Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

Catheter-related infections: practical aspects in 2003

A joint meeting of the *Société Belge d'Infectiologie et de Microbiologie Clinique / Belgische Vereniging voor Infectiologie en Klinische Microbiologie* (21st meeting) and the *Groupement pour le Dépistage, l'Etude et la Prévention des Infections Hospitalières / Group ter Opsporing, Studie en Preventie van Infecties in de Ziekenhuizen*

Thursday 20th November 2003

Catheter-related blood stream infections: antimicrobial treatment.

Dirk Vogelaers MD PhD
Section for Infectious Diseases
Internal Medicine Department
University Hospital Gent

Key reference

Mermel et al. Guidelines for the management of intravascular catheter-related infections. CID 2201; 32: 1249-72

Table 1. Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Short term venous catheters

- **Short term for CVC = < 30 days.**
- **Most likely pathogens**
  - **coagulase negative staphylococci**
  - **S. aureus**
  - **Enterobacteriaceae**
  - **Candida spp.**

Long-term venous catheters in impaired host (burns, neutropenia)

- **Most likely pathogens**
  - **CNS**
  - **S. aureus**
  - **Enterobacteriaceae**
  - **Other GNB**
  - **Candida spp.**
  - **Corynebacterium jeikeium**
  - **(Aspergillus spp.)**

