

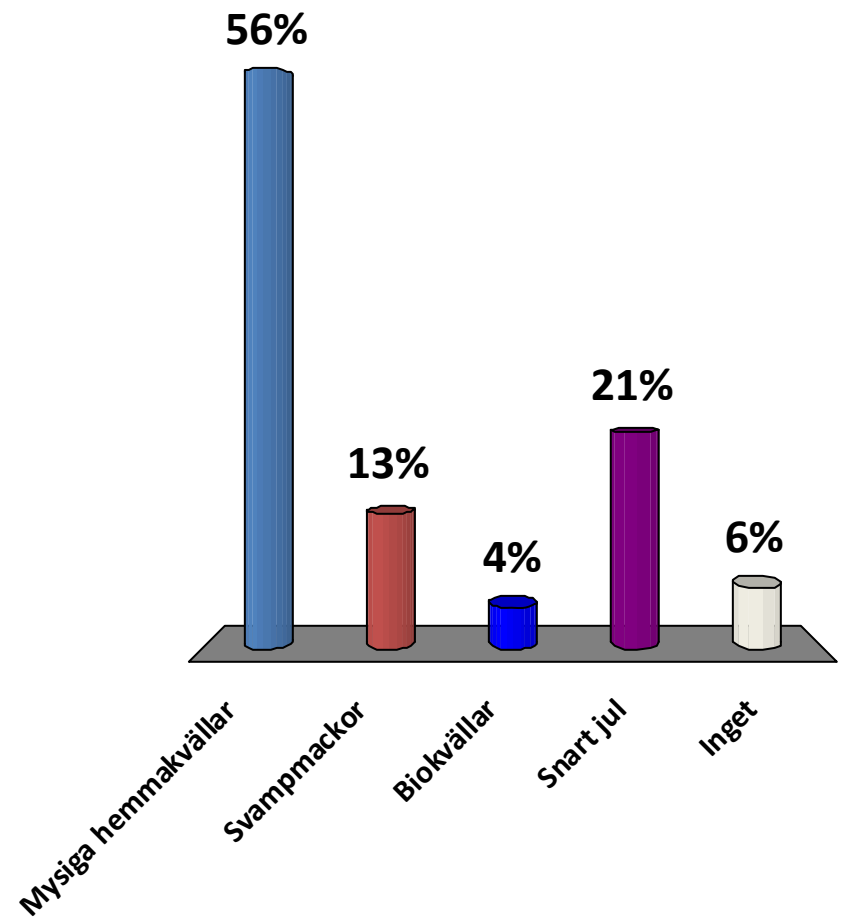
**Treatment of sepsis/BSI in high level  
resistance settings:  
interactive discussion on how broad to go.**

**Håkan Hanberger, Sweden**

**Bojana Beovic, Slovenia**

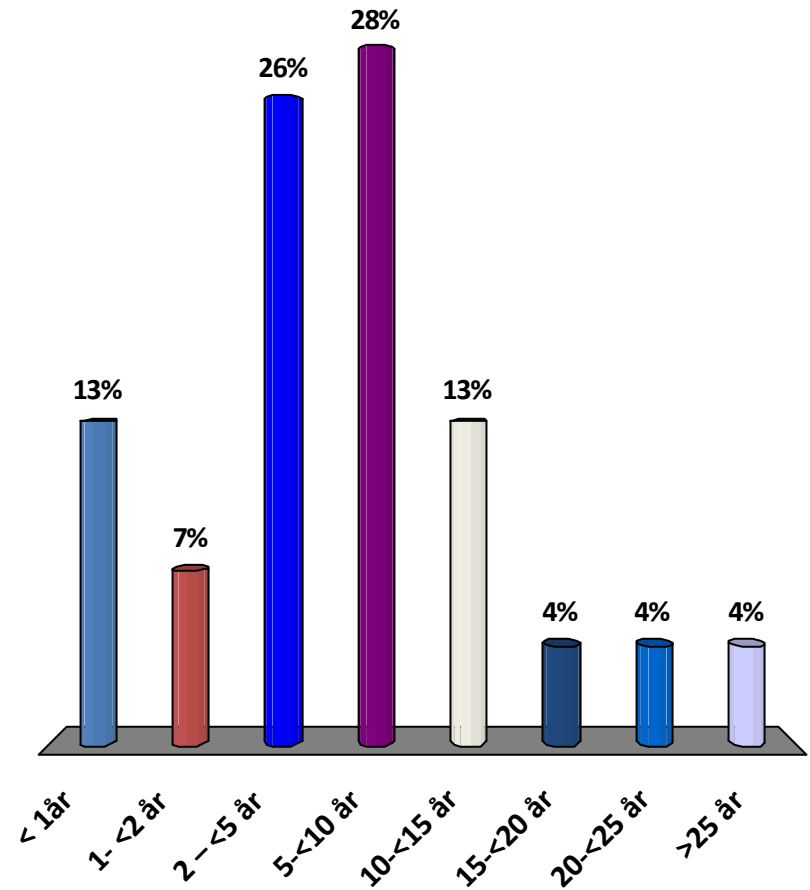
# Vad är bra med Hösten?

