# *« Treating S. aureus infections: from guideline to practice. »*

- ***A University Symposium***
- ***UCL Woluwe***
- 5 October 2012

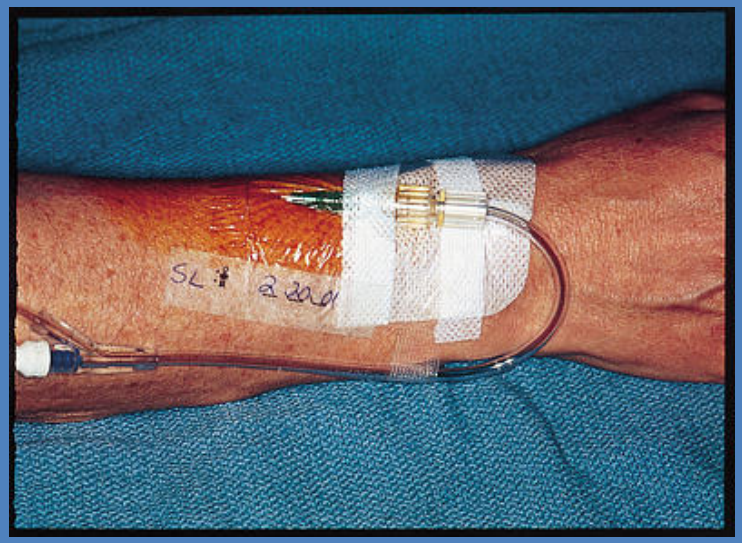

- *Dr F. Frippiat*
- *Service des Maladies Infectieuses*
- *Département de Médecine Interne*
- *CHU Sart Tilman Liège*




# Case report :

- 66-year-old man
- Emergency room for sudden back pain (12/7/2012)
- → diagnosis of sciatica
- → lumbar epidural steroid injection (day 2)
- → MRI: no significant herniation (day 4)

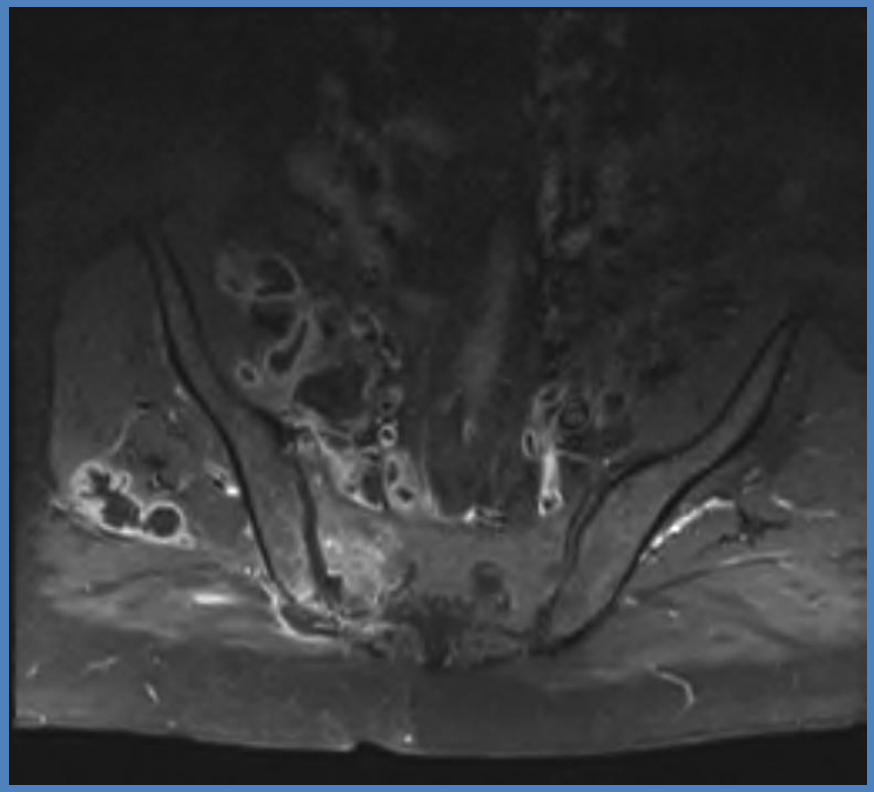
- → 17/7 (day 5)
  - Temperature
  - ↑ back pain → morphinics
  - right forearm catheter related phlebitis



- → **blood culture + *Staphyloccocus aureus***
- → augmentin *then* vancomycin *then* IV oxacillin (2g q4h) for MSSA 
- → CT scan: lumbar abscess
- → carbonarcosis induced by morphinics
- → ICU (NIV)

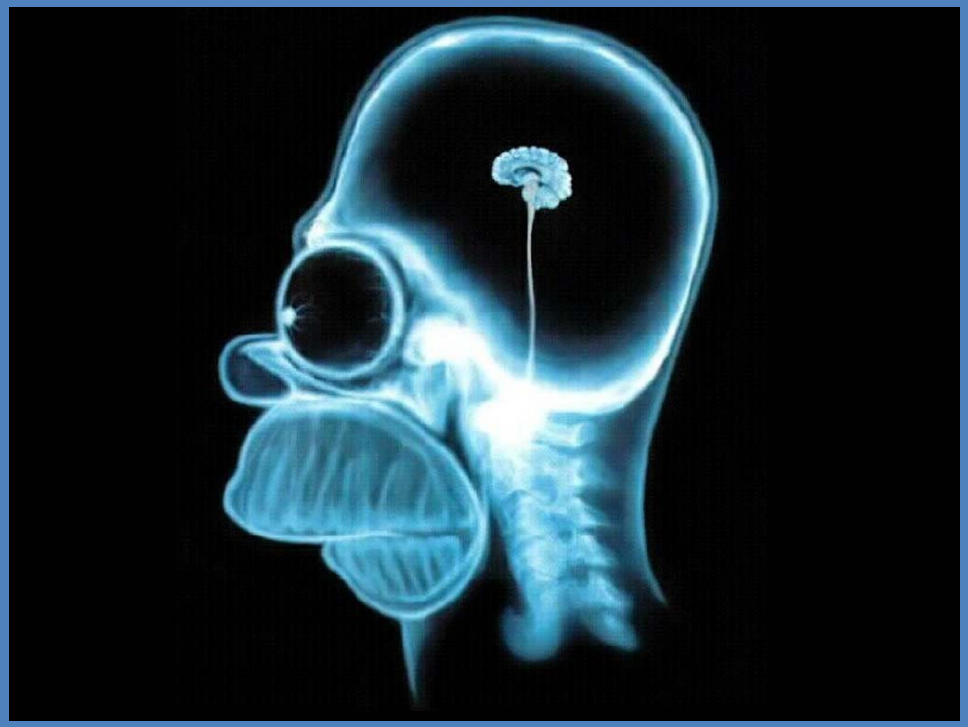
- → ***transfered to our institution for surgical drainage***

- MRI:
  - Extensive abscess (21 cm): L4-L5 → psoas
  - Right sacro-ileitis
  - Spondylodiscitis (L5-S1)