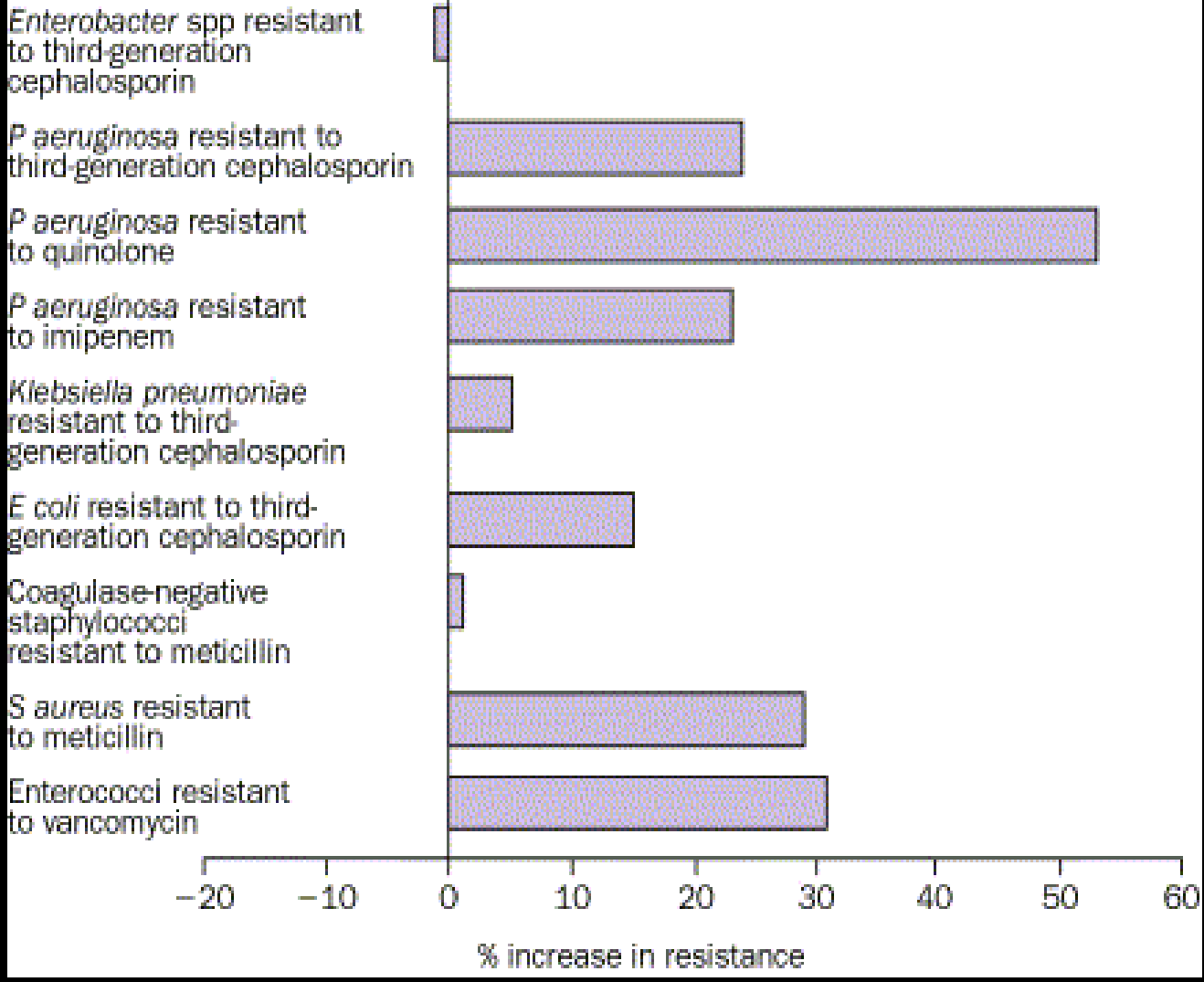


Figure 2. Increases in rates of antibiotic resistance for selected pathogens when comparing resistance rate of January to December, 2000, with mean rate resistance over previous 5 years (1995–99)

JL Vincent The Lancet June 14 2003

Empiric antimicrobial treatment.

- Glycopeptide logic choice in vieuw of frequency distribution of pathogens involved in CR-BSI (activity on methicillin-resistant CNS and S. aureus) (large majority of pts).
- Additional empiric coverage for enteric GNB + P. aeruginosa with 3d or 4th generation Pceph or FQ in severely ill or immunocompromised pts with suspicion of CR-BSI.
- Additional IV fluco or AmB (caspofungin) with suspicion of fungemia (risk factors to be considered for infection with fluco-R or –I non-albicans Candida spp).

Duration of therapy in documented CR-BSI

- No compelling data to support specific recommendations on duration of therapy for device-related infections.
- Possible distinction between:
  - complicated infections (septic thrombosis, endocarditis, osteomyelitis, possible metastatic seeding)
  - uncomplicated bacteremia

Short term venous catheters

- if catheter culture positive + blood cultures negative after 48 hrs

  →stop treatment if favourable clinical condition

Antibiotics with positive catheter tip cultures?

- Catheter tip cultures with significant semiquantative or quantative growth in absence of positive blood cultures

→ no data in the literature

→ close followup for signs of infection

→ consideration of short 5-7 day course of ab in febrile pts with risk factors

  →valvular heart disease

  → neutropenia (<1000 cells/µl)

  →cath tip culture with significant growth of S. aureus or C. albicans (more likely than enterococci or GNB to be associated with CR-BSI or complications)

Short term venous catheters

- CNS in several vs. single pos blood culture
  - →Problem of differentiation from contamination (± 20 % of single pos cultures significant)
  - →In pts without risk factors stop treatment 48 hrs after defervescence
  - →Risk factors:
    - prosthetic devices
    - severe immunosuppression
    - neutropenia
    - valvular disease
    - neonates
    - burns
  - →consider longer (7 days?) GP

Duration of therapy in CR-BSI: IDSA guidelines.

- With prompt response to initial ab (+ catheter removal!) + without immunocompromise, underlying valvular heart disease or intravascular prosthetic device 10-14 days for pathogens other than coagulase-negative staphylococci.
- 4-6 wks with persistent bacteremia after catheter removal (suggestive of septic thrombosis or IE).
- 6-8 wks in osteomyelitis.