- A. Mysiga hemmakvällar
- B. Svampmackor
- C. Biokvällar
- D. Snart jul
- E. Inget



# Hur länge har du varit infektionsspecialist?

1. < 1år
2. 1- <2 år
3. 2 – <5 år
4. 5-<10 år
5. 10-<15 år
6. 15-<20 år
7. 20-<25 år
8. >25 år



# Risk assessment of Antibiotic resistance



- Country prevalence of MRSA, ESBL, PNSP?
- Hospital/Ward prevalence of MRSA, VRE, ESBL, MDR Gram-neg
  - Endemic spread or Ongoing outbreak?
- Patient risk factors for ABR
  - Known colonization or previous infection with MRSA, ESBL, VRE, MDR G-neg
  - Hospital acquired infection
  - Transferred from another hospital/ward
  - Recent antibiotic treatment
  - Travel
  - Occupation: pig farmer

# Case

**High level resistance settings e.g. South East Europe or Asia**

- 40 y old female patient
- Polytrauma, external fixation of the left femur
- No underlying diseases, no past medical history
- Transferred from another hospital known to be endemic for MRSA, stable, no sign of infection

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**Which actions do you take?**

40 y old woman in High level resistance settings e.g. South East Europe or Asia

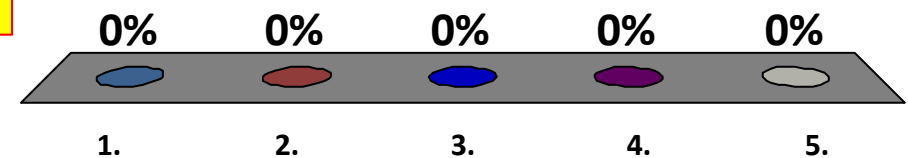
# Which actions do you take?

- ✓ 1. Screening of MRSA and put on isolation
- ✓ 2. 1+ nasal mupirocin
- 3. 2 + prophylactic vancomycin
- 4. No action - wait and see
- 5. I don't know

## Diskussion

Båda 1 och 2 rätt

- 1. Screening och isolering viktigast
- 2. Mupirocin i avvaktan på screeningsvar om pat skall genomgå akuta operativa interventioner eller om pat ej kan isoleras



40 y old woman in High level resistance settings e.g. South East Europe or Asia

# Case

## High level resistance settings e.g. South East Europe or Asia

- Ciprofloxacin started for presumed urinary tract infection
- Central venous line in place from the first hospital
- 2<sup>nd</sup> day after admission (still awaiting surveillance culture results): fever 38.8, the CVC insertion site is slightly reddish and wet



# Which actions do you take?

1. Remove CVC
2. 1+ wait and see
3. 1 + pip-tazo
4. 1 + pip-tazo + vanko
5. 1 + meropenem
6. 1+ vancomycin + meropenem
7. 1+ start vancomycin + meropenem + echinocandins

## Diskussion

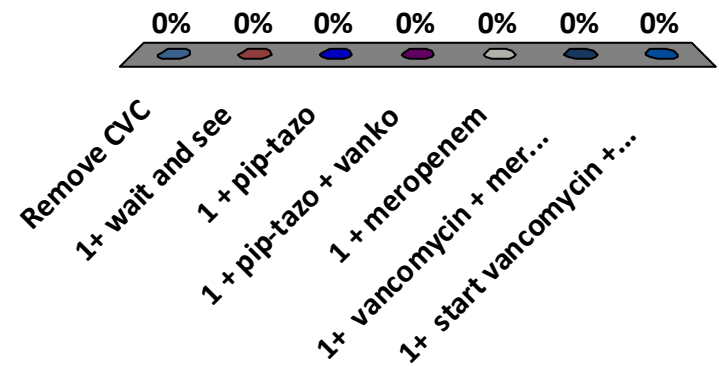
### Lite-måttlig lokal infektion, febril, opåverkad

– dra CVK och avvakta alt

- dra CVK och byt cipro till pip-tazo +/-vankomycin

### Svår lokal infektion + septisk chock

Alt 7



# Case

**Low level resistance settings e.g. Netherlands or Scandinavia**

- 40 y old female patient
- Polytrauma, external fixation of the left femur
- No underlying diseases, no past medical history
- Transferred from another hospital known to be MRSA free, no sign of infection

# Case

**Low level resistance settings e.g. Netherlands or Scandinavia**

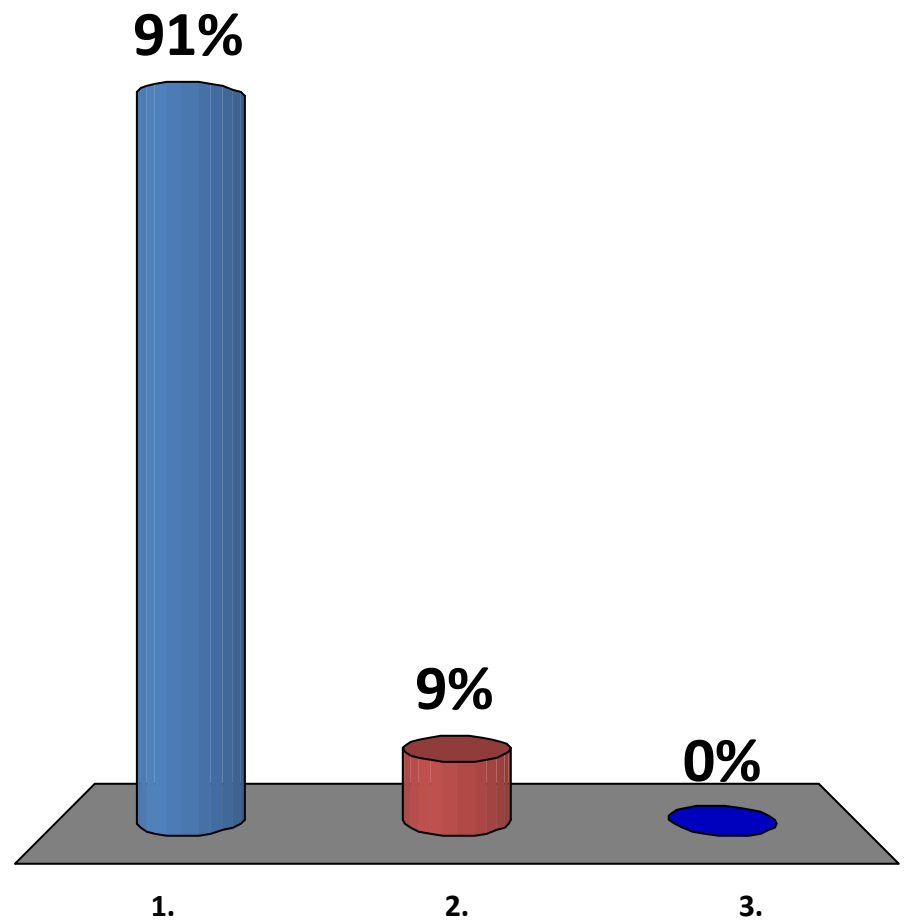
- 40 y old female patient
- Polytrauma, external fixation of the left femur
- No underlying diseases, no past medical history
- Transferred from another hospital known to be MRSA free, no sign of infection