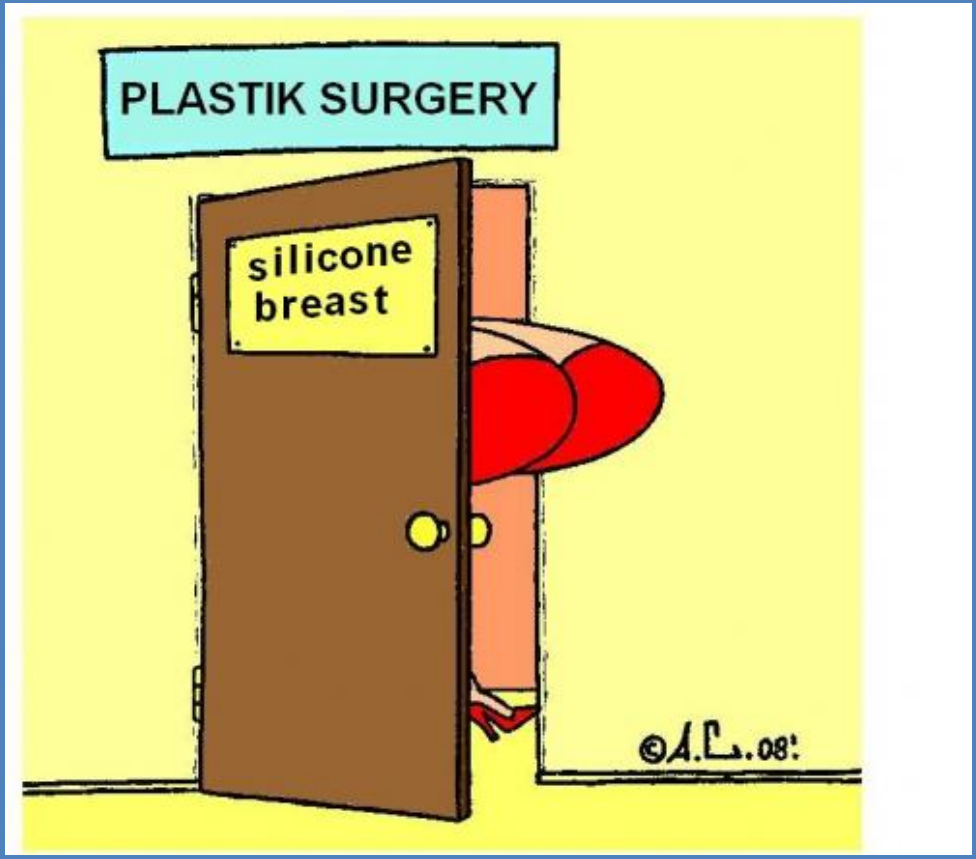
***→ surgical drainage***

- Neurosurgery: no

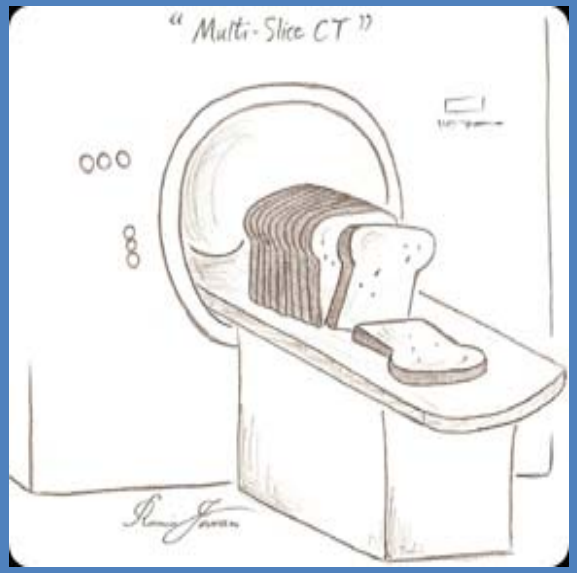


- Orthopedic surgeon: no

- Plastic surgery: no

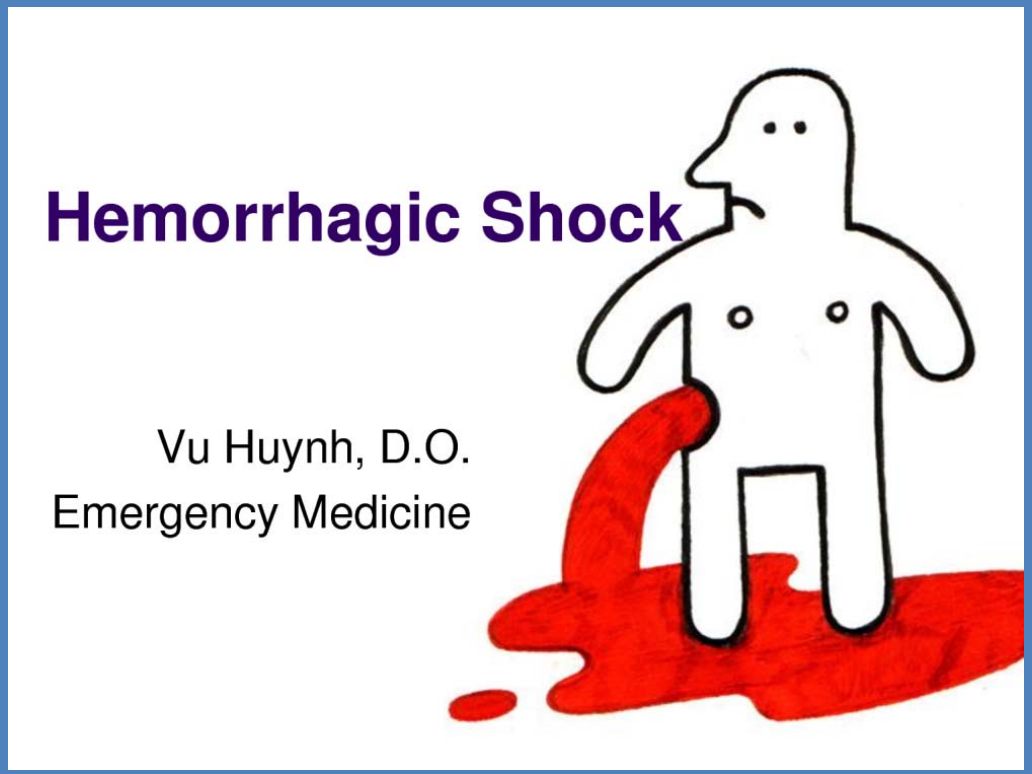


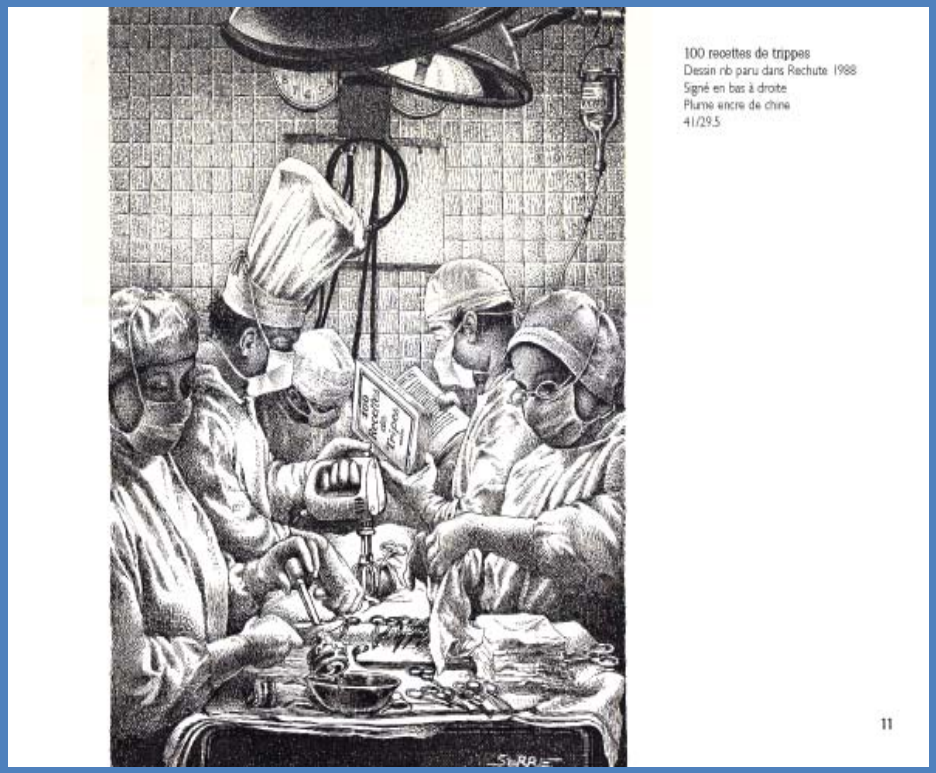
- Ask to interventional radiologist:




- But…

- →hemorrhagic shock on bleeding diverticulosis






- → digestive surgeon
- → Surgical removal of the bleeding diverticulum (partial left colectomy)
- → drainage of the abscess (1/8 = day 14)

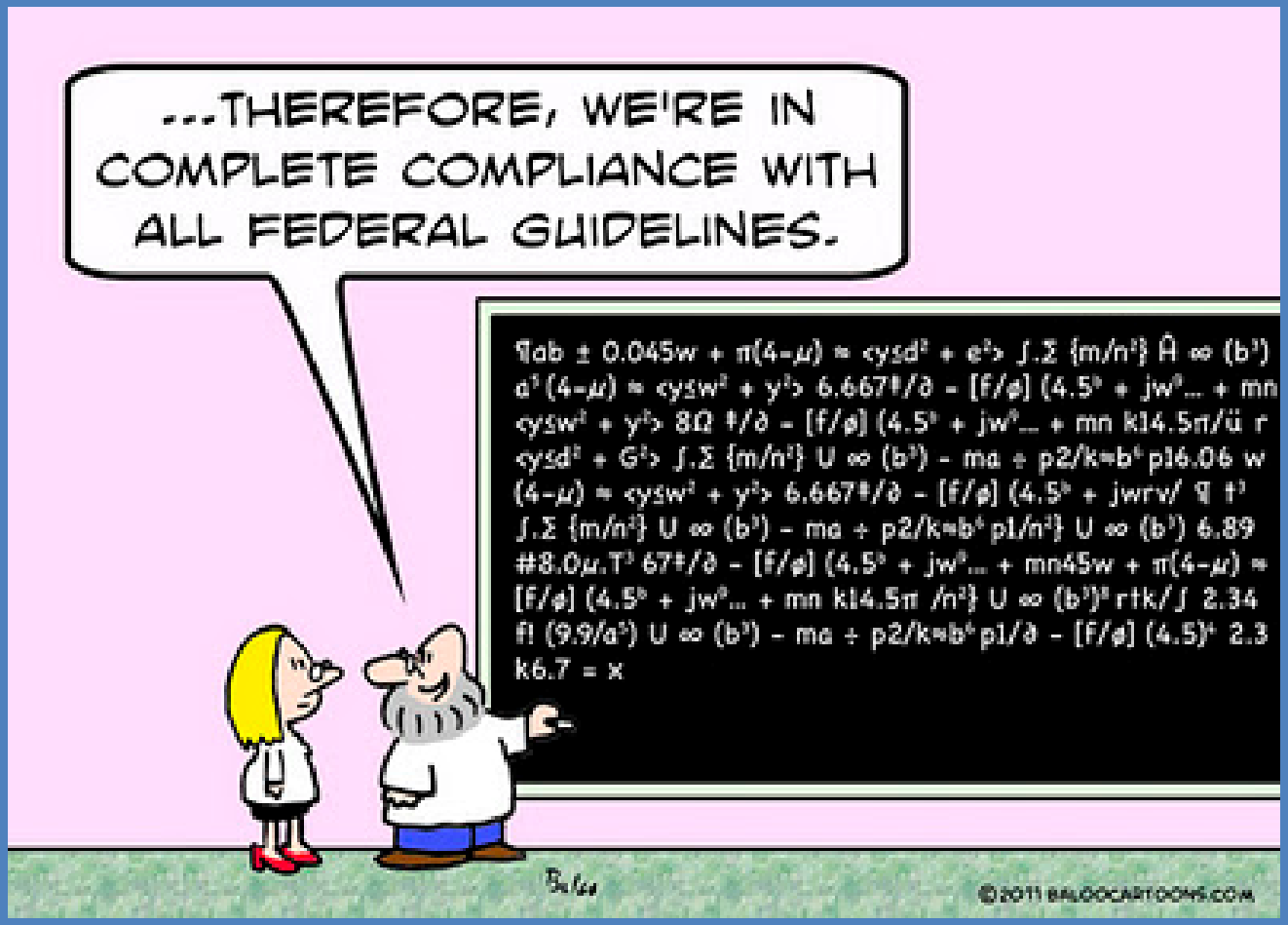
- → pus culture (+) for *S. aureus*
- → transesophageal echocardiography (-)
- → repeated blood cultures (-)