Catheter related bacteremia: outcome

- Rapid defervescence following catheter removal the rule.
- Metastatic infection (osteomyelitis, IE) or septic thrombophlebitis to be considered with persisting fever (> 72 hrs) + recurrence of bacteremia
  - TEE
  - duplex ultrasound , CT + contrast
- Metastatic infection not uncommon:
  - IE in 25 % of S. aureus bacteremia in association with IV catheter

(Fowler et al. CID 1999; 28: 106-14)

S. aureus CR-BSI

- If available, TEE to rule out vegetations (B-II)

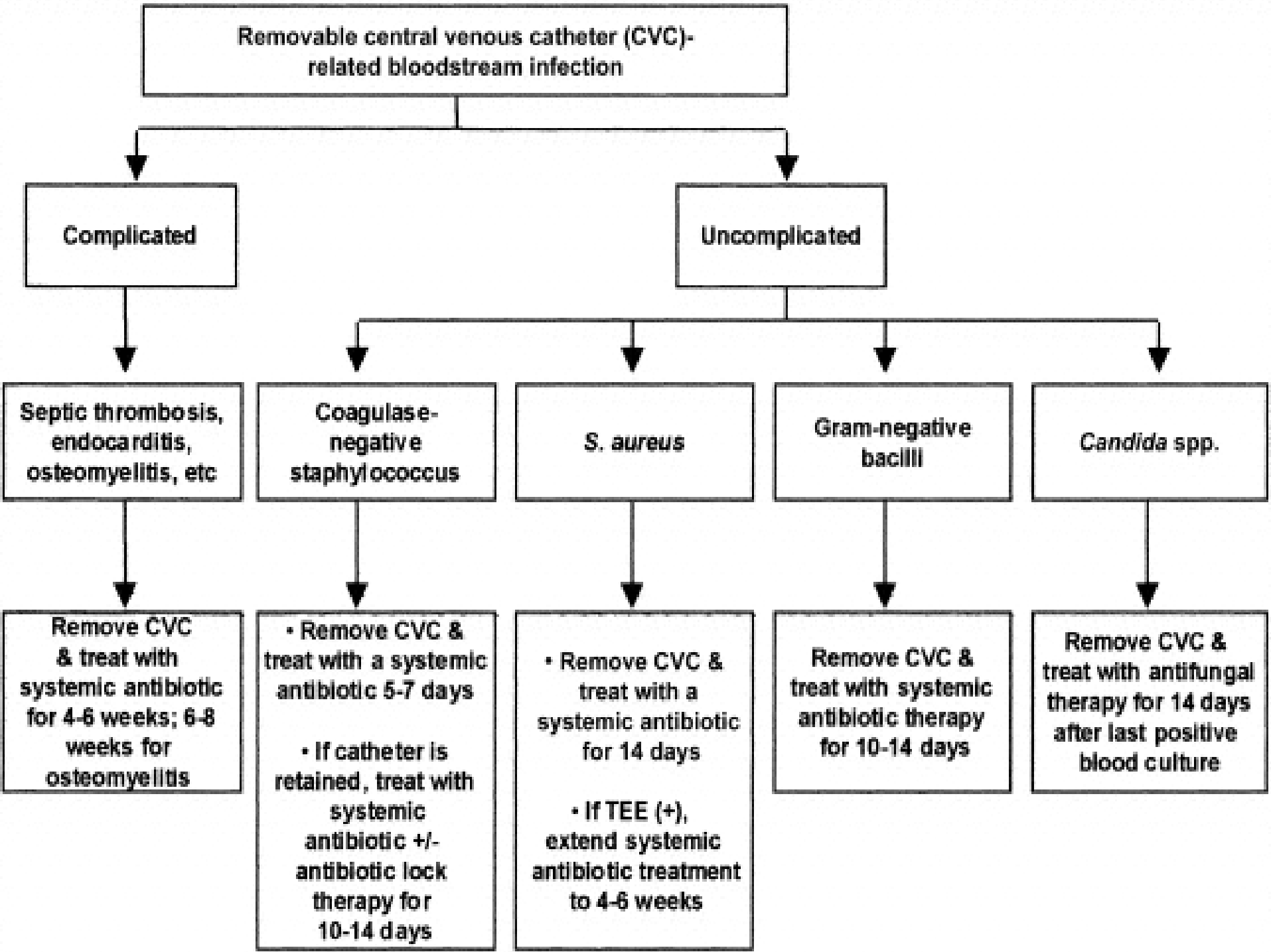
(Rosen. Ann Intern Med 1999;130:810-20)

