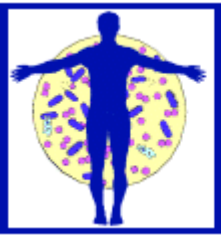
S B I M C | B V I K M



Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

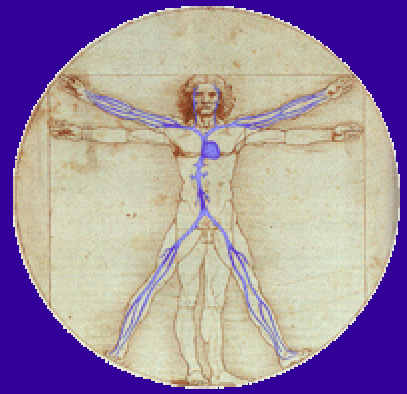
Catheter-related infections: practical aspects in 2003

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

Joint Meeting

GDEPIH/GOSPIZ - SBIMC/BVIKM

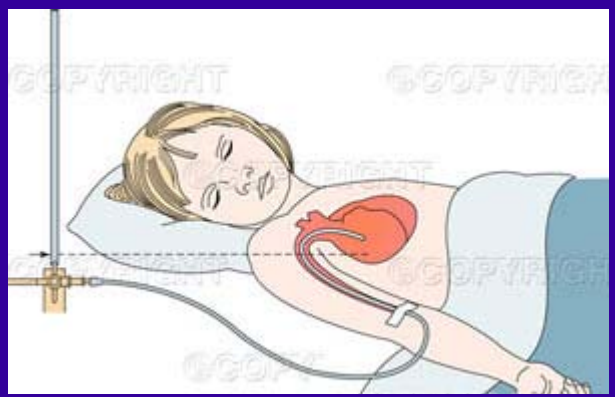


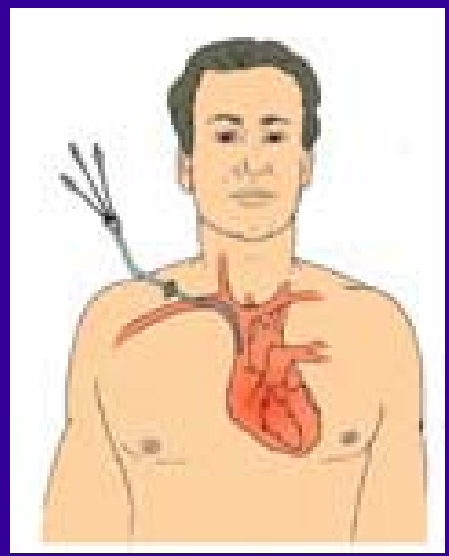
Catheter-related Infections: Microbiological Diagnosis

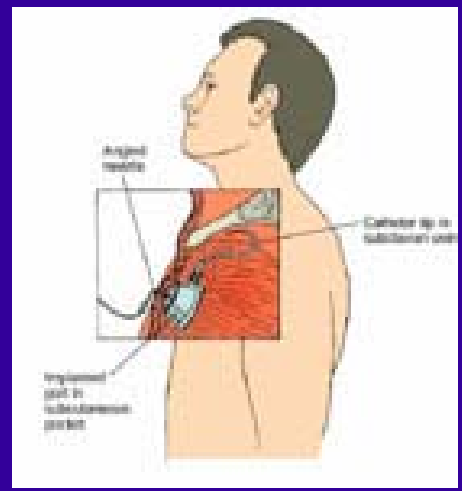
Marc Struelens
ULB-Hop Erasme

November 20, 2003

Various types of Venous Catheters







Catheter-related Infections : Definitions

- **Catheter colonization**:

  Growth of 15 or more CFU of an organism on semiquantitative culture of the tip or subcutaneous segment of the catheter.

  Growth of more than 10^3 CFU/ml on quantitative culture of broth rinse, shake or sonication of catheter tip
- **Catheter insertion site colonization**:

  Presence of 10 CFU or more of an organism per 102 cm (surface area of the agar plate).
- **Catheter hub colonization**:

  Presence of microbial growth on culture of swab specimen.

Catheter-related Infections : Definitions

- **Exit site infection:**

  Signs of skin Infection localized to within 2 cm of the exit site.

- **Tunnel or pocket infection:**

  Signs of skin/subcutaneous Infection localized over the tunnel tract/port septum ; involving more than 2 cm central from the exit site.

  Positive culture from subcutaneous fluid aspiration.

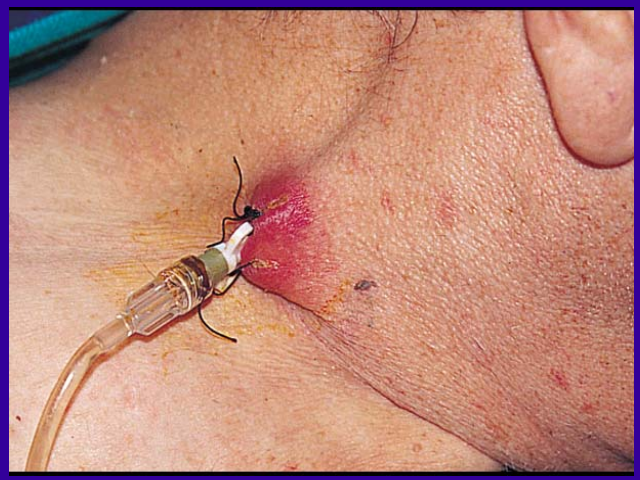
Hickman catheter tunnel infection

Catheter-related Infections : Definitions

- **Catheter-related bloodstream infection**:
- **Clinical features of bloodstream infection. No other identified source.**
- **Isolation of the same organism from both the device (>/= 15 CFU or 1000 CFU/ml) and the blood.**
- **Sample from the device has 5 or10 times the CFU than the peripheral blood sample.**
- **In the absence of peripheral blood cultures, more than 100 CFU's obtained through the device.**