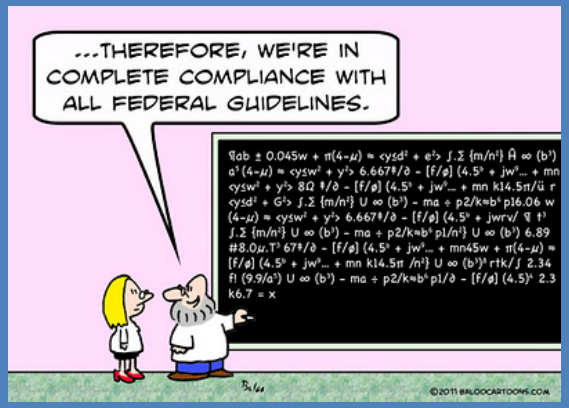
- → 2 weeks course of fluclox 2gq4h
- Then
- → rifampin 600 mgq12h + moxifloxacin 400mgq24h orally for 3 months (ongoing)
- → discharged on day 22

# 1 patient, 4 problems

- (I) abscess
- (II) SAB
- (III) catheter- related infection
- (IV) bone and joint infection

# « Treating S. aureus infections: from guideline to practice. »

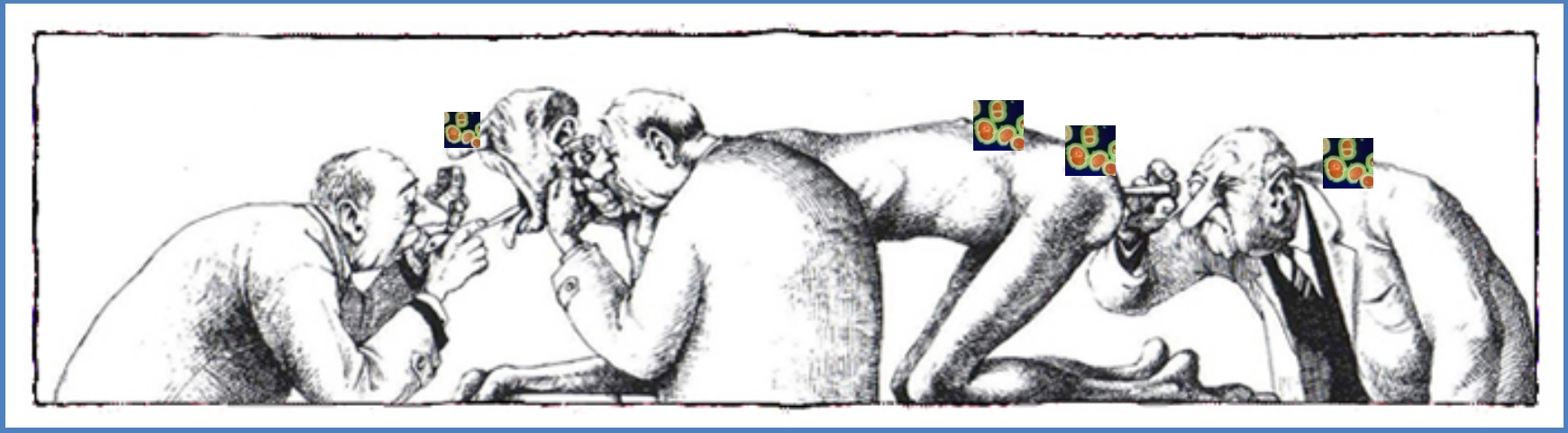





# Guidelines

# ↓

# good clinical practice



# Pubmed, sept 15 2012:

- *Staphylococcus aureus* guidelines: 1264 ref.
- *Staphylococcus aureus* guideline: 616 ref.
- MRSA guidelines: 780 ref.

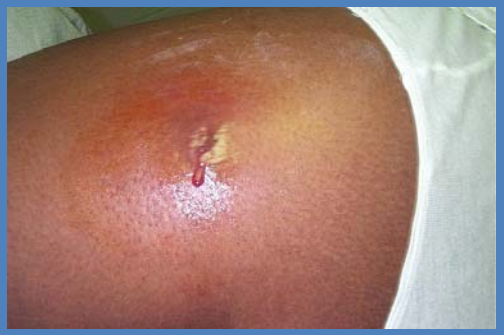
# Pubmed, sept 15 2012:

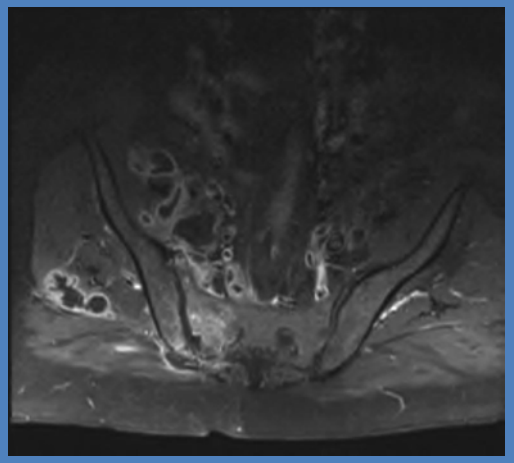
- *Staphylococcus aureus* guidelines ***bacteremia*** : 125 ref.
- *Staphylococcus aureus* guidelines ***pneumonia***: 158 ref.
- *Staphylococcus aureus* guidelines ***skin soft tissue***: 52 ref.
- *Staphylococcus aureus* guidelines ***endocarditis***: 51 ref.
- *Staphylococcus aureus* guidelines ***osteomyelitis***: 31 ref.
- *Staphylococcus aureus* guidelines ***arthritis***: 20 ref.
- *Staphylococcus aureus* guidelines ***meningitis***: 17 ref.

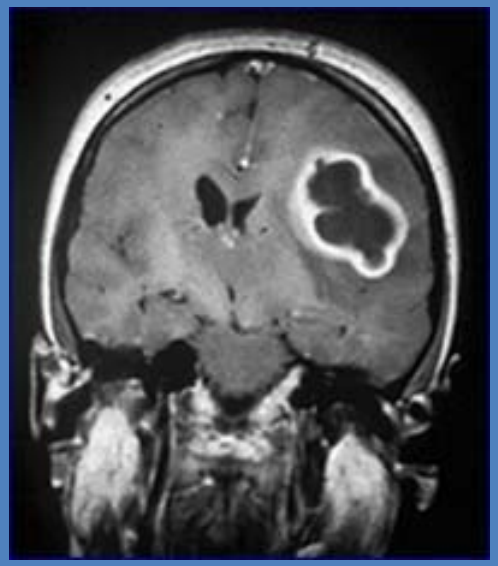
- Focus on:
  - **The Australian Society for Antimicrobials Staphylococcus aureus Working Party**. Intern Med J 2005;35: S1-S140
  - **Clinical Overview of Gram-Positive Bloodstream Infections** CID 2009;48: S231-270 → ***No clear guideline***
  - **Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection**: 2009 Update by the Infectious Diseases Society of America. **Mermel** LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK. Clin Infect Dis. 2009 Jul 1;49(1):1-45**.**
  - **Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus** infections in adults and children: executive summary.Liu C, et al.Clin Infect Dis. 2011 Feb 1;52(3):285-92.
  - **Clinical management of Staphylococcus aureus bacteraemia**. **Thwaites** GE, et al; UK Clinical Infection Research Group.Lancet Infect Dis. **2011** Mar;11(3):208-22. **Review**. → ***Surprisingly little evidence is available to guide the management of SAB***

# I: *S. aureus* abscess

- incision and ***drainage*** is the primary treatment.







→ easy to say
→ sometimes difficult to obtain

# II: *S. aureus* bacteremia

- Surprisingly ***little evidence is available*** to guide the management of SAB.
- ***clinical practice is driven by the results of observational studies and anecdote.***
- **Thwaites** GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME, Walker S, Wertheim HF, Wilson P, Llewelyn MJ; UK Clinical Infection Research Group.
- Lancet Infect Dis. **2011** Mar;11(3):208-22. **Review**.