(Li. CID 2000; 30:633-8)

(Hartstein. J Clin Microbiol 1992; 30:670-4)

- Ideal time to perform TEE in this setting not defined.
- If persistent bacteremia/fungemia > 3 days after catheter withdrawal + initiation of appropriate ab → aggressive workup for septic thrombosis, IE or other metastatic infections

(Raad. CID 1992; 14:75-82)


Removable central venous catheter (CVC)-related bloodstream infection
Complicated
Uncomplicated
Septic thrombosis, endocarditis, osteomyelitis, etc
Coagulase-negative staphylococcus
S. aureus
Gram-negative bacilli
Candida spp.
Remove CVC & treat with systemic antibiotic for 4-6 weeks; 6-8 weeks for osteomyelitis
• Remove CVC & treat with a systemic antibiotic 5-7 days
• If catheter is retained, treat with systemic antibiotic +/- antibiotic lock therapy for 10-14 days
• Remove CVC & treat with a systemic antibiotic for 14 days
• If TEE (+), extend systemic antibiotic treatment to 4-6 weeks
Remove CVC & treat with systemic antibiotic therapy for 10-14 days
Remove CVC & treat with antifungal therapy for 14 days after last positive blood culture

Long-term venous catheters in immunocompetent host

- **Most likely pathogens**
  - **CNS**
  - **S. aureus**
  - **Enterobacteriaceae**
  - **other GNB**
  - **Candida spp.**

Long-term venous catheters: general considerations.

- **Removal of catheter mandatory:**
  - **absence of improvement after 24-48 hrs**
  - **severe sepsis**
  - **persistence of positive blood cultures**
  - **tunnel infection**
  - **exit site infection with S. aureus**
  - **infection by Candida spp, Stenotrophomonas spp, Corynebacterium jeikeium.**

Tunneled CVC or implantable devices.

- Similar distinction between complicated and uncomplicated infections.
- Removal of catheter + 7-10 days ab in tunnel infection or port abscess.
- Removal + 4-6 wks ab with septic thrombosis or IE.
- Consideration of port/tunnel salvage (e.g. through antibiotic lock technique) in uncomplicated infections.
- Administration of ab via catheter left in place.