**Which actions do you take?**

40 y old woman in Low level resistance settings e.g. NL or Scandinavia

# Which actions do you take?

- ✓ 1. No action needed
- 2. Screening of MRSA and put on isolation
- 3. I don't know



40 y old woman in Low level resistance settings e.g. NL or Scandinavia

# Case

## **Low level resistance settings e.g. Netherlands or Scandinavia**

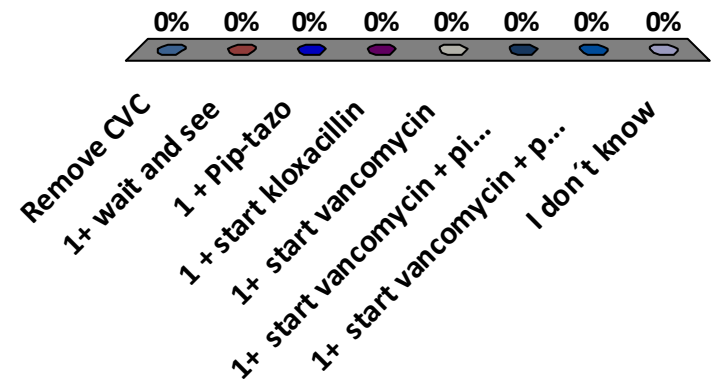
- Ciprofloxacin started for presumed urinary tract infection
- Central venous line in place from the first hospital
- 2<sup>nd</sup> day after admission : fever 38.8, the CVC insertion site is slightly reddish and wet

40 y old woman in Low level resistance settings e.g. NL or Scandinavia

# Which actions do you take?

1. Remove CVC
2. 1+ wait and see
3. 1 + Pip-tazo
4. 1 + start kloxacillin
5. 1+ start vancomycin
6. 1+ start vancomycin + piperacillin-tazobactam
7. 1+ start vancomycin + piperacillin-tazobactam + echinocandins
8. I don't know

Se kommentarer nästa sida



40 y old woman in Low level resistance settings e.g. NL or Scandinavia

# Which actions do you take?

Fredrik Hammarskjöld ÖL Ryhov IVA, CVK-inf-expert

**Patienten har feber men inte är svårt septisk/septisk chock**

Jag tycker att handläggningen blir den samma oavsett hög eller lågrisk

Isolera patienten screena för MRSA/VRE/ESBL

Sen beror det lite på hur "pusigt"/infekterat insticksstället är.

**Alt Våldigt infekterat.** Ta bort CVK. Ge antibiotika. Täck för S aureus/KNS/enterococker. Mindre sannolikt med svamp/G-

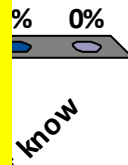
**Alt Lite infekterat:** Parad blododling med tidskillnad. Avvakta antibiotika om ni inte är nervöst lagda. När insticksstället är endast lite/eller inte rodnat kan det växa vad som helst men jag brukar vänta med vanco till odlingsvvar då KNS oftast inte ger så stormiga förlopp, eller hur.

**Om det är en IVA patient** hade jag om det gått mer än typ 10 dar givit caspofungin också.

**Är Patienten svårt septisk hade jag givit:** 1 nos Nebcina, Tacozin eller Meronem och caspofungin. Ev vanco också men kanske avvaktat med motiveringen ovan

Bifogar nationella riktlinjer där vi medvetet är lite fega vad gäller antibiotikaval.

Vi håller på med en uppdatering av dessa och Pseudomonas börjar hamna i gruppen S aureus/Svamp. Dvs alltid bort vid CVK-infektion.



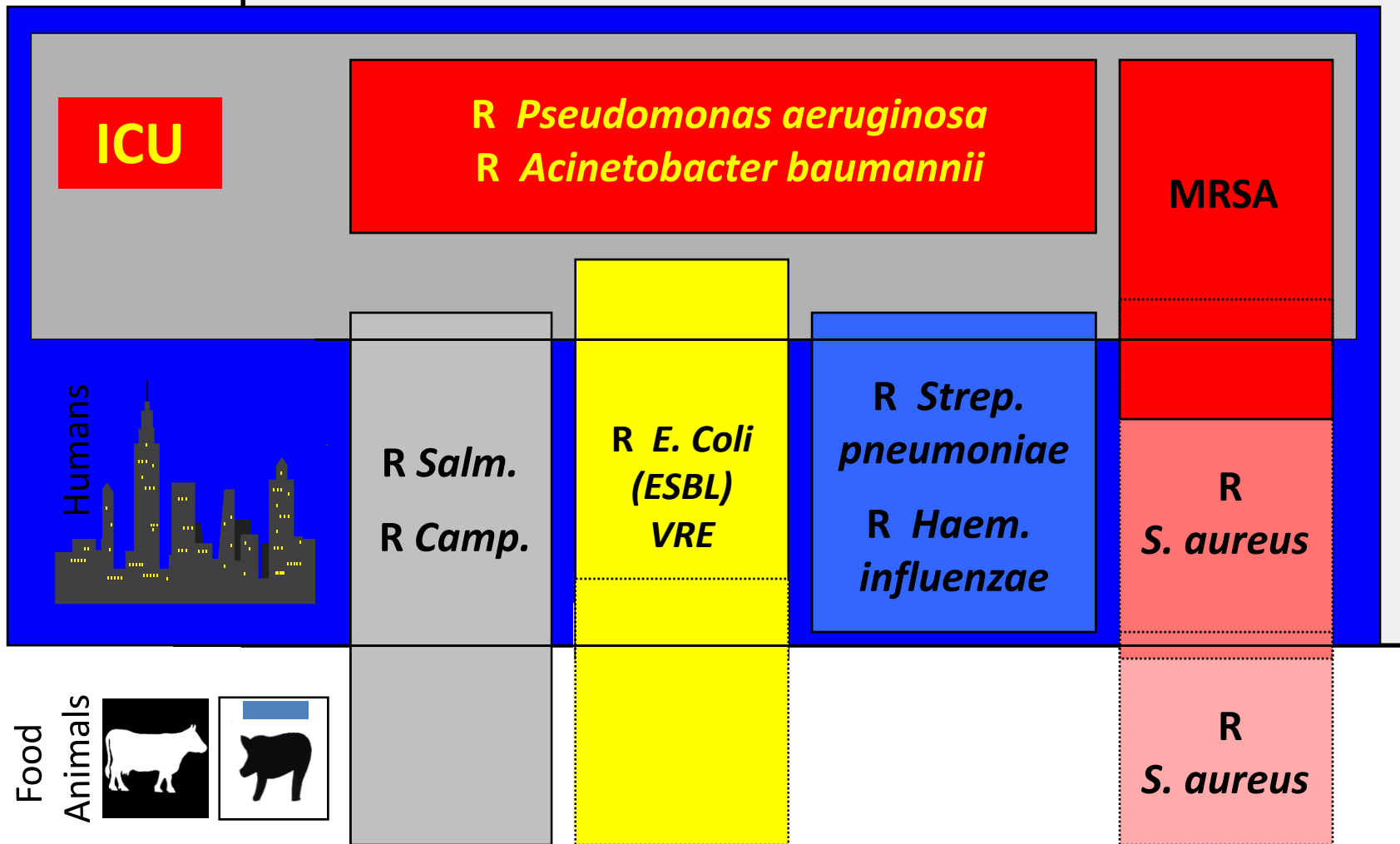
# Coagulase-negative staphylococcal bacteremia: the impact of inappropriate empirical antibiotic treatment