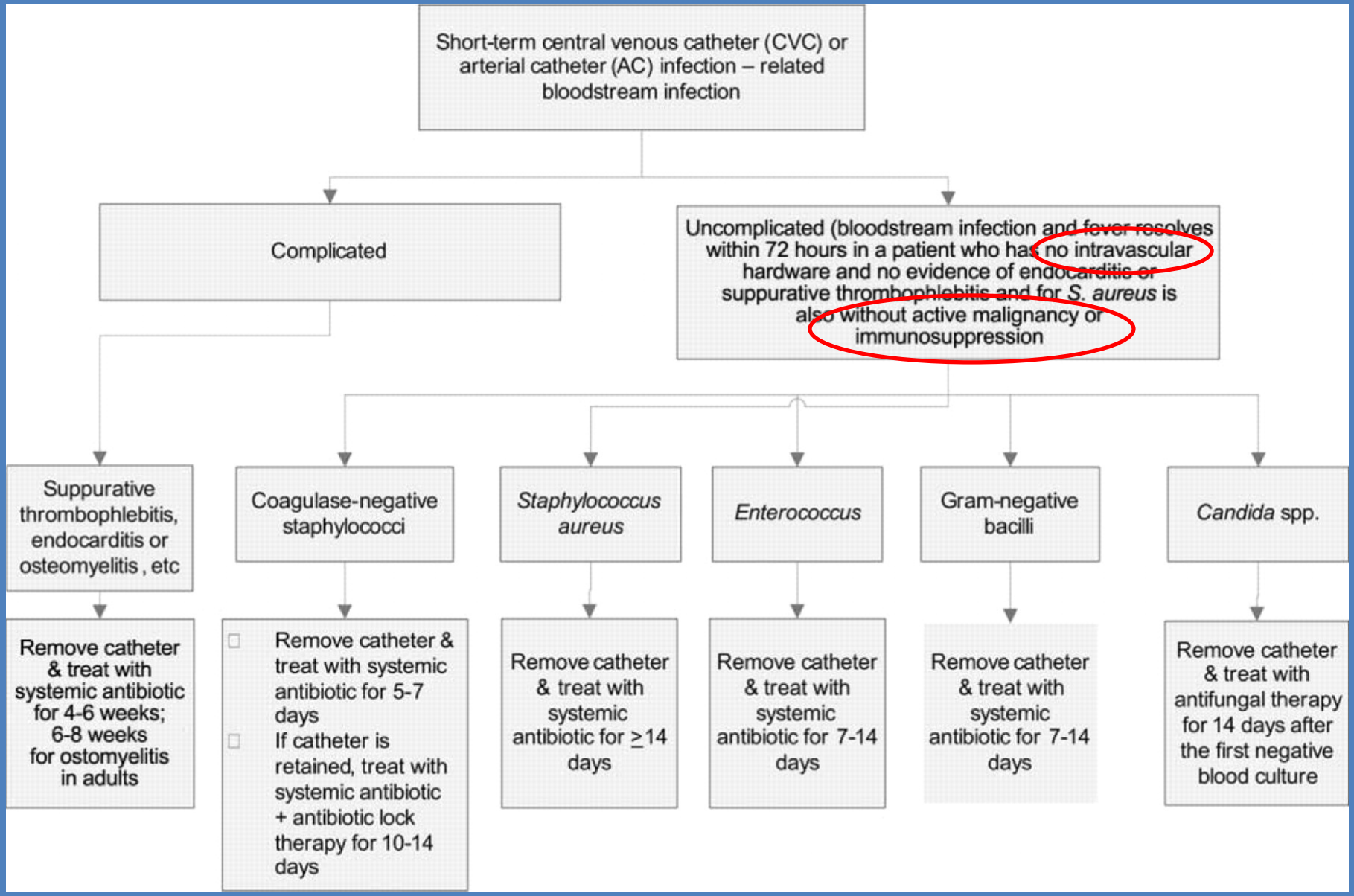
- No clear guideline in the absence of a known or suspected underlying ***site of infection***.

- Corey GR. CID 2009;48:S254-9

- Unknown portal of entry or associated infected site:
    - BSI in general : 25.6% Seifert H CID 2009;48:S238-45
    - SAB: ***40-50%*** (only 3-5% if nosocomial) del Rio A et al CID 2009;48:S246-53

- ***If SAB:***
- ***→ goal:***
  - Search site of infection
    - SAB coming from (source)
    - SAB going to (seeding)
  - distinguish complicated/uncomplicated SAB
- ***→ this should allow:***
  - choice best regimen: ***which drug(s)?***
  - Determination the optimal duration of antibiotherapy : ***how many time?***

- *→ goal: distinguish complicated/uncomplicated SAB*
- → uncomplicated SAB:
- (1) Catheter-associated infection (with the catheter removed)
- (2) Defervescence within 72 h of starting active therapy
- (3) Sterile follow-up blood culture
- (4) Normal TOE
- (5) No prosthetic material in any joint or vessel
- (6) No clinical signs suggestive of metastatic infection
- *Proposed definition, not universally accepted*
- Fowler et al Arch Intern Med 2003; Corey CID 2009; Naber et al CID 2009; Thwaites et al TLID 2011;




**Mermel L A et al. Clin Infect Dis. 2009;49:1-45**

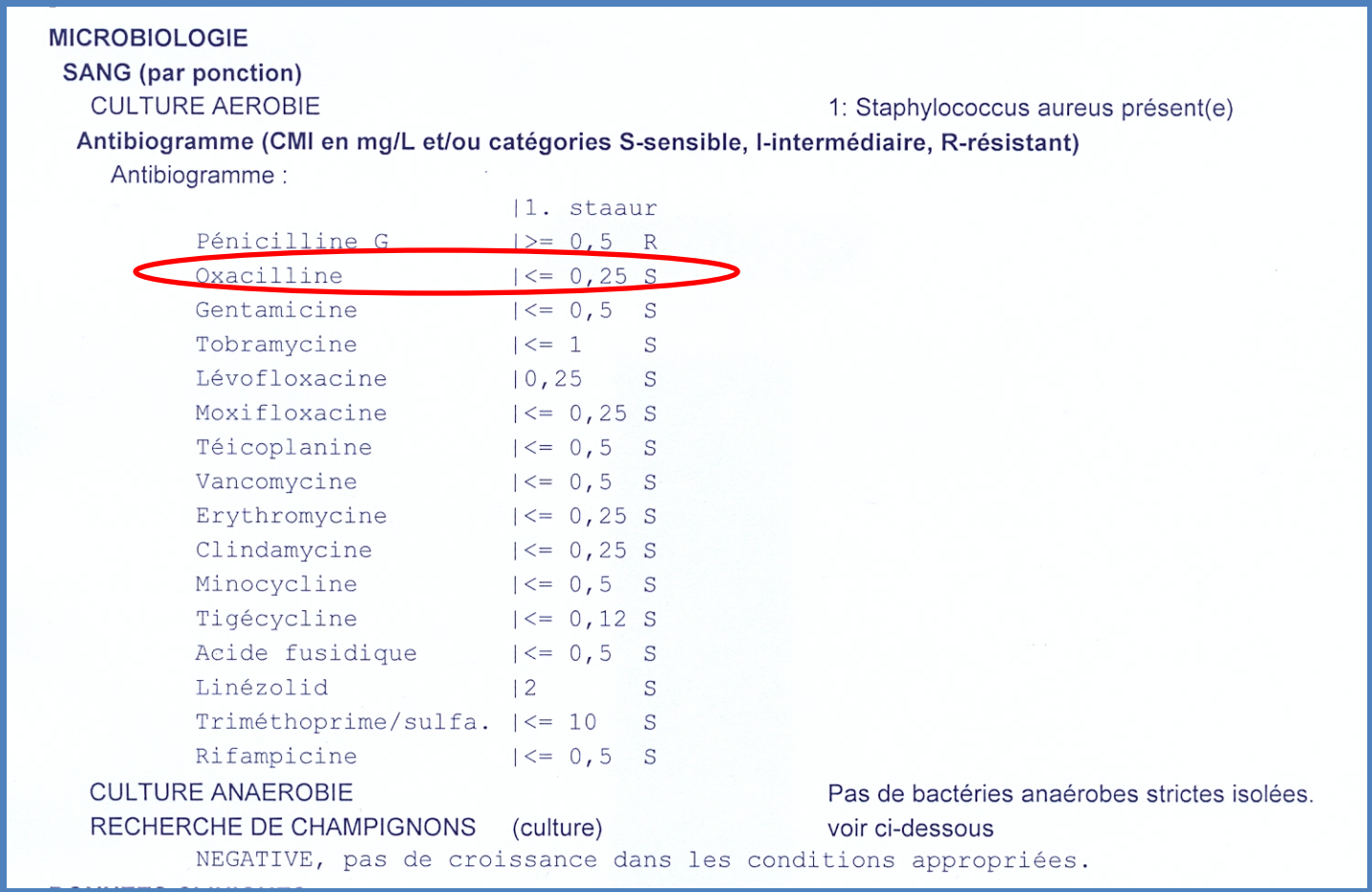
- ***On a practical point of view:***
  - → meticulous physical examination
    - → source of infection and/or
    - → metastatic infection
  - → if catheter:
    - → removed (unless exception) and
    - → cultured
  - → perform blood cultures every 48-72h until (-)
    - ***Positive blood cultures ≥ 3 d after start of effective AB = the strongest predictor of compicated SAB.***
  - → perform TOE for all patients

# Choice of regimen in SAB:

- ***the best drugs, dose, mode of delivery, and duration of therapy are uncertain***, a situation compounded by emerging *S aureus* strains that are resistant to old and new antibiotics.

- **Thwaites** GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME, Walker S, Wertheim HF, Wilson P, Llewelyn MJ; UK Clinical Infection Research Group.
- Lancet Infect Dis. **2011** Mar;11(3):208-22. **Review**.