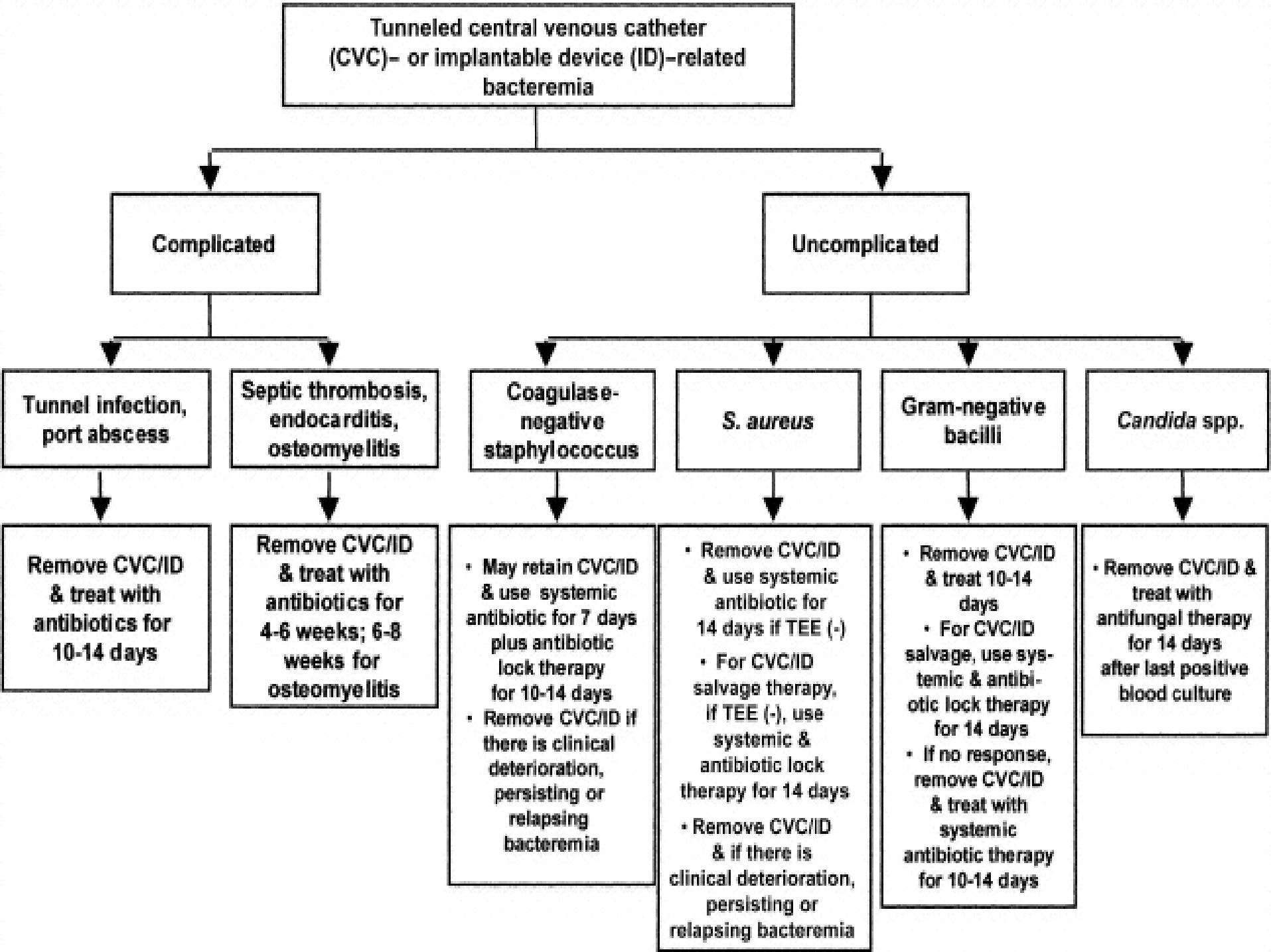

Tunneled central venous catheter (CVC)– or implantable device (ID)–related bacteremia
Complicated
Uncomplicated
Tunnel infection, port abscess
Septic thrombosis, endocarditis, osteomyelitis
Coagulase-negative staphylococcus
S. aureus
Gram-negative bacilli
Candida spp.
Remove CVC/ID & treat with antibiotics for 10-14 days
Remove CVC/ID & treat with antibiotics for 4-6 weeks; 6-8 weeks for osteomyelitis
• May retain CVC/ID & use systemic antibiotic for 7 days plus antibiotic lock therapy for 10-14 days
• Remove CVC/ID if there is clinical deterioration, persisting or relapsing bacteremia
• Remove CVC/ID & use systemic antibiotic for 14 days if TEE (-)
• For CVC/ID salvage therapy, if TEE (-), use systemic & antibiotic lock therapy for 14 days
• Remove CVC/ID & if there is clinical deterioration, persisting or relapsing bacteremia
• Remove CVC/ID & treat 10-14 days
• For CVC/ID salvage, use systemic & antibiotic lock therapy for 14 days
• If no response, remove CVC/ID & treat with systemic antibiotic therapy for 10-14 days
• Remove CVC/ID & treat with antifungal therapy for 14 days after last positive blood culture

Table 1. Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Specific pathogens: CNS.

- Empiric treatment with GP (vancomycin) + change to semi-synthetic penicillin if susceptible isolate (A-II)

(Chambers. Ann Int Med 1988; 109:619-24)

- Combination therapy with vanco + genta or rifampin not recommended for routine therapy (D-III) (all references from early 80's)

(Kobasa. Rev Infect Dis 1983;5:S533-7)

- If the CVC is removed, appropriate systemic antibiotic therapy recommended for 5-7 days (B-III)

(Herrmann. In: Seifert et al, eds. Catheter related infections. New York: Marcel Dekker, 1997; 79-109)

Specific pathogens: CNS.