Inflammation at the insertion site is not predictive of CVC-related bacteremia

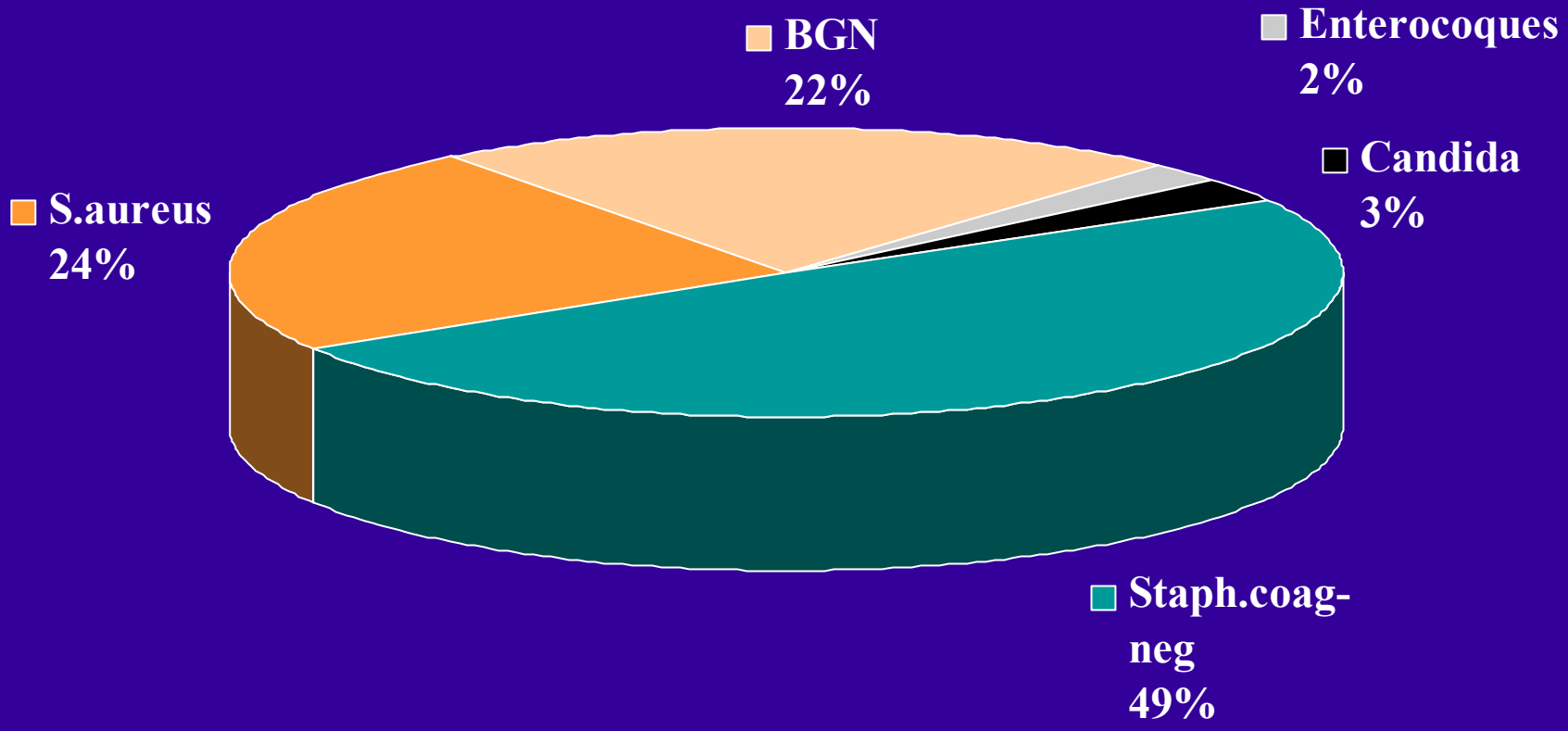
- Poor sensitivity of local inflammatory signs for diagnosis of CVC-related BSI : 0-3 %
- Overt inflammation predictive of S.aureus or Gram-negative rod

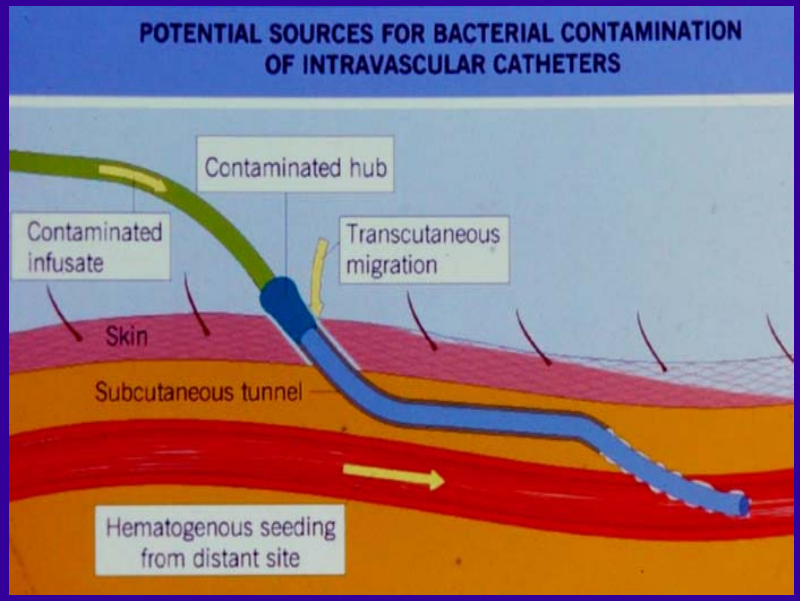


Sadfar & Maki *Crit Care Med* 2002;30:2632

Micro-organismes des bactériémies sur cathéter,

Hop Erasme, 1995-98 (n=319)





Sources of Catheter-Related Infections:

Implications for Surveillance Cultures

- Extraluminal : endogenous skin flora
  - skin surveillance culture
- Hub and cocks : exogenous skin flora from HCWs
  - hub surveillance culture
- Contaminated infusate : exogenous flora (water or blood products)
  - sterility control of iv fluids, drugs & blood products
- Hematogenous

Comparison of Biotyping, Ribotyping, and Pulsed-Field Gel Electrophoresis for Investigation of a Common-Source Outbreak of *Burkholderia pickettii* Bacteremia

H. CHETOUI,[1]* P. MELIN,[1] M. J. STRUELENS,[2] E. DELHALLE,[1] M. MUTRO NIGO,[1] R. DE RYCK,[2] AND P. DE MOL[1]

TABLE 1. Clinical and microbiological features of *B. pickettii*-infected patients[a]

Sex/age (yr)	Underlying disease	Unit	Permanent venous catheter	No. of positive blood cultures (mo)	No. of positive catheter cultures (mo)
M/44	Tonsil neoplasia	Oncology	Port-à-Cath		1 (June)
F/69	Diabetes	Dialysis	Hickman	1 (July)	
F/64	Diabetes	Dialysis	Hickman	2 (August)	
F/72	Breast carcinoma	Oncology	Port-à-Cath	2 (August)	1 (August)
F/72	Breast carcinoma	Oncology	Port-à-Cath	2 (August)	1 (August)
M/46	Testicular carcinoma	Hematology	Port-à-Cath	2 (August)	

Comparison of Biotyping, Ribotyping, and Pulsed-Field Gel Electrophoresis for Investigation of a Common-Source Outbreak of *Burkholderia pickettii* Bacteremia

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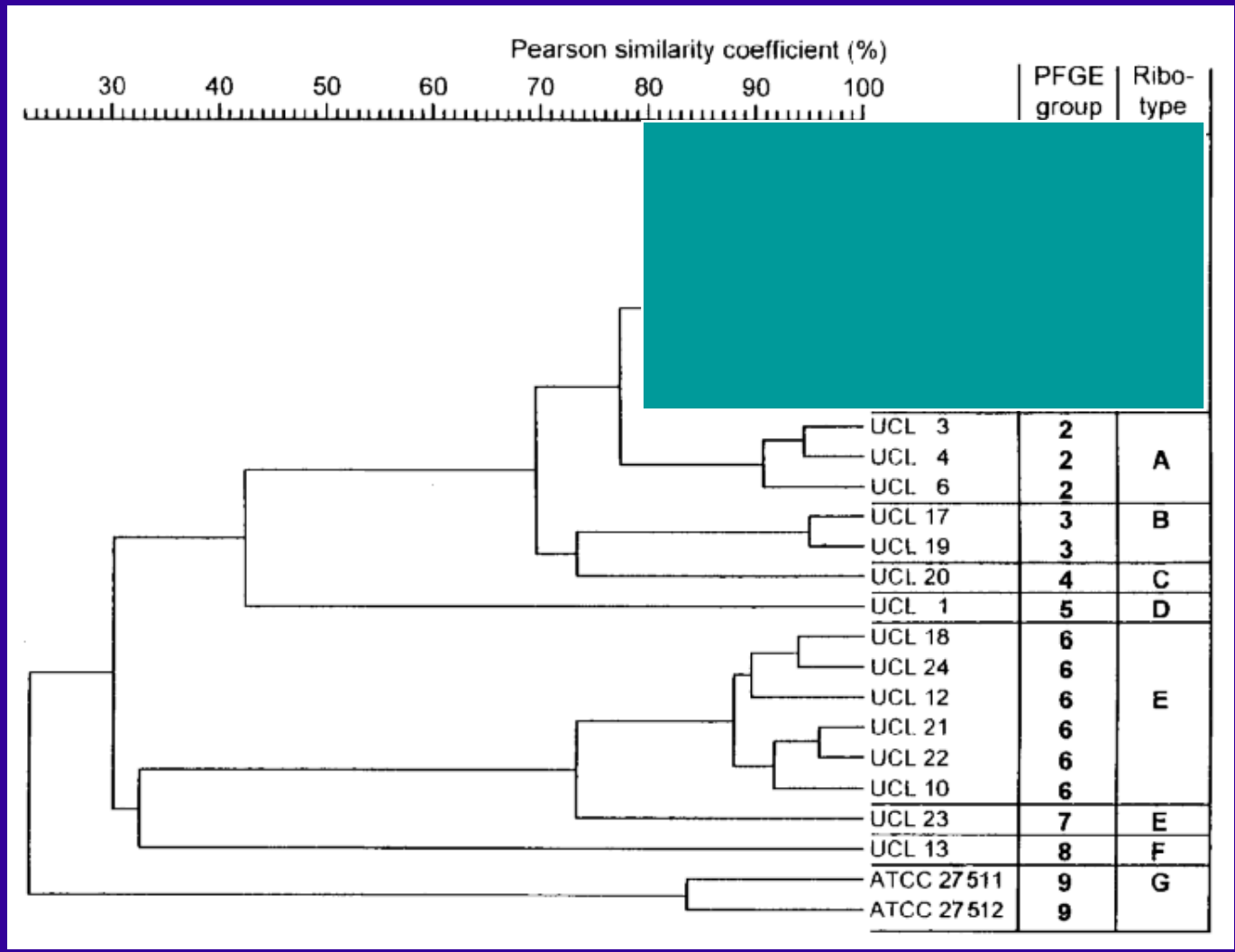