*Park SY, et al. Eur J Clin Microbiol Infect Dis. 2015 Apr 1.*

- **109 patients with CoNS bacteremia**
- **71% of patients received appropriate empirical antibiotic therapy**
- **Inappropriate empirical antibiotic treatment was **not related to mortality.****



# Human antibiotic resistant bacteria and their habitat



# Does MRSA colonisation matters?

Large retrospective cohorts study: one year risk for MRSA infection (only 12% invasive):

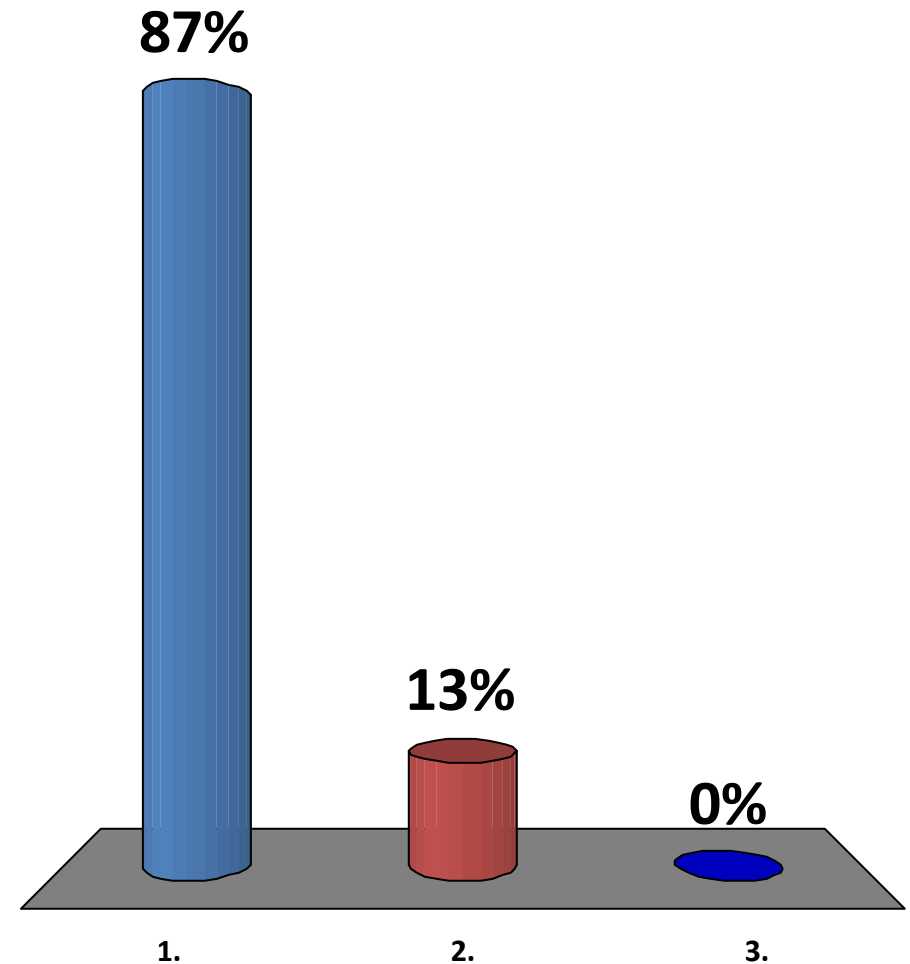
- colonisation determined by nasal PCR + culture: 7%
- colonisation determined by nasal PCR and not culture: 3.4%
- nasal PCR negative: 0.5%
- even higher risk in patients with previous clinical culture positive!