- **Classically:**
- → MSSA → IV isoxazolypen (or Pceph1)



**MICROBIOLOGIE**

**SANG (par ponction)**

CULTURE AEROBIE — 1: Staphylococcus aureus présent(e)

**Antibiogramme (CMI en mg/L et/ou catégories S-sensible, I-intermédiaire, R-résistant)**

Antibiogramme :

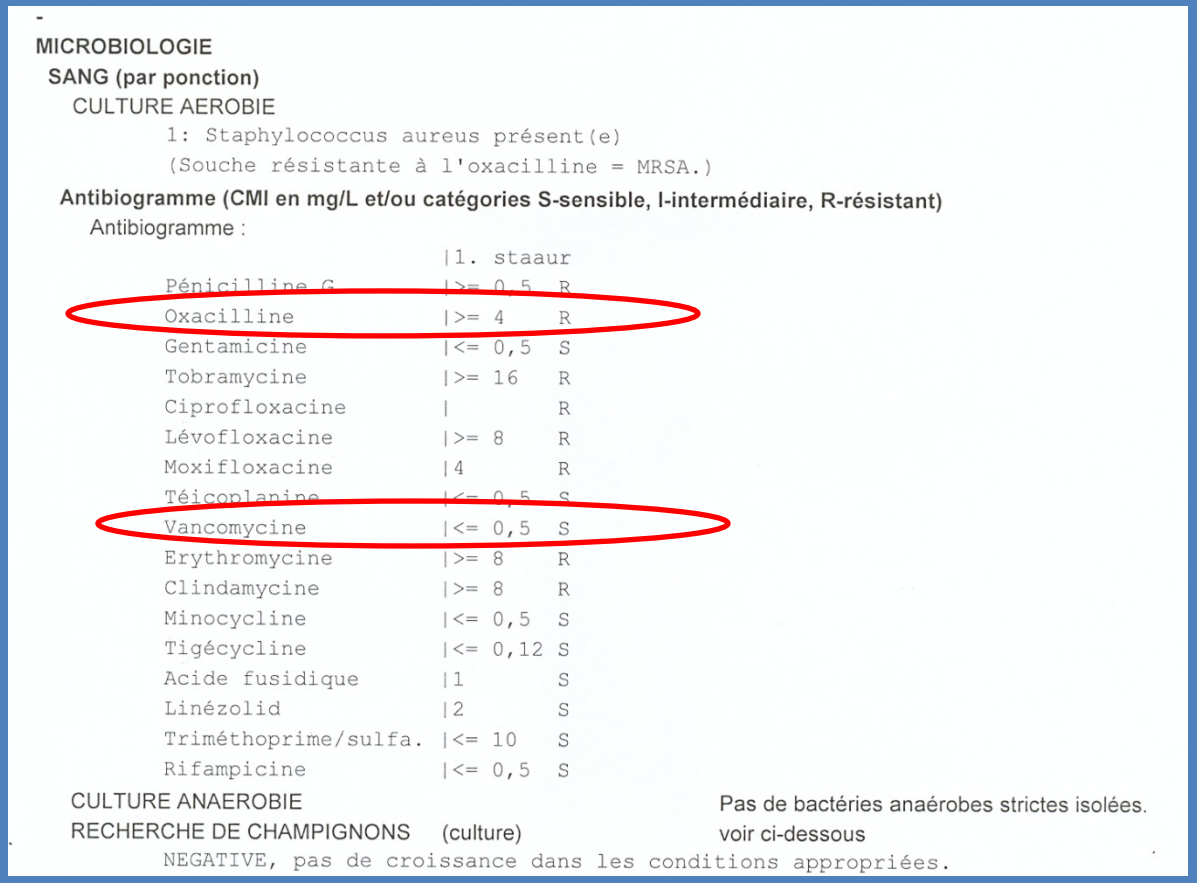
| | 1. staaur | |
|---|---|---|
| Pénicilline G | >= 0,5 | R |
| Oxacilline | <= 0,25 | S |
| Gentamicine | <= 0,5 | S |
| Tobramycine | <= 1 | S |
| Lévofloxacine | 0,25 | S |
| Moxifloxacine | <= 0,25 | S |
| Téicoplanine | <= 0,5 | S |
| Vancomycine | <= 0,5 | S |
| Erythromycine | <= 0,25 | S |
| Clindamycine | <= 0,25 | S |
| Minocycline | <= 0,5 | S |
| Tigécycline | <= 0,12 | S |
| Acide fusidique | <= 0,5 | S |
| Linézolid | 2 | S |
| Triméthoprime/sulfa. | <= 10 | S |
| Rifampicine | <= 0,5 | S |

CULTURE ANAEROBIE — Pas de bactéries anaérobes strictes isolées.

RECHERCHE DE CHAMPIGNONS (culture) — voir ci-dessous

NEGATIVE, pas de croissance dans les conditions appropriées.

- **Classically:**
- → MSSA → IV isoxazolypen (or Pceph1)
- → MRSA → IV vancomycin



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MICROBIOLOGIE

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1: Staphylococcus aureus présent(e)
(Souche résistante à l'oxacilline = MRSA.)

Antibiogramme (CMI en mg/L et/ou catégories S-sensible, I-intermédiaire, R-résistant)

Antibiogramme :

| | 1. staaur | |
|---|---|---|
| Pénicilline G | >= 0,5 | R |
| Oxacilline | >= 4 | R |
| Gentamicine | <= 0,5 | S |
| Tobramycine | >= 16 | R |
| Ciprofloxacine | | R |
| Lévofloxacine | >= 8 | R |
| Moxifloxacine | 4 | R |
| Téicoplanine | <= 0,5 | S |
| Vancomycine | <= 0,5 | S |
| Erythromycine | >= 8 | R |
| Clindamycine | >= 8 | R |
| Minocycline | <= 0,5 | S |
| Tigécycline | <= 0,12 | S |
| Acide fusidique | 1 | S |
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| Triméthoprime/sulfa. | <= 10 | S |
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NEGATIVE, pas de croissance dans les conditions appropriées.

# *S. aureus* bacteremia

- **<u>Empirical therapy, pending antibiogram:</u>**
- MSSA: isoxazolypen (or Pceph1)
- If risk for MRSA: ***add*** vancomycin

- **!! Do not replace isoxa with vancomycin!!**
- **Adaptation based on definitive antibiogram**

- →repeated demonstration that vanco is associated with a significant worse outcome when used for patients with MSSA infection
- → ***including for HD dependent patients***
- Stryjewski ME et al CID 2007;44:190-6
- Naber C K CID 2009;48:231-7

- Those receiving nafcillin or cefazolin had ***79% lower mortality hazards*** compared with those who received vancomycin alone (adjusted hazard ratio (HR): 0.21; 95% confidence interval (CI): 0.09, 0.47). Among the 122 patients who initially received vancomycin empirically, those who were switched to nafcillin or cefazolin (66/122) had ***69% lower mortality hazards*** (adjusted HR: 0.31; 95% CI: 0.10, 0.95) compared to those who remained on vancomycin.

- Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible **Staphylococcus aureus bacteremia**.
- Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, McGregor JC, Thom KA, **Cosgrove** SE, Sakoulas G, Perencevich EN.
- BMC Infect Dis. **2011** Oct 19;11:279.

# Doses:

- isoxazolypen or Pceph1 dosage:
  - **(Flu) cloxaxillin or oxacillin**:
    - 2g IV q4-6h (or 8g CI)
      - Mitchell DH, Howden BP. Intern Med J 2005;35:S3-16
      - Baddour et al Circulation 2005
      - Sanford Guide Belgian/Luxembourg edition

  **- Cefazolin:**
    - 2gq8h (T1/2 = 2h)

- Vancomycin dosage: ***cfr Dr S Vandecasteele***

- **Treatment and Outcome of Staphylococcus aureus Bacteremia: A Prospective Study of 278 Cases.** Allan G. Jensen, MD et al. Arch Intern Med 2002;162:25-32

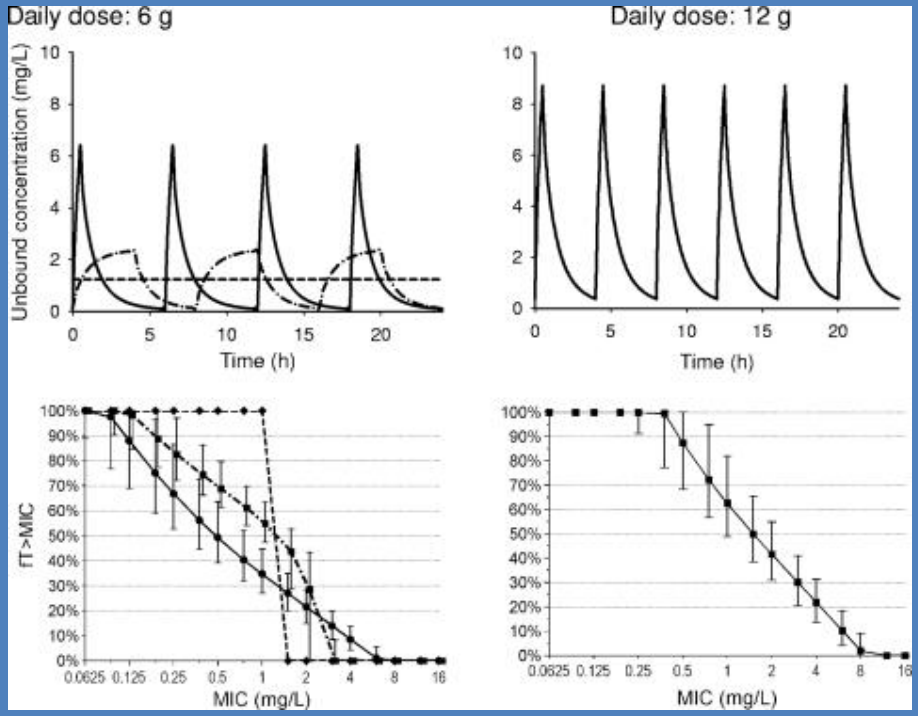
- variables statistically associated with **death**:
  - the presence of an uneradicated focus (odds ratio [OR], 6.7; 95% confidence interval [CI], 2.1-21.0);
  - the presence of septic shock (OR, 3.7; 95% CI, 1.5-9.1);
  - ***the total daily dose of penicillinase-stable penicillin less than 4 g*** (OR, 3.7; 95% CI, 1.3-11.1);
  - age 60 years or older (OR, 2.4; 95% CI, 1.1-5.3).
- variables significantly associated with **recurrence**:
  - ***the total daily dose of penicillinase-stable penicillin less than 3 g*** (OR, 3.9; 95% CI, 1.6-10.0) ;
  - the presence of a secondary focus (OR, 3.2; 95% CI, 1.3-7.7).