Microbiological Methods for Catheter-Related Infections

<u>After catheter removal</u> :

- **Broth culture**
- **Semi-quantitative culture (« roll-plate »)**
- **Quantitative culture**
- **Direct microscopic examination (Gram, Acridine)**

Microbiological Methods for Catheter-Related Infections

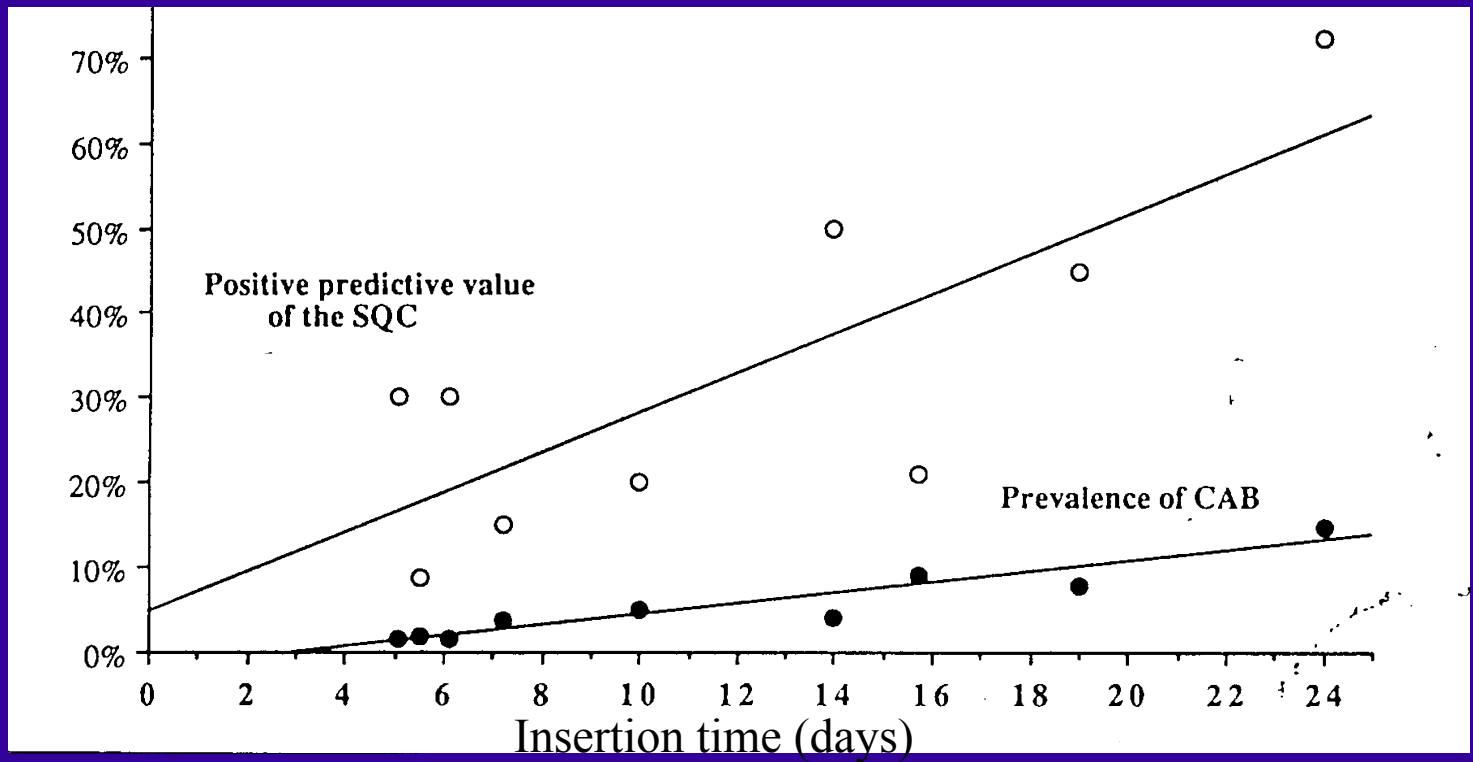
Conservative procedures :

- Superficial cultures (skin & hub)
- Endoluminal brushing
- Standard peripheral or per-KT blood cultures
- Quantitative paired (per-KT & periph) blood cultures
- Quantitative per-KT blood culture
- Direct microscopic examination of per-KT blood
- Differential time to detection from paired KT / periph blood cultures

(Semi)- Quantitative KT Culture Methods

Technique	Surface	Threshold
Roll-plate (Maki,1977)	Externe	15 CFU
Flush (Cleri,1980)	Interne	1000 CFU/ml
Vortex (Brun-Buisson,1987)	Int+ext	1000 CFU/ml
Sonication (Sherertz,1990)	Int+ext	1-100 CFU /ml

Positive Predictive Value of KT Culture Depends on Prevalence of CAB



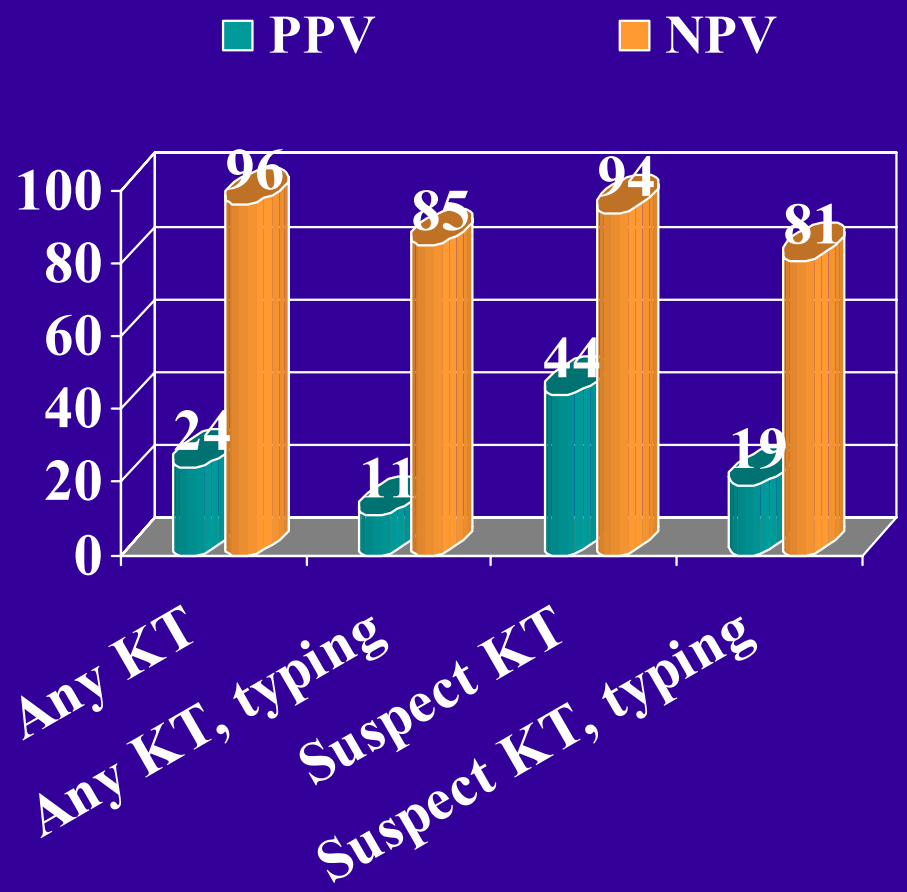
Widmer *in* Wenzel (Ed) *Prevention and Control of Nosocomial Infection* 1997