**The significant difference confirmed in multivariable model (hazard ratio 6.52 and 2.7 resp vs PCR negative patients).**

Ridgway JP, Peterson LR, Brown EC, Du H, Hebert C, et al. (2013) Clinical Significance of Methicillin-Resistant Staphylococcus aureus Colonization on Hospital Admission: One-Year Infection Risk. PLoS ONE 8(11): e79716. doi:10.1371/journal.pone.0079716

# Does appropriate empirical treatment for MRSA matters?

- ✓ 1. Yes, it lowers mortality
- 2. No, need to care
- 3. I don't know





## Impact of inappropriate empirical therapy for sepsis due to health care-associated methicillin-resistant *Staphylococcus aureus*

Jesús Rodríguez-Baño <sup>a,\*</sup>, Antonio B. Millán <sup>a</sup>, M. Angeles Domínguez <sup>b</sup>, Carmen Borraz <sup>b</sup>, M. Pau González <sup>b</sup>, Benito Almirante <sup>c</sup>, Emilia Cercenado <sup>d</sup>, Belén Padilla <sup>d</sup>, Miquel Pujol <sup>e</sup>, on behalf of GEIH/GEMARA/REIPI

209 cases of sepsis caused by HCA MRSA  
29.7% were bacteremic.

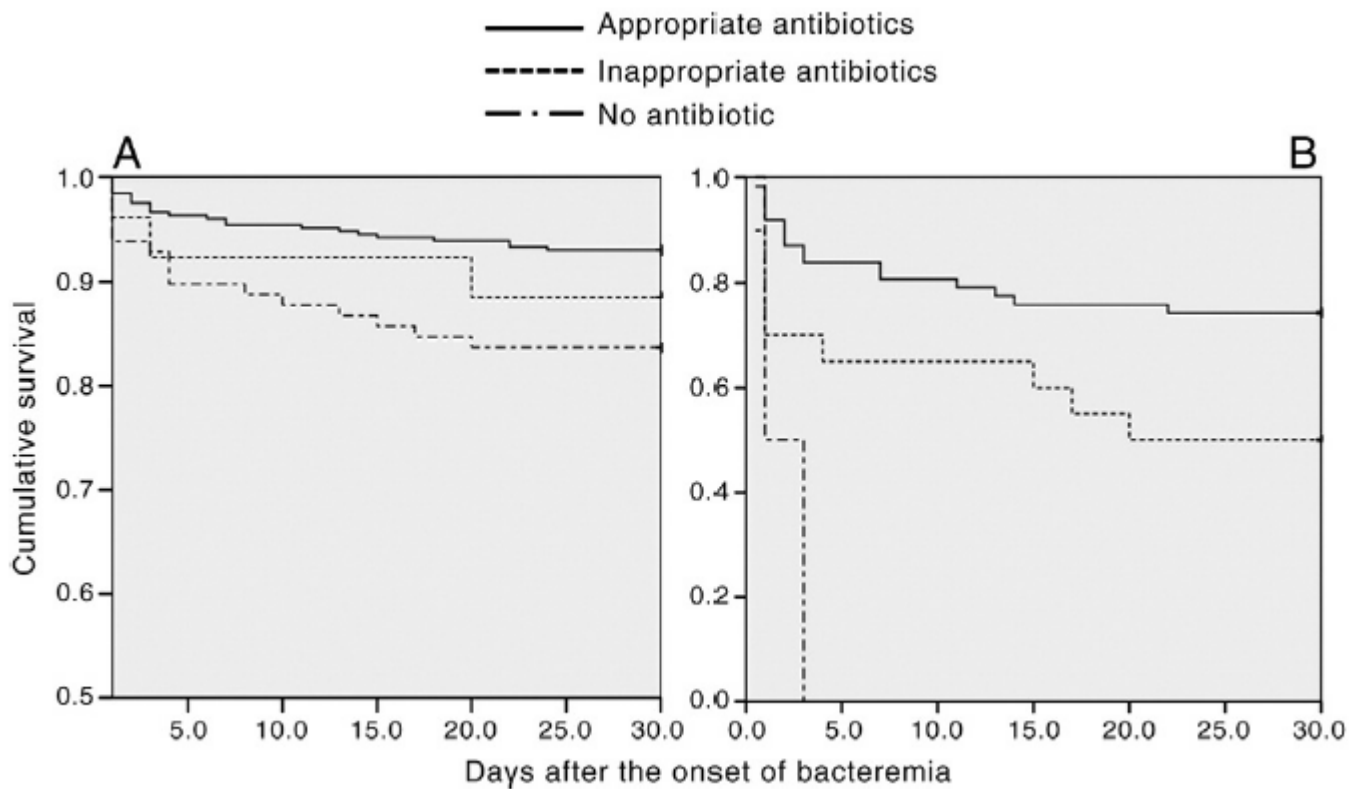
**In multivariate analysis appropriate empirical treatment was associated with lower 30 days mortality (OR 3.0, 95% CI 1.01-9).**

**Definitive antibiotic treatment was not associated with mortality.**

- Variables independently associated with **appropriate therapy**: recent surgery, central venous catheter and certain sites of infection
- Cancer patients were at an increased risk of receiving **inappropriate** therapy.

# 28-days mortality in patients with bacteremia treated in ER

Lee CC, et al. Am J Emerg Med 2012; 30: 1447-56.