- If nontunneled CVC retained + suspicion of intraluminal infection, systemic ab for 10-14 days + antibiotic lock recommended (B-III)

(e.g. Krzywda. Infect Control Hosp Epidemiol 1995; 16:596-8)

- If necessary, tunneled CVC/ID retainable in pts with uncomplicated CR-BSI (C-III)

+ 7 days systemic ab + 14 days antibiotic lock (B-II)

Specific pathogens: S. aureus.

- If susceptible isolates, β-lactams 1st choice; in penicillin allergy without anaphylaxis or angio-oedema 1st gen Pceph can be used without allergic response in 90 %; vancomycin 1st choice with IgE mediated allergy and in MRSA infection (A-II)
- Non-tunneled CVC suspected as source of S. aureus bacteremia to be removed + new catheter to be inserted at different site (B-II)

Specific pathogens: S. aureus.

- TEE indicated for pts without contra-indications, to identify IE, requiring 4-6 wks therapy + higher sensitivity than TTE (BII)

(Rosen. Ann Intern Med 1999;130:810-20)

(Fowler. J Am Coll Cardiol 1997;30:1072-8)

- Neg TEE + catheter removal → 14 d ab (BII).
- Tunneled CVC/ID with uncomplicated intraluminal infection + S. aureus bacteremia need to be removed, or, only in selected cases,retained + systemic ab + 14 day antibiotic lock therapy (BII)

(Rubin. CID 1999; 29:102-5)

(Williams. Br J Surg 1994; 81:392-4)

Specific pathogens: GNB.

- Catheter removal in GNB CR-BSI without evidence of septic thrombosis or IE + 10-14 d ab (BIII)

(Elting. Medicine 1990; 69:296-306)

(Seifert. Medicine 1995; 74:340-9)

- For CR-BSI in non(easily)-removable tunneled CVC/ID without severe sepsis, 14 day ssytemic and antibiotic lock therapy (BIII).
- Oral FQ ± rifampin (possible eradication of GNB from foreign bodies (C-III)

(Widmer. AAC 1991;35:741-6)

(Ishida. AAC 1998;42:1641-5)

(Ashby. JAC 1994;33:443-52)

Specific pathogens: GNB.

- In CR-BSI due to Pseudomonas spp other than P. aeruginosa, Burkholderia spp, Stenotrophomonas spp, Acinetobacter baumanii, catheter removal the rule, esp. in persistent bacteremia in spite of ab and/or unstable pts (A-III)
- Empiric ab for suspected gram-neg CR-BSI to include drugs active against P. aeruginosa, esp. in neutropenic pts (C-III)

Specific pathogens: GNB.

- In prolonged bacteremia after appropriate ab + catheter removal, esp. with underlying valvular heart disease, 4-6 wks ab (C-III).
- Catheter removal in CR-BSI with Bacillus and Corynebacterium spp (A-II) as well as with atypical mycobacteria (M fortuitum and chelonae (A-II)

Specific pathogens: C. albicans and other fungi

- All pts with candidemia to be treated; ampho B (caspofungin) in suspected Candida spp CR-BSI + hemodynamic instability or with prior prolonged fluco therapy (A-II); treatment with fluco for fluco-S organisms or without these risk factors (A-II)

(Rex. NEJM 1994; 331:1325-30)

(Rex. CID 2000;30:662-78)

Caspofungin vs AmB in invasive candidiasis

- Similar efficacy in mainly non-neutropenic population: successful outcome in 80/109 (73.4 %) vs 71/115 (61.7 %) with AmB
- Difference after adjustment for APACHE II + neutropenic status 12.7 % (95 % CI –0.7 – 26).
- Caspofungin superior in pts meeting prespeficied criteria for evaluation: 71/88 (80.7 %) vs 63/97 (64.9 %) (p=0.03) with AmB; difference 15.4 % (95 % CI 1.1-29.7)
- Fewer drug-related adverse events with caspofungin