- **Conclusions** ***We recommend treatment with at least 1 g of penicillinase-stable penicillins 4 times daily***

- Note:
- fluclox IV, 1g:
  - » peak 167±26.7 (total drug)
  - » T1/2 =1h;

- ***%Protein Binding > 95%***
- *(Leder et al 1999)*

- Attainment of the pharmacokinetic (PK)-pharmacodynamic (PD) target of an $fT_{>MIC}$ of ≥50% correlates best with the near maximal bactericidal activity of penicillins.
- For an $MIC_{90}$ of 0.5 mg/liter, which is typically found for flucloxacillin against MSSA:
  - ***4g/d CI = 2gq4h*** (12g/d, 5 min bolus IV)




Population pharmacokinetics at two dose levels and pharmacodynamic profiling of **flucloxacillin**. **Landersdorfer** CB, Kirkpatrick CM, Kinzig-Schippers M, Bulitta JB, Holzgrabe U, Drusano GL, Sörgel F. Antimicrob Agents Chemother. **2007** Sep;51(9):3290-7.

- ***Penicillin-susceptible S. aureus*** (~10%):
- MIC of pen G is ~ 0.01 mg/L in contrast of isoxazolypen which is 10-fold higher.
- ***→ thus penicillin G remains one of the best choices against pen-S staphylococci***.
- Rayner,C, Munckhof WJ Intern Med J 2005;35:S3-16
- Que YA, Moreillon Ph In ***Mandell*** 7th edition 2010, pp2543-78
    - Penicilline G: 18 to 24 MIU/day div q4h iv or CI

# Optimum duration of therapy for SAB:

- **Uncomplicated SAB:**
  - ***at least 14 days***
  - « ***10–14 days*** of intravenous therapy seems to be sufficient for most cases of uncomplicated, catheter-associated SAB, provided that the catheter has been removed and the risk of endocarditis is low. Whether intravenous therapy can be shortened to ***7 days***, or replaced by ***oral antibiotics*** after initial intravenous treatment, is uncertain. “ Thwaites 2011

**Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis.** Crit Care. ***2011***;15(6):R267. Epub 2011 Nov 15. Havey TC, Fowler RA, Daneman N.

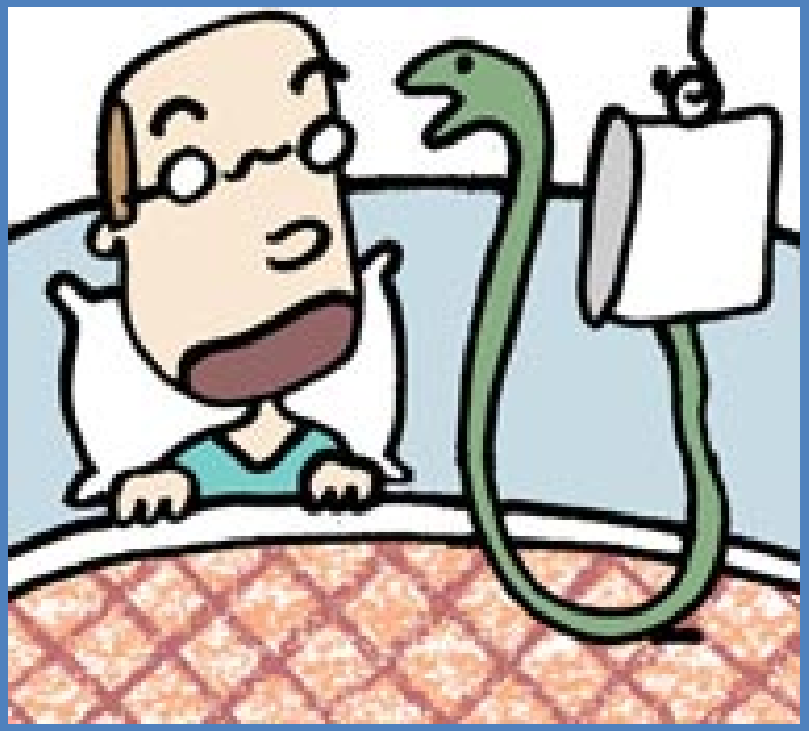
- The optimal duration of treatment for bloodstream infections is **understudied**.
- Available data from bacteremic subgroups of prior randomized controlled trials suggest that shorter-duration therapy (not more than **7 days**) **may be as effective as longer-duration therapy** in achieving clinical cure, microbiologic cure, and survival among most patients with bloodstream infections.
- This review highlights the potential importance of **considering *S. aureus* bacteremia separately** from other pathogens in the context of adequately powered trials in the future.

- A large dedicated randomized trial of treatment duration for bacteremia is urgently needed.

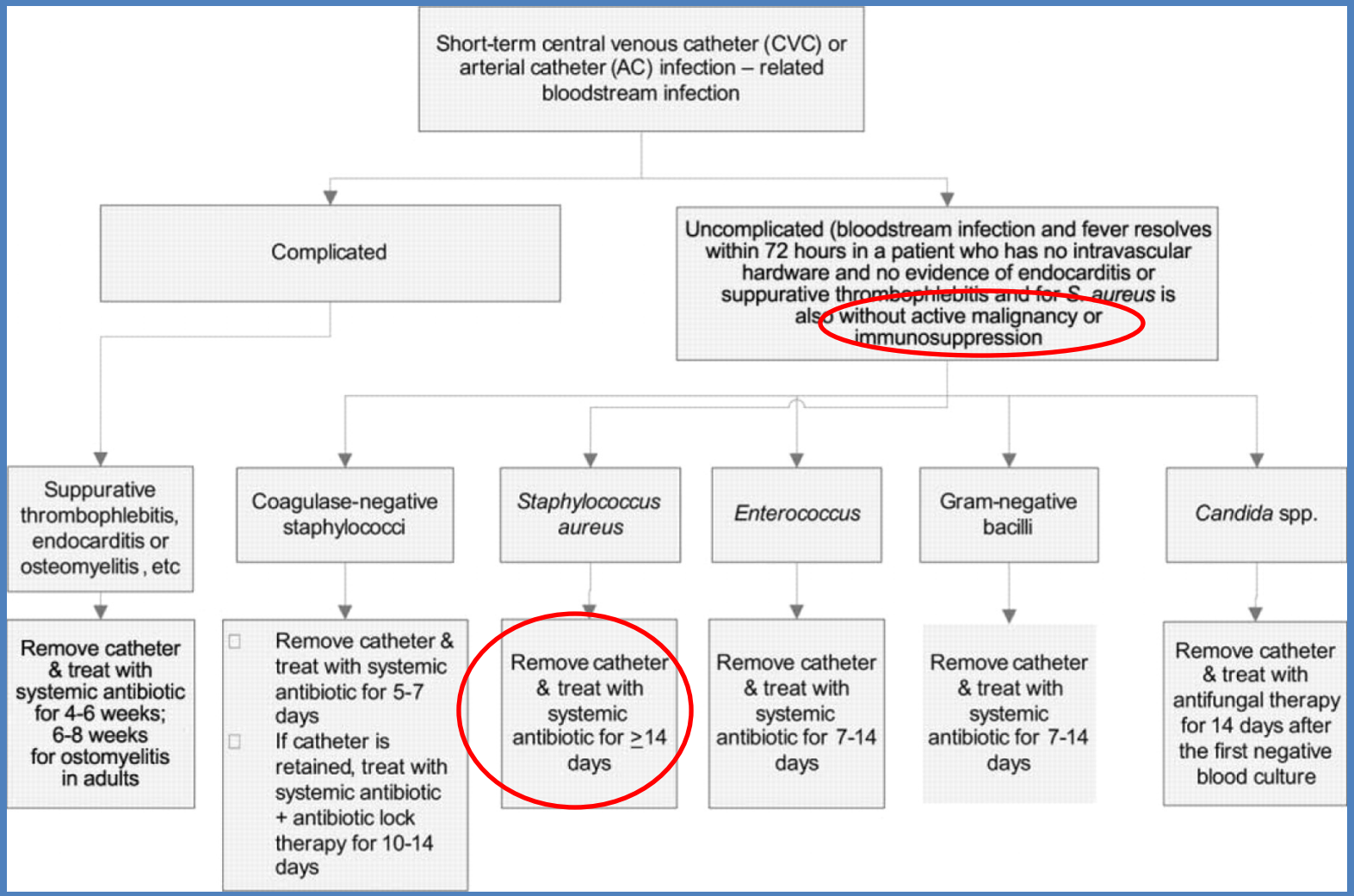
**Complicated case:**

- all others situations, ***including patients with unidentified primary focus:***
- ***4-6 weeks of AB, at least***
- ***At least 2 weeks IV before considering oral switch therapy with « other drugs », depending of the site of infection.***

# III: *S. aureus* catheter-related infection



# Approach to the management of patients with *short-term* central venous catheter-related or arterial catheter-related bloodstream infection.