CRB Positive Predictive Value of KT Culture Depends on the Micro-Organism

Micro-organism	Positive Predictive Value		
	Sonication		Roll-plate
	>1	>1000	>15 CFU
S.aureus	60	68	53
Candida	69	82	0
Enterobacteria	43	46	37
CoNS	32	44	20
Enterococci	23	36	0

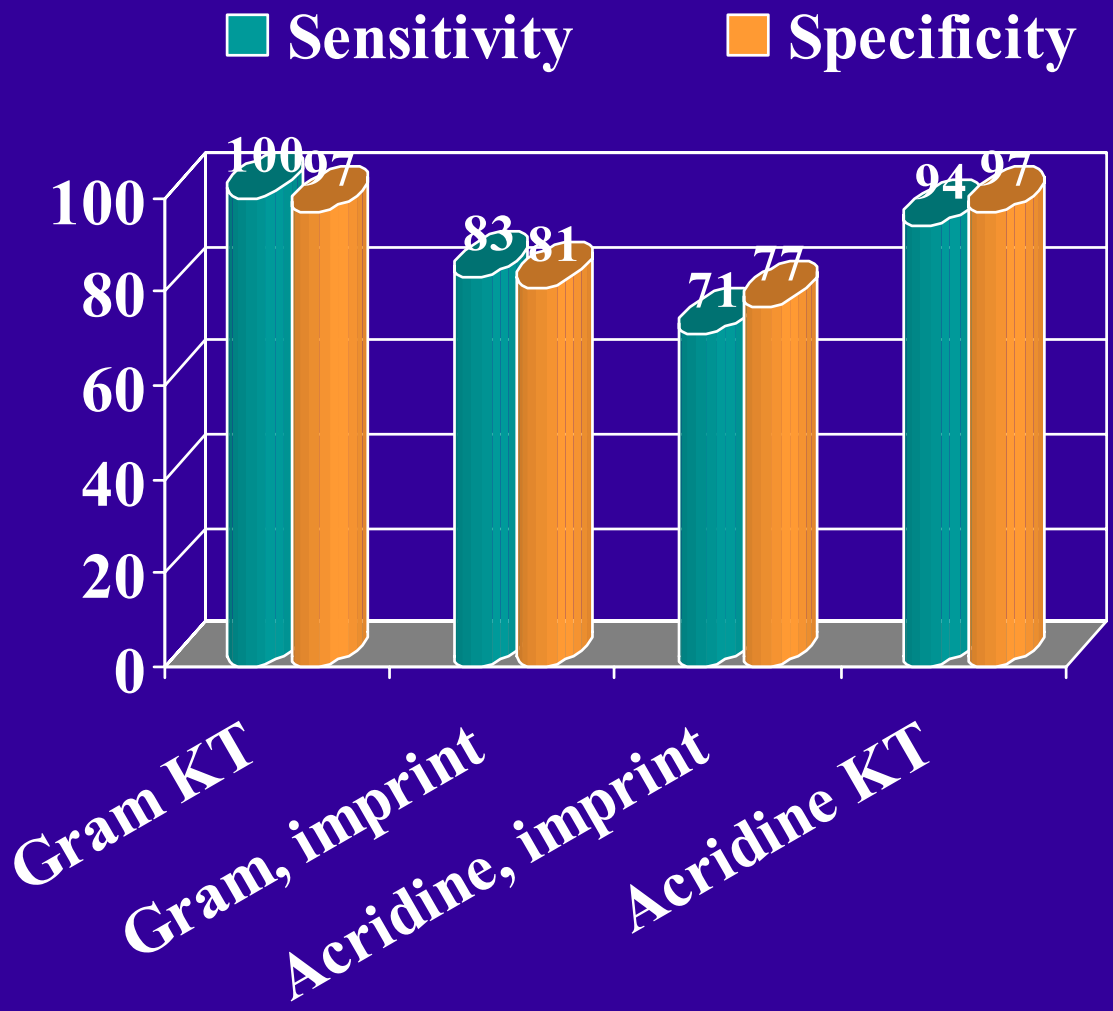
Sources : Sherertz, Struelens

How Predictive is CVC Surveillance Culture of Insertion Site & Hub for CRB in ICU patients ?



Atela *J Clin Microbiol* 1997;35:1784

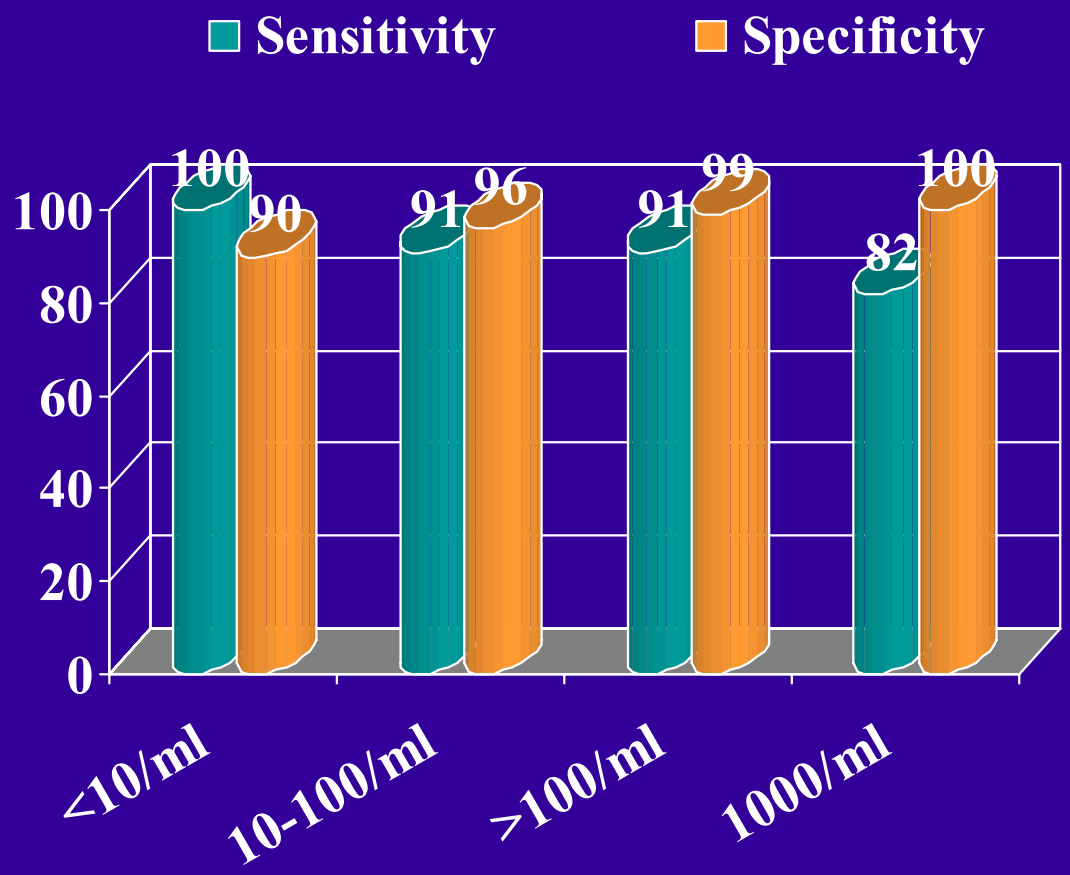
Microscopic Examination of Catheter Tip



Diagnostic Value of Quantitative Blood Cultures for CRB

- Methods
  - pour-plate or Isolator 1.5 ml ; serial dilutions
  - paired KT & peripheral samples or per-KT sample only
- Interpretation
  - paired KT:peripheral CFU/ml ratio > 3-10
  - > 10-100 CFU/ml of per-KT blood
- Advantages
  - accuracy (long & short term catheters)
  - avoids 70-85 % unnecessary KT removal
  - direct microscopic of blood cytospin
  - cost-effective ?