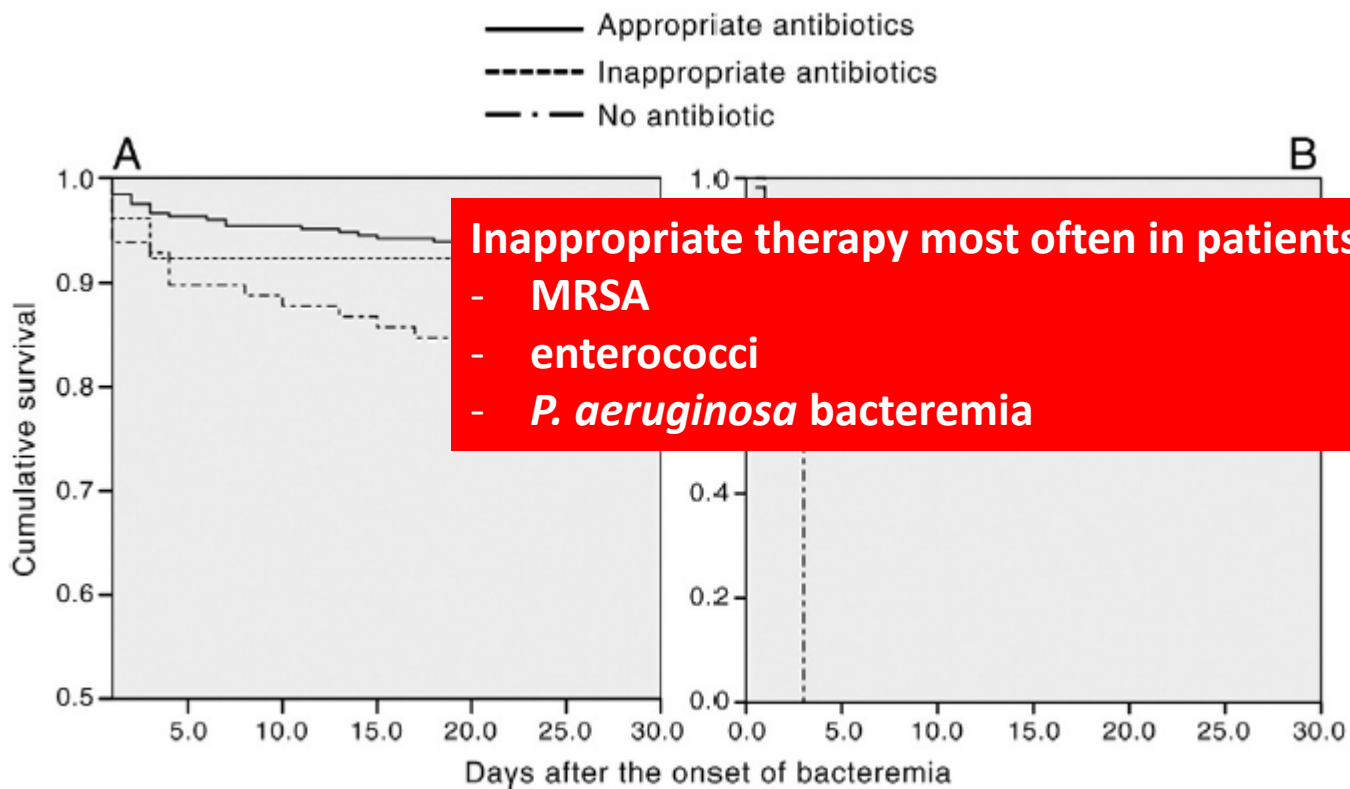


A: All bacteremia cases

B: Critically ill patients

# 28-days mortality in patients with bacteremia treated in ER

Lee CC, et al. Am J Emerg Med 2012; 30: 1447-56.



# Time is money...

*Roisin S, et al. PLoS ONE 9(5): e96310. doi:10.1371/journal.pone.0096310*

- **PCR-screening for MRSA vs culture reduces the median test reporting time from admission from 88 to 11 hours ( $p < 0.001$ )**

*Opota O, et al. Clin Microbiol Infect 2015, Jan 16.*

- **Rapid diagnostic tests: MALDI-TOF, FISH, PCR, other molecular-based tests**

*Between Scylla and Charibdis:  
to choose between two evils*







- **Appropriate antibiotic treatment of bacteremia is crucial for patients' survival.**
- **Broad-spectrum antibiotic use is one of the major drivers of antibiotic resistance.**
- **Antimicrobial resistance increases the risk of inappropriate empirical antibiotic treatment.**

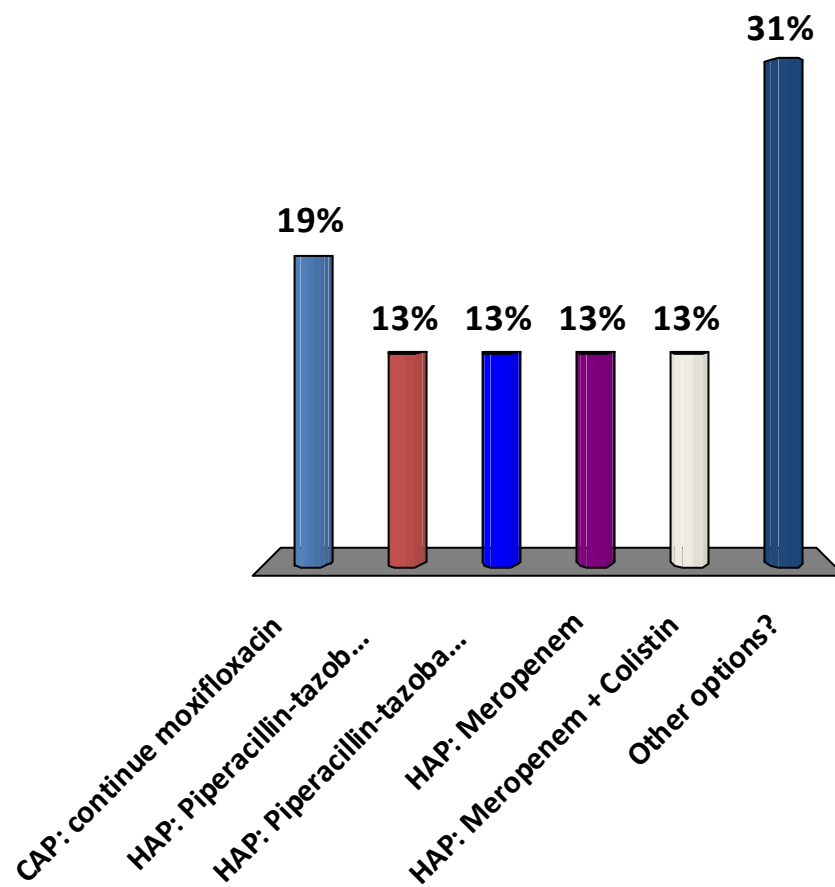
**Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago**  
**High level resistance settings e.g. South East Europe or Asia**

- She was subjected successfully in autologous bone marrow transplantation 8 months before.
- Entered the hospital due to pneumonia (Urine ag pos for pneumococci) but by the intensivist treated with Cotrimoxazole, Meropenem, Moxifloxacin, Cymevene, Liposomal amphotericin.
- **On day 3**; improved and stepdown to oral Moxifloxacin plus Cotrimoxazole.
- **On day 10**, while the patient is afebrile and leucocytes are normal she becomes tachypnoic.
- A new HRCT of the lungs reveals a similar picture with the previous one plus a new consolidation at the interior part of the right middle lobe.
- The radiologist believes that the new CT shows the expected evolution of pneumococcal pneumonia.

Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago  
High level resistance settings e.g. South East Europe or Asia

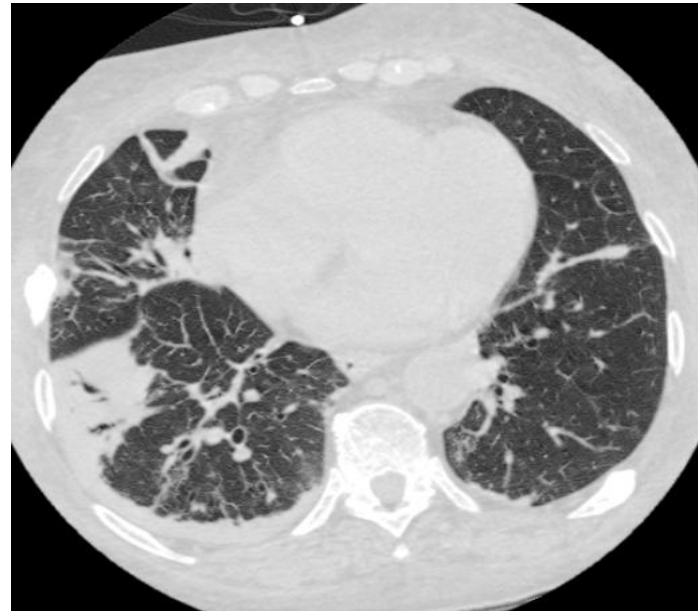
## Which antibiotic do you chose?

- ✓ 1. CAP: continue moxifloxacin
2. HAP: Piperacillin-tazobactam
3. HAP: Piperacillin-tazobactam + colistin
4. HAP: Meropenem
5. HAP: Meropenem + Colistin
6. Other options?



**Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago**  
**High level resistance settings e.g. South East Europe or Asia**

- The radiologist believes that the new CT shows the expected evolution of pneumococcal pneumonia.
- Therefore the intensivists discontinue cotrimoxazole and continue Moxifloxacin monotherapy.



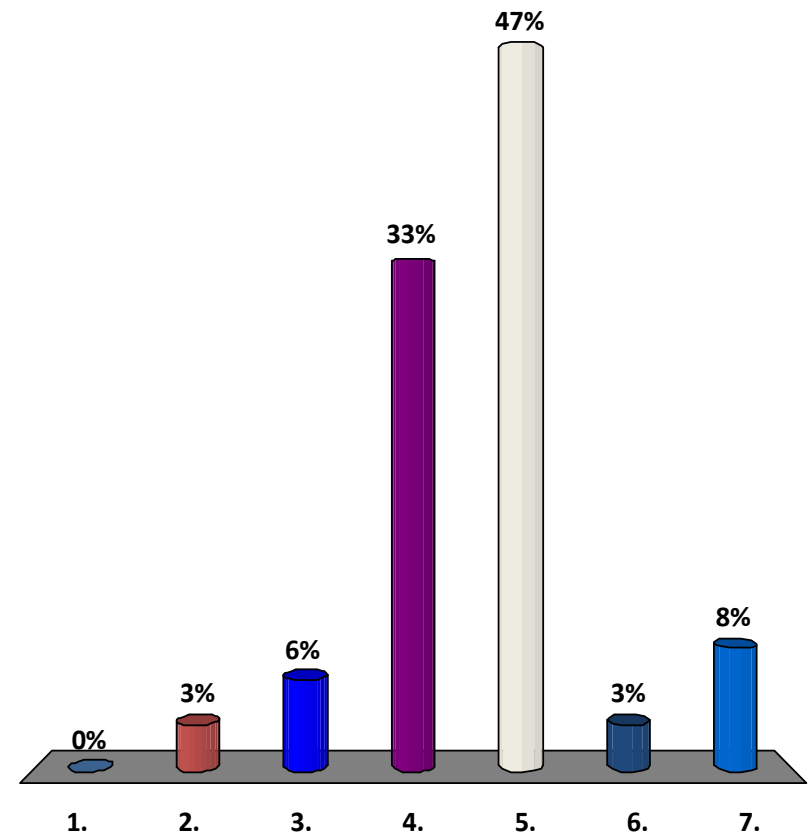
Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago  
**High level resistance settings e.g. South East Europe or Asia**

- **On day 13:** fever relapses (39C) with deterioration in lung function (on moxifloxa).
- Blood cultures and BAL are performed and central lines are changed.

Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago  
**High level resistance settings e.g. South East Europe or Asia**

## Which antibiotic do you chose?

1. Continue moxifloxacin
2. HAP: Piperacillin-tazobactam
3. HAP: Meropenem
4. HAP: Meropenem + Colistin
- ✓ 5. HAP: meropenem + colistin + vancomycin
6. HAP: Pip-tazo + Colistin
7. HAP: Pip-tazo + colistin + vancomycin



**Day 13:** Pip-tazo is added to moxifloxacin.

**Day 14 and 15;** BAL and blood cultures reveals *P. aeruginosa* sensitive only to colistin. The patient is given (in addition to Pip-tazo) Colistin.