**Mermel L A et al. Clin Infect Dis. 2009;49:1-45**

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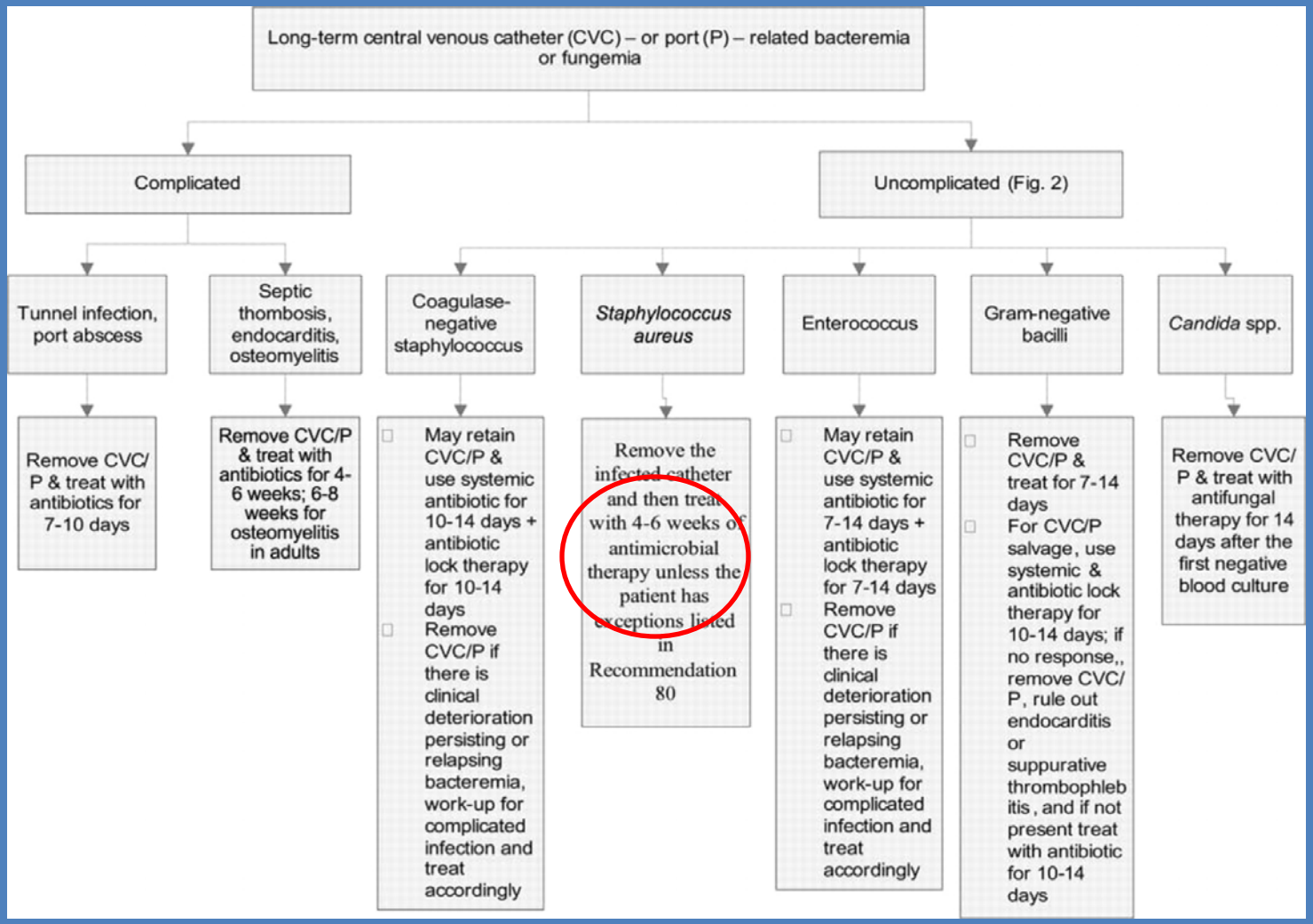
Clinical Infectious Diseases

# Approach to the treatment of a patient with *a long-term (surgically implanted – Hickman, Broviac,...)* central venous catheter (CVC) or a port (P)-related bloodstream infection.

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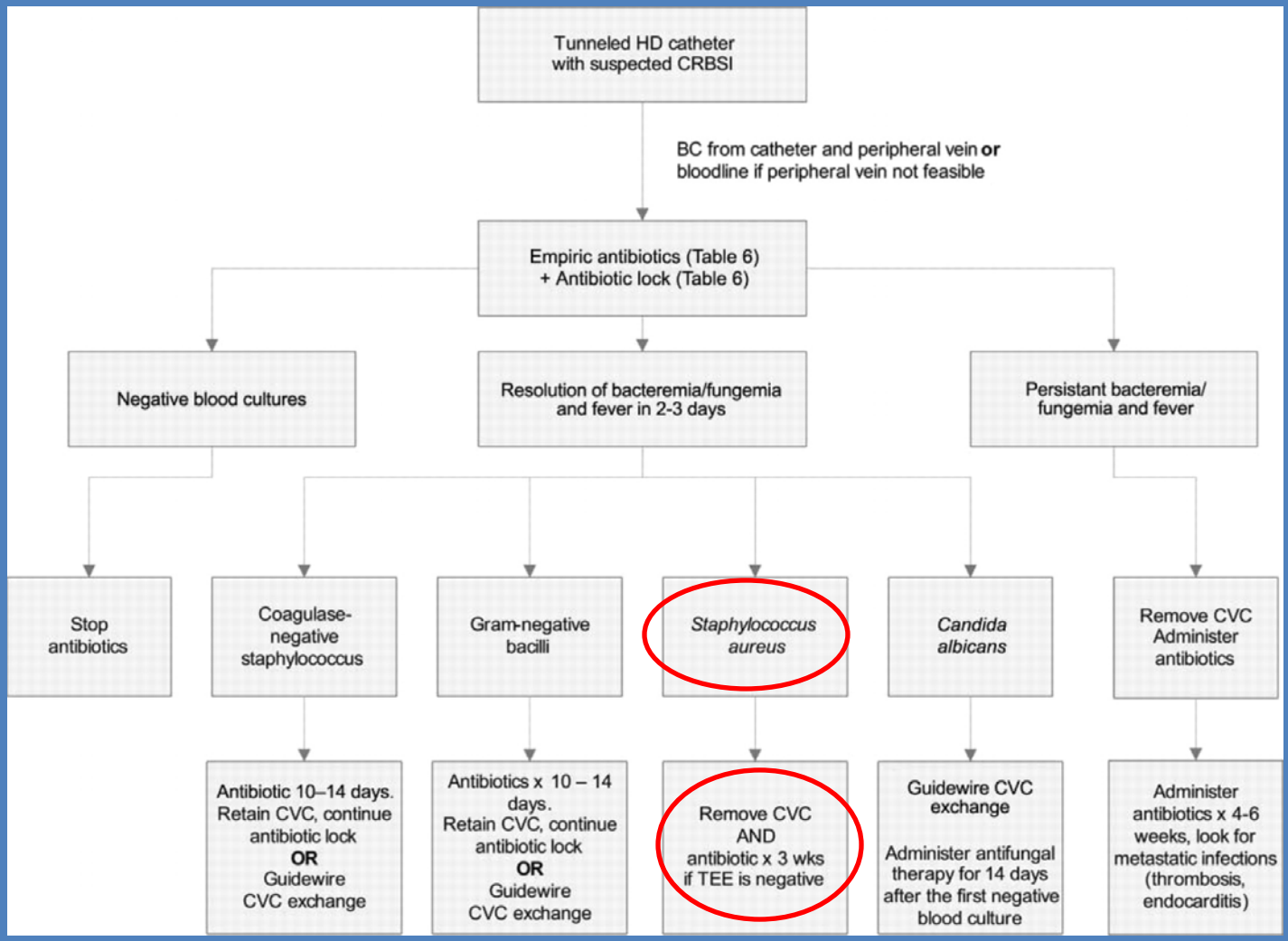
# Catheter-related blood stream infection (CRBSI) among patients who are undergoing hemodialysis (HD) with tunneled catheters.