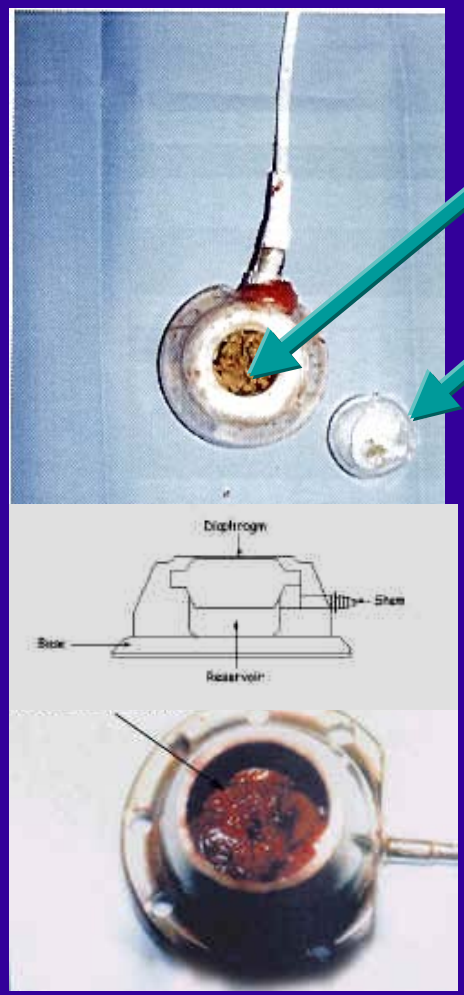
Quantitative per-KT Blood Culture vs KT/périph >5:1 Paired Cultures



N= 124 patients, Hop. Erasme, 1997-98,
11 CRB with surgically implanted KT

Diagnosis of Venous Access Port-Related infections

Douard et al CID 1999;29:1197



Fibrin debris

Septum

Before Port removal:
Paired quantitative BC :
sensitivity 77 %
specificity 100%

After Port removal :
sensitivity of culture from tip : 46 %
reservoir/septum: 93 %

Meta-Analysis of Diagnostic Methods for Catheter-related Infection

Siegman-Igra *J Clin Microbiol* 1997; 35:928

Method	Sensitivity	Specificity	$ Cost per exact result
• **Qual. KT cult**	**95**	**75**	**467**
• **KT SQC**	**85**	**85**	**401**
• **KT QC**	**94**	**92**	**415**
• **Paired QBC**	**78**	**94**	**282**
• **Hub QBC**	**78**	**96**	**198**

Difference in Time to Detection from Catheter vs Peripheral Blood in BC Automated System

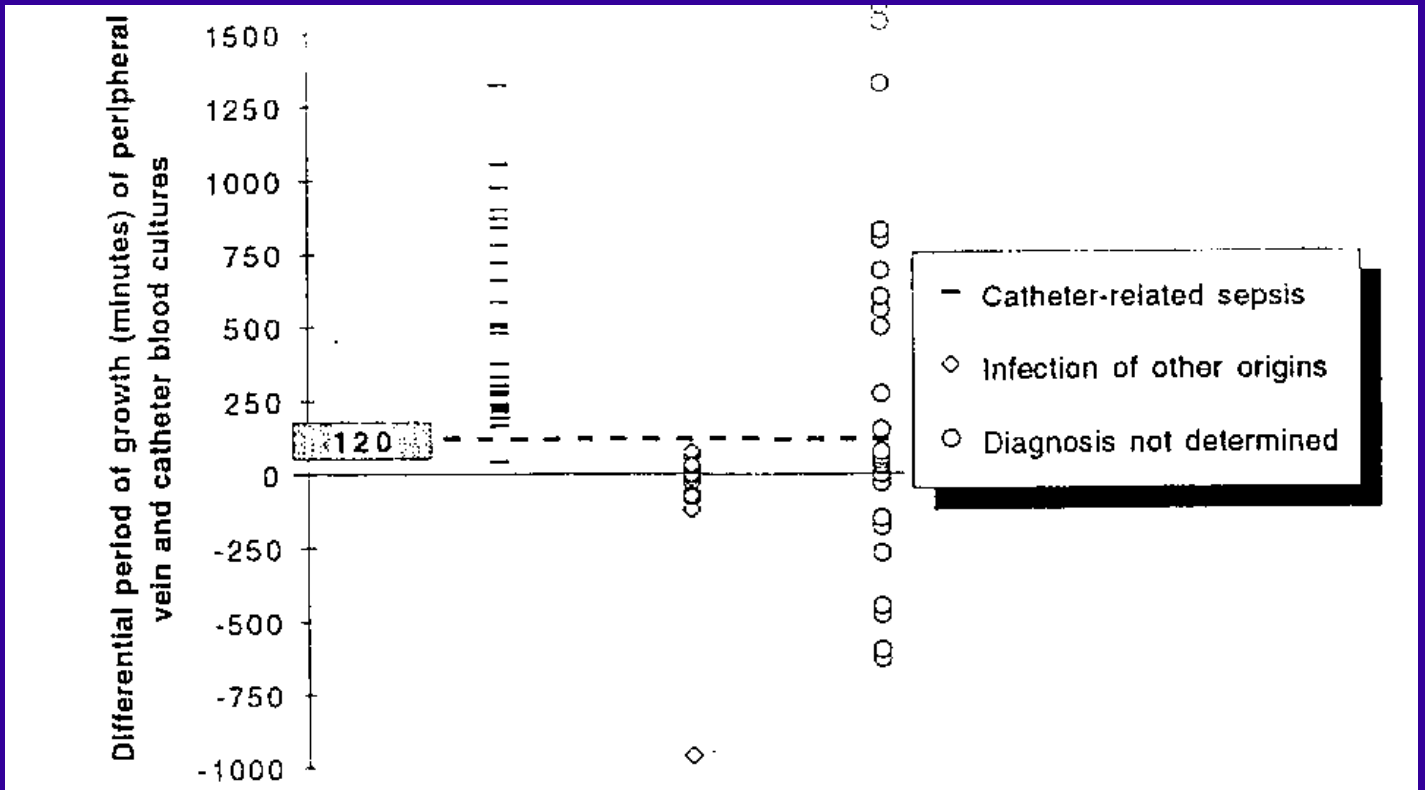


FIG. 2. DPT of blood cultures for patients with CRS, infections of other origins, or an indeterminate diagno

