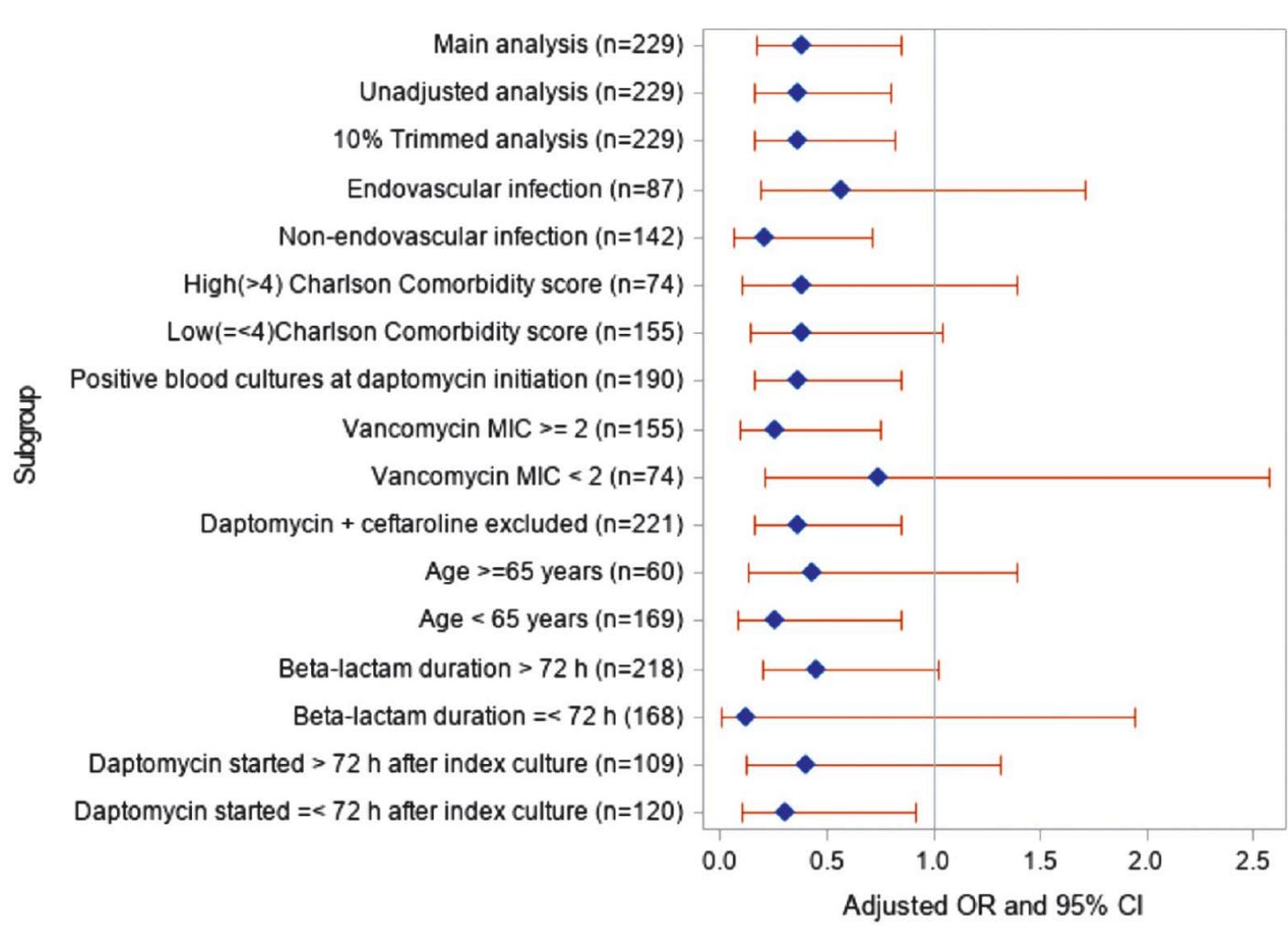
- Observational study, 2008-2018
- Primary criteria = day 60 mortality or relapse



Reason for the addition of a $\beta$ -lactam, n (%)	...
Empiric	33 (45.8)
Anticipated synergy	25 (34.7)
Concurrent infection	14 (19.4)

$\beta$ -Lactam, n (%)	...
Cefepime	31 (43.1)
Cefazolin	18 (25.0)
Ceftaroline	7 (9.7)
Ceftriaxone	7 (9.7)