(J Mora-Duarte. NEJM 2002;347:2020-9)

Specific pathogens: C. albicans and other fungi

- Duration of antifungal treatment in candidemia 14 days after last positive blood culture and resolution of signs/symptoms of infection (A-III)
- Catheter-related C. krusei infections to be treated with ampho B (A-II) (to be replaced by caspofungin?
- Tunneled CVC/ID to be removed in documented catheter-related fungemia (A-II).
- Salvage therapy not recommended, because of low salvage rates with systemic antifungal + antibiotic lock therapy (30 % for Candida spp) (D-II)

Specific pathogens: Malassezia furfur-CRBSI

- Discontinuation of intralipids + catheter removal, esp. with non-tunneled catheter infections (B-III)
- Treatment with ampho B (B-III)

Long-term venous catheters: general considerations.

- Antibiotic concentrations must be 100-1000-fold higher to kill sessile (biofilm) vs planktonic (in solution) bacteria.
- Antibiotic lock still controversial + not indicated for S. aureus, Candida, Corynebacterium spp infections

(Panagea. Lancet 1998; 351: 1738-9)

Antibiotic lock: practical considerations.

- In vitro no problems of precipitation with amika, cipro, flucloxacillin, genta, linezolid or teicoplanin.
- Solution vanco (0.5-2 mg/ml) or cefta (0.5 mg/ml) + heparin 100 IU/ml stable during 1 week.

Antibiotic-heparin lock: in vitro stability in CVC

- 10 mg/ml vanco + 5000 IU/ml heparin: after 72 hrs 29.7 % ↓ in vancomycin-concentration

→ probably not relevant as 5 mg/ml considered sufficient for antimicrobial efficacy

(Pharmacotherapy 2000;20:394-9)

→ vanco 10 mg/ml, genta 5 mg/ml + heparin 5000 IU/ml: significant reduction of MRSE microbial burden in vitro following single 48 hrs instillation

(JAC 2002;49:693-6)

Antibiotic lock technique for therapy of "highly needed" catheters

- Concentrations used:
  - 1-2 mg/ml vanco 2 ml
  - 5 mg/ml vanco
- Clinical experience in home TPN:
  - 1 mg/ml vanco 2 ml for 12 hrs daily (mean of 15 days)
  - 2 mg/ml vanco (in children) 2 ml for 12 hrs daily (10-14 days)
  - 5 mg/ml vanco 3 ml for 13 hrs daily (8 days)

(Clin Microbiol Infect 2002; 8: 282-9)

Antibiotic lock technique for therapy of "highly needed" catheters

- Clinical experience in AIDS/cancer pts:
  - 5 mg/ml vanco (in combination with systemic treatment)
  - 1 mg/ml vanco (once daily for 5 days)
- Most experience in tunneled catheters vs implantable ports.
- No data from RCT, nor on optimal concentrations or duration of therapy

  → not "evidence-based" approach.

  (Clin Microbiol Infect 2002; 8:282-9)

Estimated efficacy of antibiotic lock therapy.

- Exit site infection more likely to respond than tunnel or pocket infections.
- CNS more likely to respond than S. aureus or P. aeruginosa.
- Recurrent bacteremia in CNS CR-BSI 20 % within 12 wks vs only 3 % if catheter removed.
- 66.5 % salvage (342/514 episodes in standard parenteral therapy for treatment of CR-BSI in tunneled catheters (data from 14 open trials, mostly from 80's)

Estimated efficacy of antibiotic lock therapy.

- Probable salvage of up to 82.6 % of tunneled catheters (138/167 episodes in open trials ± systemic ab) and 2/3 of implanted ports.
- Higher likelihood of catheter salvage (RR 1.24; 95 % CI 1.13-1.36, p=0.0001) vs cumulated open trials with systemic ab alone.
- No head-to-head randomised comparison with parenteral ab only.