Blot et al *J Clin Microbiol* 1998;36:105

Differential Time to Positivity of Hub vs Peripheral Blood Culture

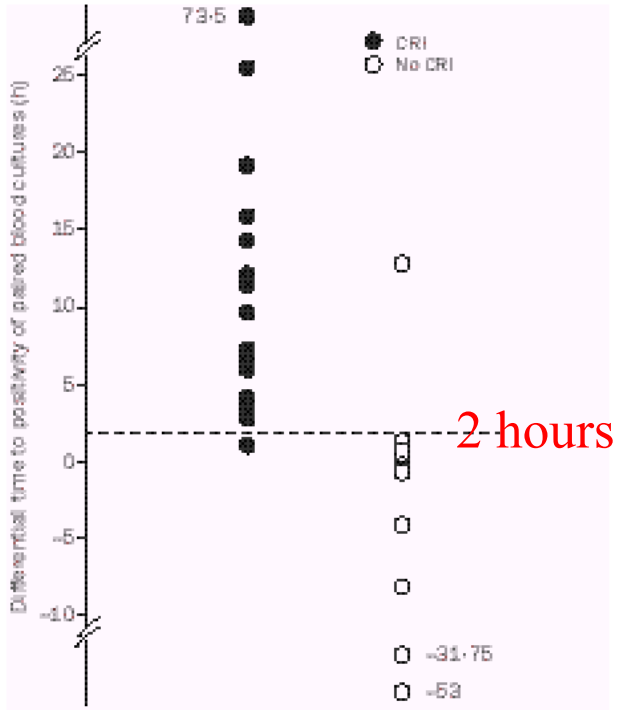
Study	Setting	No. patients	Blood culture system	Golden standard
Blot, 1998	Cancer centre	64	Vital	Quantitative KT (Brun-Buisson)
Blot, 1999	ICU cancer centre	28	Vital	Quantitative KT (Brun-Buisson)
Reynders, 2001	Med-surg. ICU	10	BacT/Alert	Quantitative KT (Sherertz)
Bussy, 2001	Cancer centres	30	BacT/Alert	Paired Isolator > 5 H/P
Seifert, 2003	Hemato-onco dept	51	Bactec Plus A/Ana	Paired Isolator > 5 H/P
Gaur, 2003	Pediatric cancer centre	33	Bactec Plus A/Ana	Paired Isolator > 5 H/P

Differential Time to Positivity of Hub vs Peripheral Blood Culture

Study	Setting	Significant DTP	Sensitivity %	Specificity %
Blot, 1998	Cancer centre	Yes (2 h)	97	100
Blot, 1999	ICU cancer centre	Yes (2 h)	94	91
Reynders, 2001	Med-surg. ICU	No	25	43
Bussy, 2001	Cancer centres	Yes (3 h)	81	100
Seifert, 2003	Hemato-onco dept	Yes (2 h)	82	88
Gaur, 2003	Pediatric cancer centre	Yes (2 h)	89	100

Patients and catheters	Details
Age (mean [SD])	51 (12) years
Sex (M/F)	56/31
SAPS II (mean [SD])	43 (26)
Organ-system failure (mean [SD])	1·1 (1·5)
MacCabe score	
Ultimately fatal	45
Rapidly fatal	42
Type of cancer	
Solid tumour	68
Haematologic malignancy	19
Reasons for ICU admission	
Suspicion of CRI	14
Septic shock	18
Acute respiratory failure	19
Postoperative survey	19
Miscellaneous	17
Types of catheters	
Totally implanted ports	9
Tunnelled catheters	16
Non-tunnelled single-lumen catheters	20
Multi-lumen catheters	26
Dialysis catheters	10
Arterial catheters	12
Site of insertion	
Internal Jugular	17
Subclavian	47
Femoral	18
Radial	11
Duration of placement	
Median (range)	12 days (2 days to 4 years)
≤30 days:	70
>30 days:	23

Blot *Lancet* 1999;354:1071



Differential time to positivity between paired (peripheral minus catheter hub-blood) cultures for patients with catheter-related bacteraemic infection or infection from other source

JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2003, p. 118–123 Vol. 41, No. 1
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.1.118–123.2003

Bloodstream Infection in Neutropenic Cancer Patients Related to Short-Term Nontunnelled Catheters Determined by Quantitative Blood Cultures, Differential Time to Positivity, and Molecular Epidemiological Typing with Pulsed-Field Gel Electrophoresis

Harald Seifert,[1]* Oliver Cornely,[2] Kerstin Seggewiss,[1] Mathias Decker,[1] Danuta Stefanik,[1] Hilmar Wisplinghoff,[1] and Gerd Fätkenheuer[2]

Nontunneled, non-coated triple lumen CVC (median 12 days)

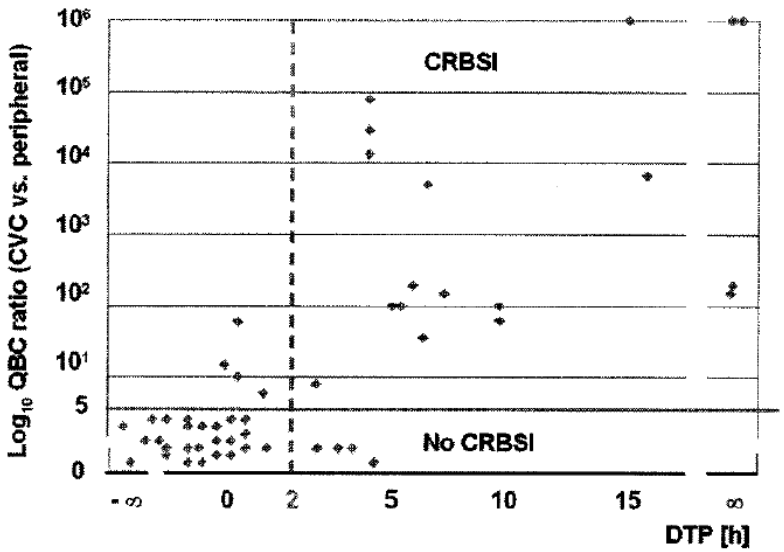


FIG. 1. QBC ratio (CVC versus peripheral) and DPT of blood cultures from neutropenic patients with and without CRBSI.

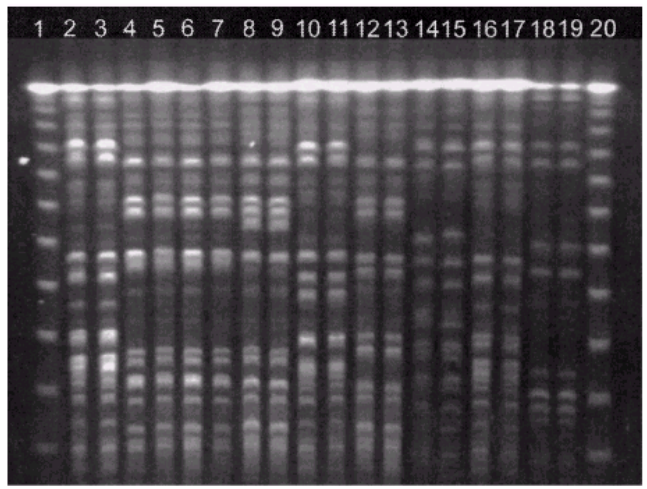


FIG. 2. Fingerprint patterns of CoNS genomic DNA obtained by PFGE after restriction with *Sma*I. Lanes: 1 and 20: molecular size marker; 2 to 17, corresponding *S. epidermidis* blood isolates obtained from the catheter hub and from peripheral sites in seven patients; 18 and 19, *S. haemolyticus* blood isolates.