MIC( $\mu\text{g/ml}$ )	IMIP	P/T	CAZ	AMK	CIP	COL
<i>Ps.aeruginosa</i> MBL pharyngeal culture one day before intubation	>8	>64/4	>16	>32	>2	0.75
<i>Ps. aeruginosa</i> MBL(+) in BAL	>8	>64/4	>16	>32	>2	0.75
<i>Ps. aeruginosa</i> MBL(+) in blood	>8	>64/4	>16	>32	>2	0.75

**Day 16:** patient dies in septic shock

Paul M, et al.

**Systematic Review and Meta-Analysis of the Efficacy of  
Appropriate Empiric Antibiotic Therapy for Sepsis**  
Antimicrob Agents Chemother 2010; 54: 4851–63.

- **48 studies**
- **Inappropriate empirical antibiotic treatment was associated with significantly higher mortality**
- **Higher mortality risk with inappropriate treatment in patients with septic shock**
- **Higher mortality regardless of the pathogen**



## Influence of Multidrug Resistance and Appropriate Empirical Therapy on the 30-Day Mortality Rate of *Pseudomonas aeruginosa* Bacteremia

Morata et al AAC 2013

- ❑ MDR PAB is associated with a higher mortality than non-MDR PAB.
  - This may be related to a higher rate of inappropriate empirical therapy and probably also to amikacin as frequently the only appropriate empirical therapy given to patients with MDR PAB.
  - needs for revision of the empirical regimens for patients at risk of MDR PAB

**TABLE 4** Multivariate analysis of risk factors associated with 30-day mortality in *P. aeruginosa* bacteremia

Factor	OR (95% CI)	P value
Age	1.02 (1.002–1.033)	0.022
Septic shock	6.58 (4.022–10.767)	<0.0001
Liver cirrhosis	3.30 (1.423–7.649)	0.005
Risk level of infection source		
Low (<15%)	(Used as reference)	
Intermediate (15–30%)	2.47 (1.410–4.326)	0.002
High (>30%)	7.27 (4.092–12.928)	<0.0001
Empirical antibiotic therapy		
Non-MDR with appropriate agent	(Used as reference)	
Non-MDR with inappropriate agent	2.18 (1.215–3.899)	0.009
MDR and inappropriate agent	4.09 (2.156–7.778)	<0.0001
MDR and appropriate agent	2.25 (0.930–5.436)	0.072

Sources of infection were grouped according to their mortality risk as follows: (i) low risk (<15%), urinary tract, vas-cular catheter, skin and soft tissue, biliary tract, and bone and joint; (ii) intermediate risk (15 to 30%), unknown, abdominal, and other infections (pacemaker infection, endocarditis, and otolaryngology infections); (iii) high risk (>30%), respiratory.

# **The combination therapy?**

- **To increase efficacy over monotherapy?**
- **To be performed on new B-lactam/B-lactamase combination antibiotic**

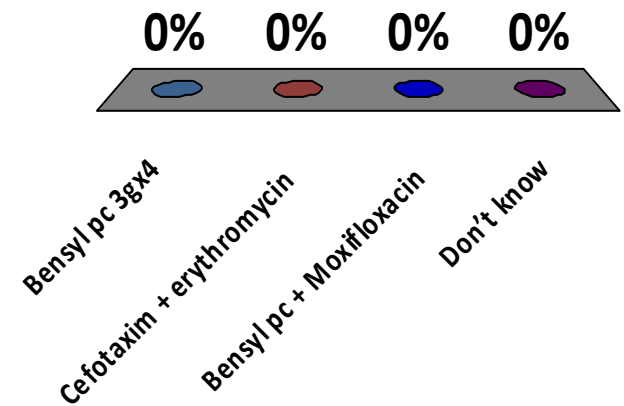
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**Low level resistance settings e.g. NL and Scandinavia**

- She was subjected successfully in autologous bone marrow transplantation 8 months before.
- Entered the hospital due to pneumonia (Urine ag pos for pneumococci)
- Saturation 96%, Respiration 22/min, BP 120/80, Normal Kidney function

Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago  
**Low level resistance settings e.g. NL and Scandinavia**

## Which antibiotic do you chose?

- ✓ 1. Bensyl pc 3gx4
- 2. Cefotaxim + erythromycin
- 3. Bensyl pc + Moxifloxacin
- 4. Don't know



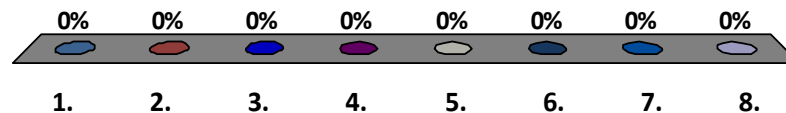
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Case: 53 year old woman suffering from multiple myeloma diagnosed 2 ½ years ago  
**Low level resistance settings e.g. NL and Scandinavia**

## Which antibiotic do you chose?

- ✓ 1. HAP: Piperacillin-tazobactam
- ✓ 2. HAP: Meropenem
- 3. HAP: Pip-tazo + Cipro
- 4. HAP: meropenem + Cipro
- 5. HAP: Meropenem + Colistin
- 6. HAP: meropenem + colistin + vancomycin
- 7. HAP: Pip-tazo + Colistin
- 8. HAP: Pip-tazo + colistin + vancomycin



# „People behind the curtain“

- **To treat individual patient**



- **To avoid antimicrobial resistance**  
**= preserve antibiotic efficacy for future patients**

# Bonus material



# Appropriate empirical treatment of enterococcal bacteremia and mortality

*Cho CY, et al. BMC Infectious Diseases 2013, 13:504.*

- **91 neutropenic patients with enterococcal bacteremia**
- **no impact of delayed (> 48 hours) adequate antibiotic treatment on 30-days mortality (but the severity of the underlying disease)**

*Rosa RG, et al. BioMed Res Int 2014. Article ID 958469*

- **35 patients with VRE bacteremia**
- **linezolid treatment related to lower mortality in multivariate analysis.**
- **time to linezolid (3 days mean) did not have an impact.**

# Not only the choice of antibiotic, this is the time that matters

2731 patients with septic shock

Kumar A, et al. Crit Care Med 2006; 34:1589-96.