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## MICROBIOLOGIE

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| Tigécycline | <= 0,12 | S |
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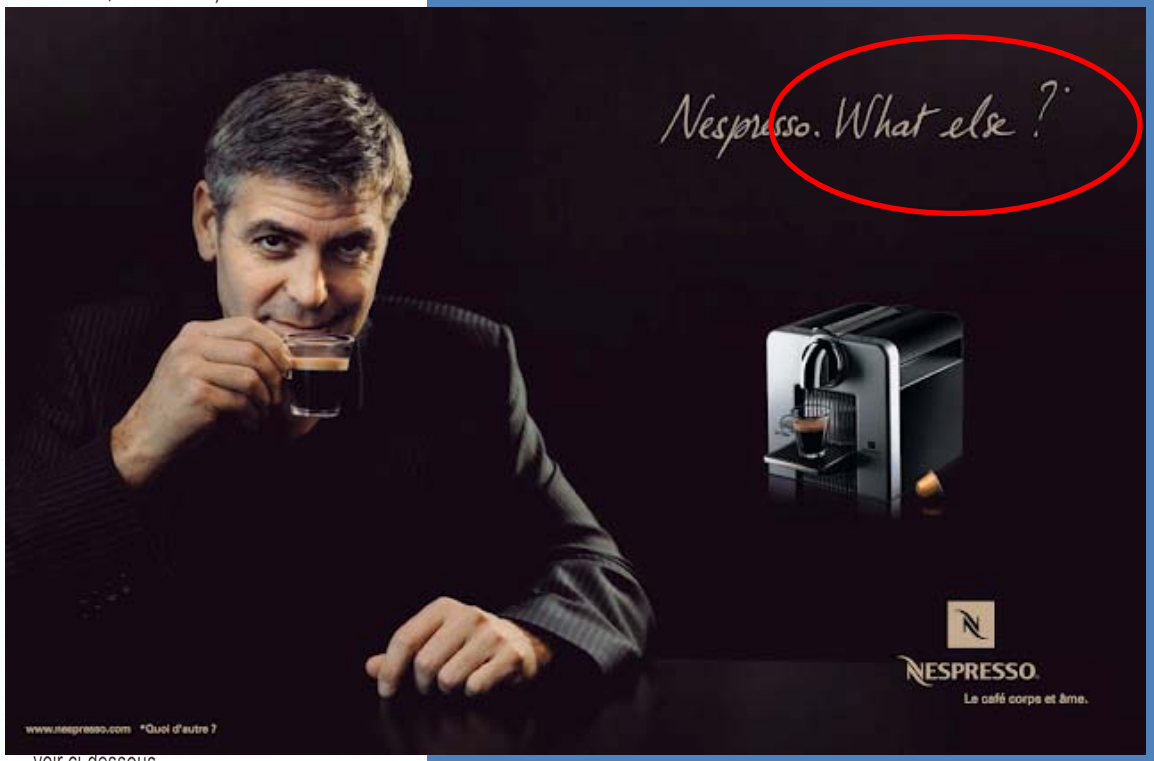

# Aminoglycoside:

- **<u>Gentamycin:</u>**
  - → no proven benefits, in particular in S. aureus IE
    Falagas ME, Matthaiou DK and Bliziotis JA. The role of aminoglycosides in combination with a β-lactam for the treatment of bacterial endocarditis***: a meta-analysis*** of comparative trials. J Antimicrob Chemother **2006**;57:639-47
  - initial low-dose gentamicin in this setting is associated with rapid, relevant and durable renal impairment Cosgrove SE, Vigliani GA, Campion M, et al. Initial low-dose gentamicin for *S. aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis **2009**; 48:713–21

  → OAD? TID?

  → ***My opinion: don't use genta in SAB***

# Rifampin:

- → in vitro:
  - Synergy+
  - Antogonism +
  - Indifference +
  - Penetration in biofilm, phagocytes and abscess
  - Kills organism in stationnary phase Deresinski CD 2009;49:1072-79
- → in vivo:
  - IE + vanco:
    - prolongation of bacteremia by 2 days
    - no difference in clinical outcomes
    - Increased hepatotoxicity
    - Levine DP, et al. *Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Ann Intern Med 1991;115:674-80;*
    - Riedel DJ, et al. *Addition of rifampin to standard therapy for treatment of native valve endocarditis caused by Staphylococcus aureus. Antimicrob Agents Chemother 2008;52:2463-7.*

- Rifampin dosing: quite variable throughout literature:
  - 600 mg OAD
  - 300-450 mg BID (IE and prosthetic valve: 300 mg TID)
  - PK/PD:
    - Concentration dependent (AUC/MIC)
    - after ~ 6 days: ↑ own metabolism → ↓T1/2 ~ 3-(5)h
    - ***→ 450 (< 60 kgs)-600 mg (> 60 kgs) BID = CHU Liège***
    - No published data to guide the timing of adding rifampin (Risk of emergence of resistance if given during initial bacteremia and/or high bacterial load)

# Quinolones:

- **Guidelines** (bone and joint infections/right-sided IE):
  - Cipro > levo
- **In vitro**:
  - Moxi> levo > cipro
- .
- **Levofloxacin does not decrease mortality in Staphylococcus aureus bacteraemia when added to the standard treatment: a prospective and randomized clinical trial of 381 patients.**
- Ruotsalainen E, et al. J Intern Med. 2006 Feb;259(2):179-90.

# IV: *S. aureus* bone and joint infection

- ***Surgical debridement and drainage*** of associated soft-tissue abscesses is the mainstay of therapy and should be performed whenever feasible
- The ***optimal route of administration*** of antibiotic therapy has ***not been established***. Parenteral, oral, or initial parenteral therapy followed by oral therapy may be used depending on individual patient circumstances

- The ***optimal duration of therapy*** for MRSA osteomyelitis is ***unknown***. A minimum 8-week course is recommended **(A-II).** Some experts suggest an additional 1–3 months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities

- Clinical practice **guidelines** by the infectious diseases society of america for the treatment of **methicillin-resistant Staphylococcus aureus** infections in adults and children: executive summary.Liu C, et al.Clin Infect Dis. 2011 Feb 1;52(3):285-92.

- CHU liège:
- 5-15 d IV then oral therapy with rif + mox or mino;
- Total: minimum 6 weeks (→ 3 months )

# Linezolid:

- **<u>SAB:</u>**
  - No specific study
  - 1 **meta-analyse**: 99 pts with SAB from 5 comparative trials
  - → no difference in outcome vs vancomycin
  - Shorr et al JAC 2005
  - 1 **meta-analysis**: 255 pts with SAB from 12 trials
  - → linezolid was more effective than glycopeptides or beta-lactams (odds ratio [OR] 2.07 [95% CI 1.13-3.78]). Mortality was similar between the groups (OR 0.97 [0.79-1.19]). Falagas et al TLID 2008

- **<u>Pneumonia: LNZ vs vanco</u>**
- No differences in clinical cure in 2 studies designed for noninferiority Rubinstein E, et al. *Clin Infect Dis 2001;32:402-12.* Wunderink RG, et al. *Clin Ther 2003;25:980-92.*
- pooled post hoc analyses showed significant advantages in favor of linezolid for both clinical cures and mortality. Kollef MH, et al. *Clinical cure and survival in gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med 2004;30:388-94.*

- → numerous critics about methodology.

- Wunderink RG, et al. *Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis **2012**;54:621-9.*
- → *« good doses » of vanco*
- → significantly better clinical cure with linezolid (58%) compared with vancomycin (47%).
- →These results were also favorable for linezolid in terms of microbiological cure (58% vs 47%).
- → However, there was ***no difference in mortality*** at 60 days between the 2 arms.
- → rates of renal adverse effects were twice as high in the vancomycin arm (7.3% vs 3.7%) as in the linezolid arm.

- … but:
  - more than half the patients who received vancomycin failed to achieve trough concentration >15 µg/mL on days 3 and 6.
  - we cannot disregard the ***cost*** of the antibiotic
    - LNZ 600 mg: 65 euros → 130 euros/d
    - Vanco 1g: 17 euros → 3g/d = 51 euros/d + TDM
  - potential appearance of outbreaks of MRSA resistant to linezolid.
- Editorial Torres A Clin Infect Dis. 2012 Mar 1;54(5):630-2: Antibiotic treatment against methicillin-resistant Staphylococcus aureus hospital- and ventilator-acquired pneumonia: ***a step forward but the battle continues***.
- ; **Linezolid versus vancomycin for methicillin-resistant Staphylococcus aureus nosocomial pneumonia: *controversy continues*.** Masuta K, Oba Y, Iwata K. Clin Infect Dis. 2012 Jul;55(1):161. Epub 2012 Mar 29.

# Persistent SAB and/or signs of uncontrolled infection:

- Perform appropriate imaging to look for metastatic infection sites.
- Remove foci of infection with drainage and/or surgical debridment.

- **IDSA guidelines 2011:**
  - Persistent bacteremia
  - → daptomycine: 10 mg/kg/d (Cubicin, 117 euros/500 mg) +
    - Genta 1mg/kg/8h or
    - Rif 600 mg OAD or 300-450 mg BID IV/PO or
    - LNZ 600 BID or
    - TMP/SMX 5 mg/kg BID or
    - B-lactam (synergistic effect in vitro)
  - if ↓ S to vanco and dapto
    - Q/D or TMP/SMX or LNZ or telavancin, alone or in combination
- **S Cosgrove, IDSA 2010, Boston:**
  - Continue vanco HD + « something » before switch to dapto
  - ***No genta, no rif***

# *Conclusions:* Staphylococcus aureus infections.

- Still a matter of debate.
- Still high rates of severe complications and mortality.
- Needs for active prevention.
- Needs for aggressive multidisciplinary approaches to improve outcome.
- Needs studies with new active drugs.

# *Conclusions:* Staphylococcus aureus infections.

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- Still high rates of severe complications and mortality.
- Needs for active prevention.
- Needs for aggressive multidisciplinary approaches to improve outcome.
- Needs studies with new active drugs…
- … but also old drugs!