Gaut *Clin Infect Dis* 2003;37:469

Pediatric oncology patients, 70 % neutropenic
Tunneled, long-term (Hickman) CVCs

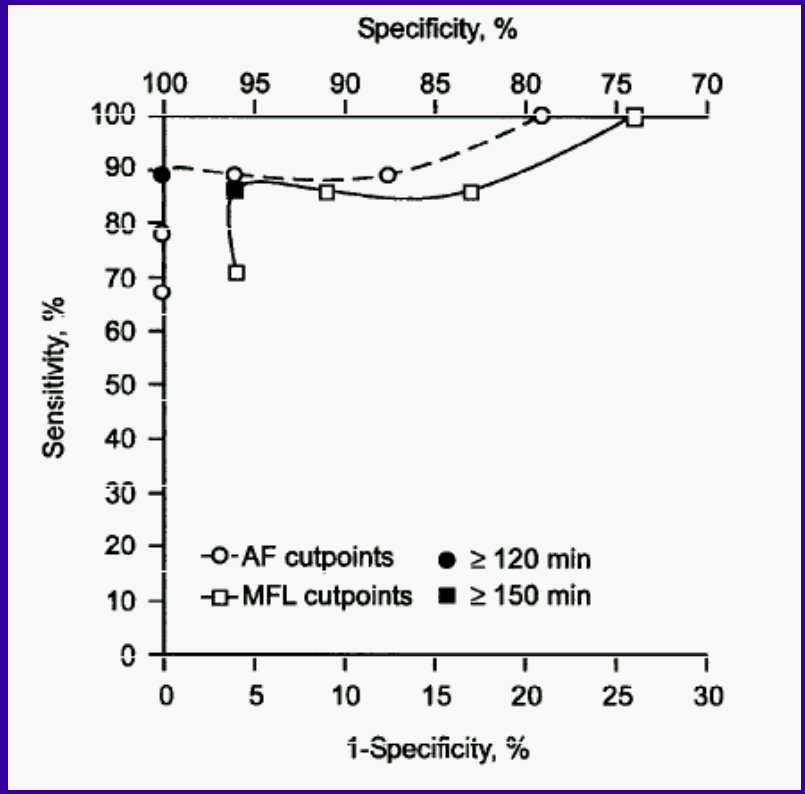
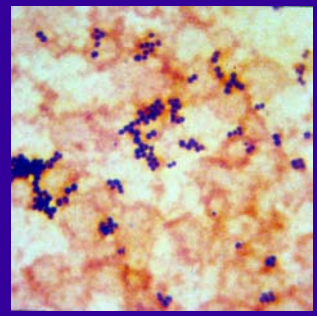


Figure 1. Receiver operating characteristic curve plotting the sensitivity and 1-specificity for various differences in time to detection (DTD) cut points. DTD thresholds of 30–210 min were evaluated, in 30 min increments. Selected thresholds are shown for each media type (shortest to longest duration, depicted from right to left, respectively), with optimal cut points indicated in filled symbols. AF, BACTEC Plus Aerobic/F culture vial (Becton Dickinson); MFL, BACTEC MYCO/F Lytic culture vial (Becton Dickinson).

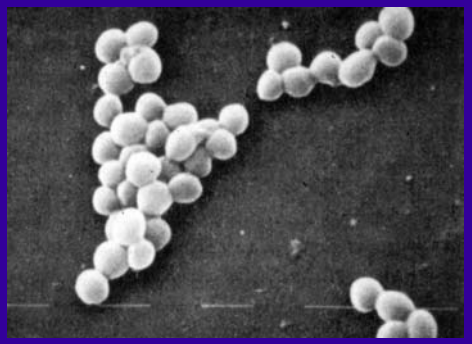
Based on prevalence estimates in US cancer centers:

PPV : 100 %
NPV : 87 - 96 %
(Aerobic Plus medium)

Direct Microscopic Examination of Hub Blood



Study	Setting	Sensitivity	Specificity
Rushford, 1993	PICU	87	94
Moonens,1994	Adult TPN	61	100
Hakim, 1998	Adult, Onco	78	100



Diagnosis of Coagulase-negative Staphylococcal Infection

- **Difficult clinical judgement to ascertain infection versus contamination**
- **Need for aggressive sampling : multiple sterile site specimens (blood, removal of implanted material)**
- **Comprehensive microbiologic work-up : quantitative catheter & blood cultures, antimicrobial susceptibility testing, speciation, clonal typing**
- **Possibility of polyclonal infection**

Interpretation of CoNS positive Blood Cultures

Herwaldt *Clin Infect Dis* 1996;22:14-20

Multicriteria model ?

- species, biotype, antibiogram
- bacterial density in Isolator BC (mean 33 CFU/ml in CRS vs 8 CFU/ml in contamination)
- number of positive BC : 2 or more in 75% of CRB vs 17 % contamination
- limited overall predictive value

Interpretation of CoNS positive Blood Cultures

Biofilm-associated gene (*ica* operon) detection ?

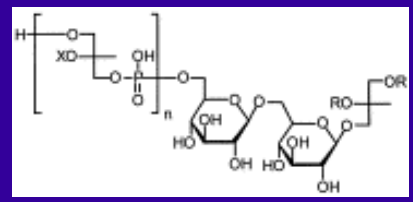
Study	% isolates *ica* positive	
	CR Infection	Controls
Zieburh, 1997	85	2
Arciola, 2001	48	0
de Silva, 2002	44	31-43
Vandecasteele, 2002	59	88

Interpretation of CoNS positive Blood Cultures

Serological Diagnosis ?

ELISA for detection of anti-lipid S-IgG

Lipid S : exocellular glycerophospholipid



<u>Pilot study</u> :

CR bacteremia (n=40) vs healthy control (n= 40)

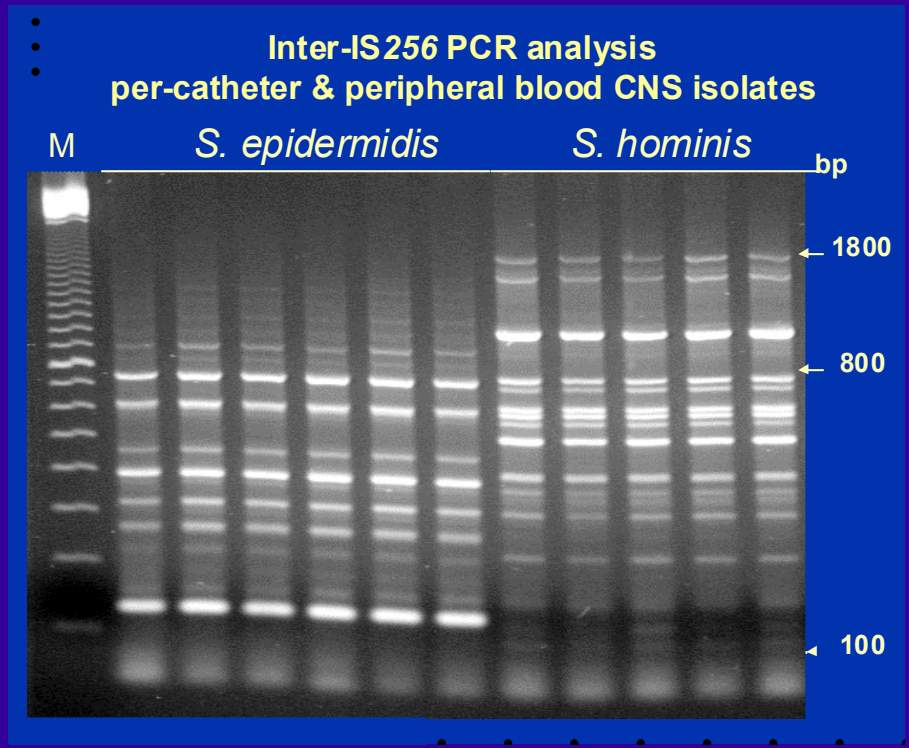
Sensitivity : 70 %

Specificity : 100 %

Worthington *J Clin Pathol* 2002;55;41

Polyclonal CoNS Catheter-Related Sepsis

- 58 yr old ALL patient
- febrile neutropenia
- 11 blood cultures including paired BC from totally implanted port
- polyclonal bacteremia with *S.epidermidis* and *S.hominis* by PFGE & IS256-PCR



Hakim *Clin Microbiol Infect* 1999;5:224

Polyclonal CoNS Endocarditis

Van Eldere *Clin Infect Dis* 2000.31:24

- 82 yr old patient with prosthetic valve endocarditis
- 15 blood cultures isolates of *S.epidermidis*
- 4 related genotypes by PFGE &AFLP
- Variation in antibiogram
- Instability reproduced in rat model of catheter infection