# Daptomycin + betalactam as salvage treatment



# Follow-up history #3

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- Daptomycin 10 mg/kg od + ceftaroline 600 mg tid + gentamicin 3 mg/kg od
- BC sterile after day 23 (2 days after ATB switch)
- Finally cured with 6 weeks of HD dapto & ceftarolin (+ gentamicin first 14 days)

# Question #3

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Regarding time-to-blood culture positivity (TTP) for *S. aureus*, what is not true among the following

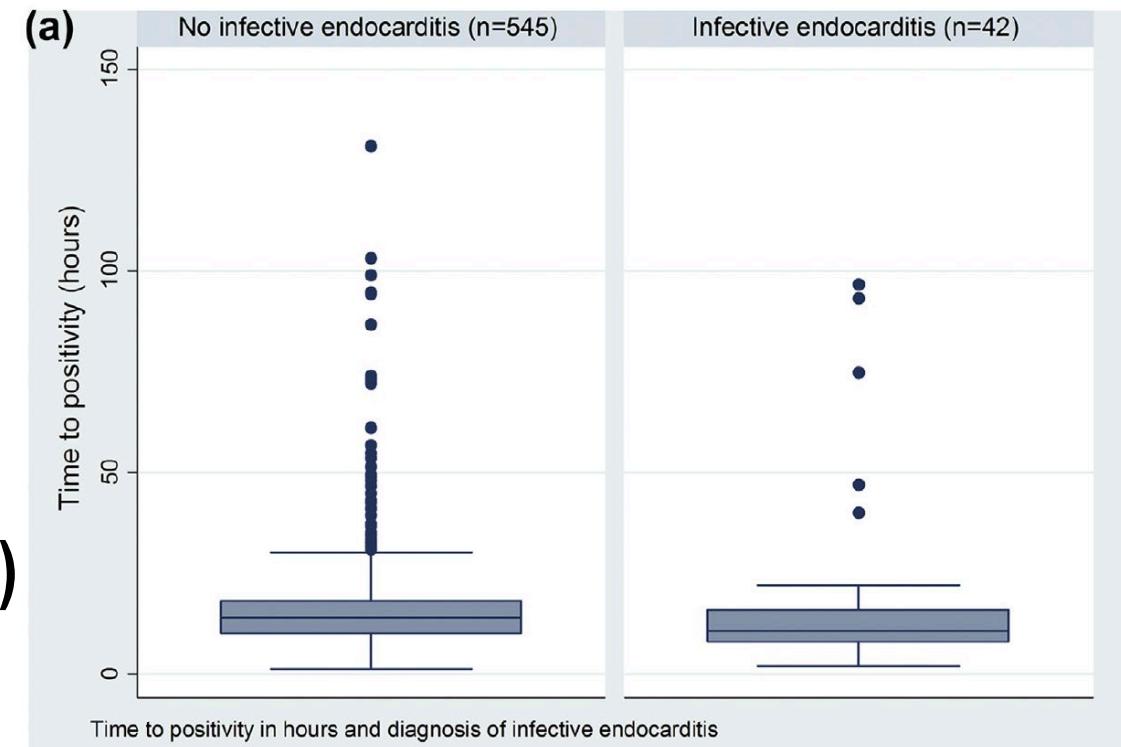
- The median TTP for *S. aureus* BSI is 14 h
- TTP mostly reflects inoculum
- TTP is shorter in patients with endocarditis
- A 50% increase in TTP after treatment start is associated with survival

# Time to blood culture positivity: An independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia

S. Siméon <sup>1</sup>, V. Le Moing <sup>2</sup>, S. Tubiana <sup>3, 4, 5</sup>, X. Duval <sup>3, 4, 5</sup>, D. Fournier <sup>6</sup>, J.-P. Lavigne <sup>7, 8</sup>, M.-L. Erpelding <sup>9</sup>, C.-A. Gustave <sup>10</sup>, S. Desage <sup>11</sup>, C. Chirouze <sup>12</sup>, F. Vandenesch <sup>10</sup>, P. Tattevin <sup>1, 13, \*</sup>, the VIRSTA/AEPEI Study Group <sup>†</sup>