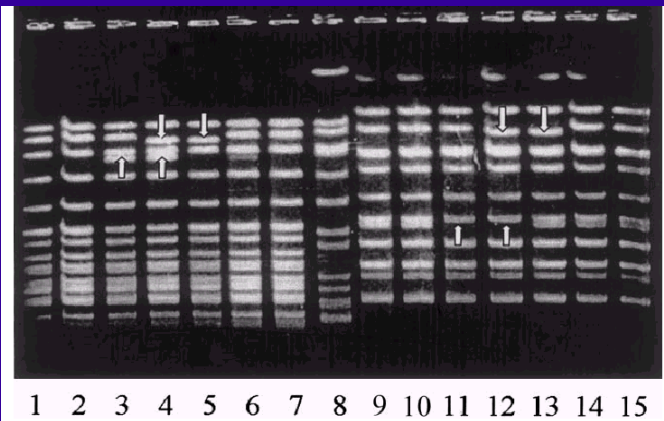


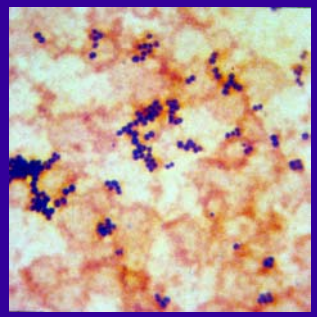
Figure 1. Macrorestriction analysis of *Staphylococcus epidermidis* strains from the patient's blood. The total genome DNA of 7 different strains (A–G) was cut with 10 U of *Sma*I *(lanes 1–7)* and *Sst*II *(lanes*

Table 2. Phenotypic and genetic characteristics of the *Staphylococcus epidermidis* strains from the rat model that differed from the original infecting strain.

Strain, by origin	PFGE banding pattern	Resistant to	*aac*A-*aph*D present[a]
Original infecting strain	1R	Pen, Ofx, Rif, Fus, Em, Cm, Gm, Tm	Yes
Rat 1			
Catheter 1	1S	Pen, Ofx, Rif, Fus	No
Catheter 1	1S	Pen, Ofx, Rif, Fus, Em, Cm	No
Catheter 1	1S	Pen, Ofx, Rif, Fus, Em, Cm	No
Catheter 3	1S	Pen, Ofx, Rif, Fus	No
Rat 2			
Catheter 2	1S	Pen, Ofx, Rif, Fus, Em, Cm	No
Catheter 2	1R	Pen, Ofx, Rif, Fus, Gm, Tm	Yes
Rat 3			
Catheter 1	1S	Pen, Ofx, Rif, Fus, Em, Cm	No
Catheter 3	1R	Pen, Ofx, Rif, Fus, Gm, Tm	Yes
Catheter 3	1R with loss of 300-kb band	Pen, Ofx, Rif, Fus, Em, Cm, Gm, Tm	Yes
Catheter 3	1S	Pen, Ofx, Rif, Fus, Em, Cm	No

NOTE. Cm, clindamycin; Em, erythromycin; Fus, fusidic acid; Gm, gentamicin; Ofx, ofloxacin; Pen, penicillin; PFGE, pulsed-field gel electrophoresis; Rif, rifampin; Tm, tobramycin.

[a] The *aac*A-*aph*D gene encodes the AAC6′ + APH2″ enzyme, which is responsible for resistance against gentamicin and tobramycin.



Clinical impact of rapid identification & oxacillin-resistant PCR detection test in staphylococcal bacteremia

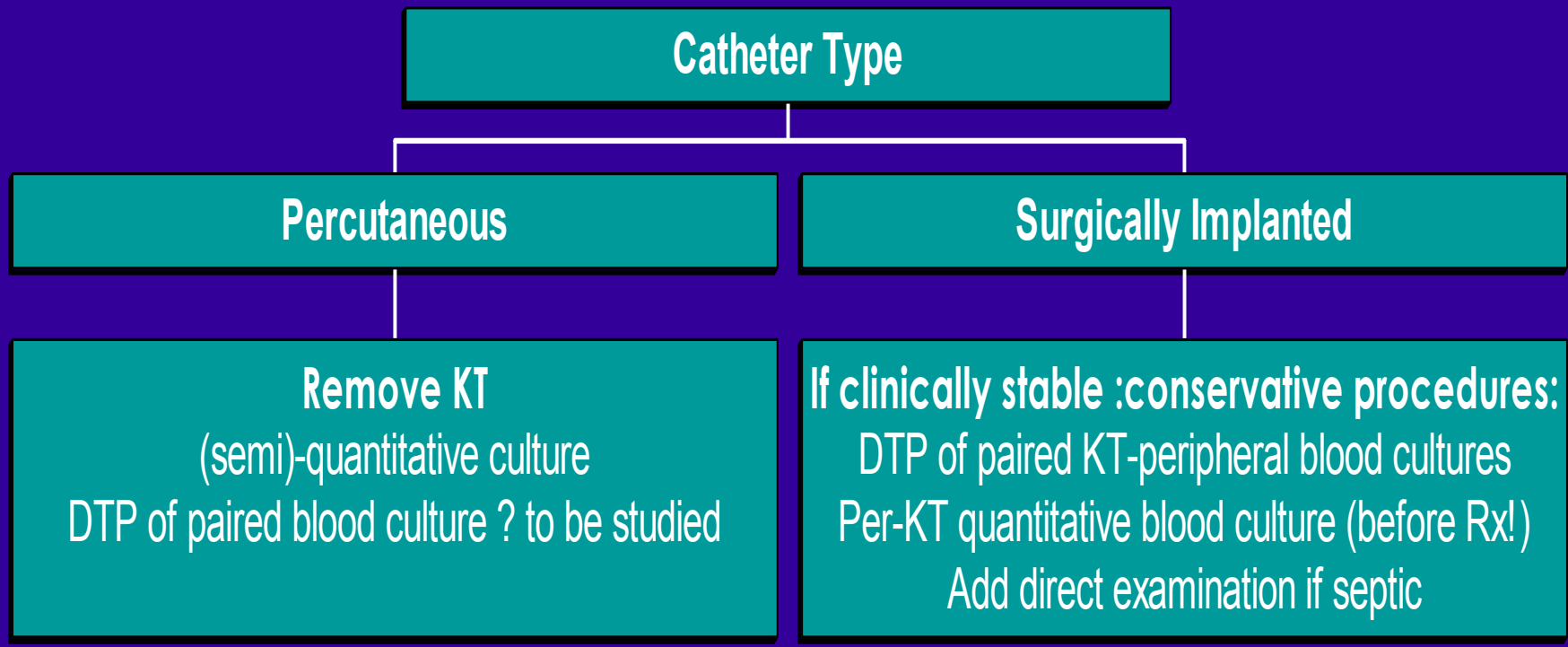
Hallin *J Clin Microbiol* 2003;41:3942

- **16S rDNA/mecA/nuc PCR directly from blood cultures with Gram positive cocci in clusters (n=28 patients)**
- **Accurate diagnosis 40 h earlier than conventional**

- **Empirical antibiotic therapy : 89 % appropriate**
- **Modification of therapy in only 25 % of cases, mostly shift to oxacillin**

- **Conclusion : not cost-effective in this setting**

Conclusion: How to Approach Microbiological Diagnosis of Catheter Infections ?



Unresolved Questions

- Difference in Time to Positivity (DTP) in paired blood cultures
  - short-term percutaneous catheters ?
  - patients with prior antibiotic therapy ?
- Discrimination of contaminant from infecting CoNS
  - serodiagnosis (lipid S, other antigens ?)
  - biofilm determinants ? ?
  - molecular typing ? Frequency of polyclonal infection ?
- Clinical usefulness & cost-effectiveness of rapid diagnostic methods on patient outcome