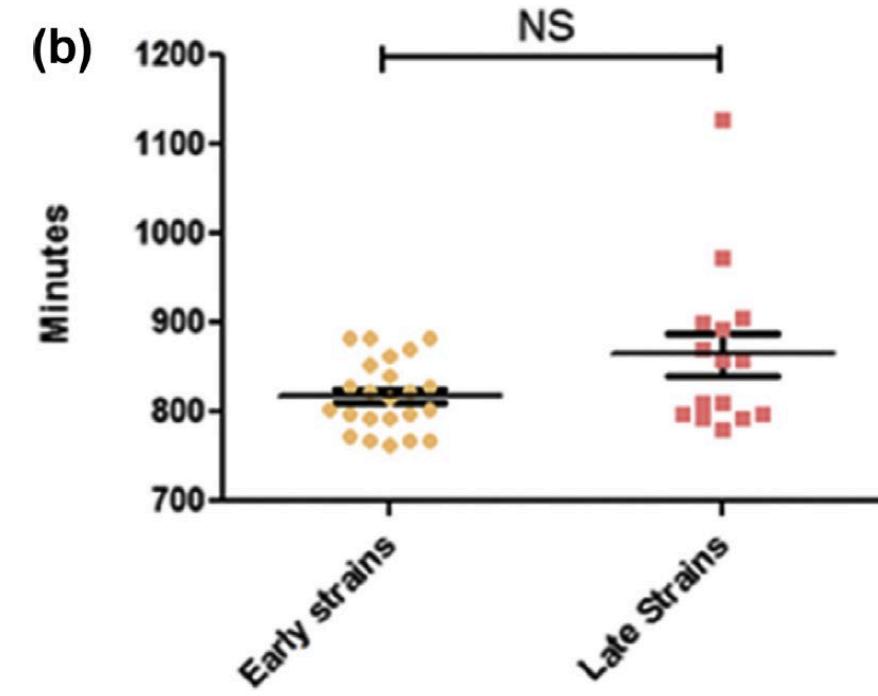
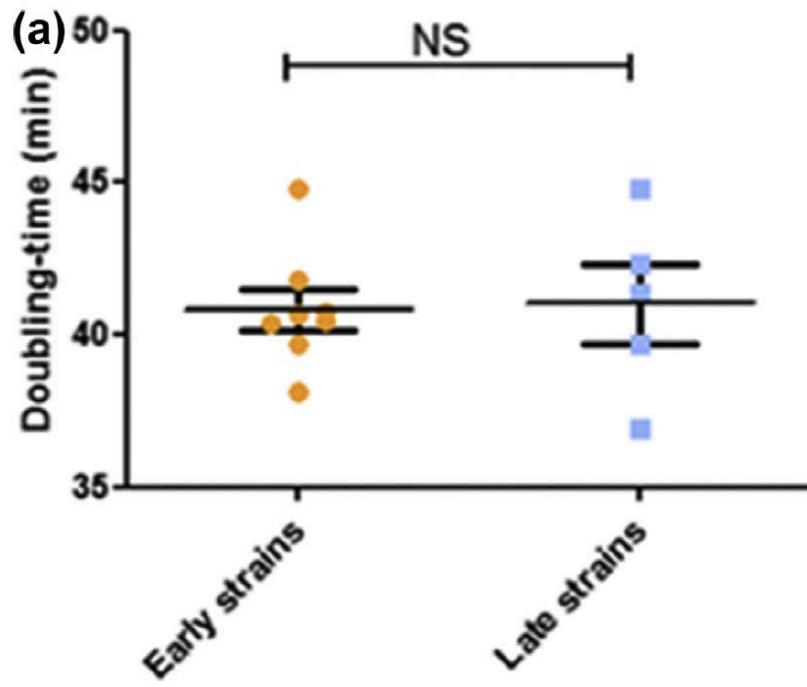
## TTP BC in *S. aureus* BSI

- Available in most automated BC system
- **Independent predictor of mortality**
  - ✓ **Baseline (cut-off, 14 h)**
  - ✓ **After treatment start (50% increase)**
- ***Not predictive of IE***
- Primarily reflective of inoculum



# Time to blood culture positivity: An independent predictor of infective endocarditis and mortality in patients with *Staphylococcus aureus* bacteraemia

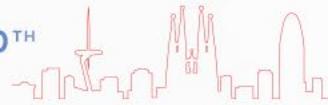
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# Take home messages

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- **No regimen has been proven superior to vancomycin monotherapy for the treatment of MRSA BSI or IE**
- **When this first-line regimen fails:**
  - Screen for 'subclinical' metastatic infections (abscess, thrombophlebitis)
  - Consider cardiac surgery
- **If you are still failing**  
=> HD daptomycin + betalactam combination (ceftaroline = first choice ?)



# Thank you !

