

**Infections sur dispositifs veineux centraux :
actualités
sur les verrous antibiotiques et non antibiotiques**

Journée des infectiologues de la région
Auvergne-Rhône-Alpes
Annecy -18 nov 2015

Gary DAVID – Villefranche / Saône

VERROUS - ACTUALITES

- Physiopathologie
- Verrous antibio curatifs
- Ethanol
- Verrous antibio préventifs
- Taurolidine
- Associations - Antibiofilms

Long-term central venous catheter (CVC) – or port (P) – related bacteremia or fungemia

Complicated

Uncomplicated (Fig. 2)

Tunnel infection, port abscess

Septic thrombosis, endocarditis, osteomyelitis

Coagulase-negative staphylococcus

Staphylococcus aureus

Enterococcus

Gram-negative bacilli

Candida spp.

Remove CVC/P & treat with antibiotics for 7-10 days

Remove CVC/P & treat with antibiotics for 4-6 weeks; 6-8 weeks for osteomyelitis in adults

May retain CVC/P & use antibiotic lock therapy for 10-14 days
 Remove CVC/P if there is clinical deterioration persisting or relapsing bacteremia, work-up for complicated infection and treat accordingly

Remove the CVC/P & use antimicrobial therapy unless the patient has exceptions listed in Recommendation 80

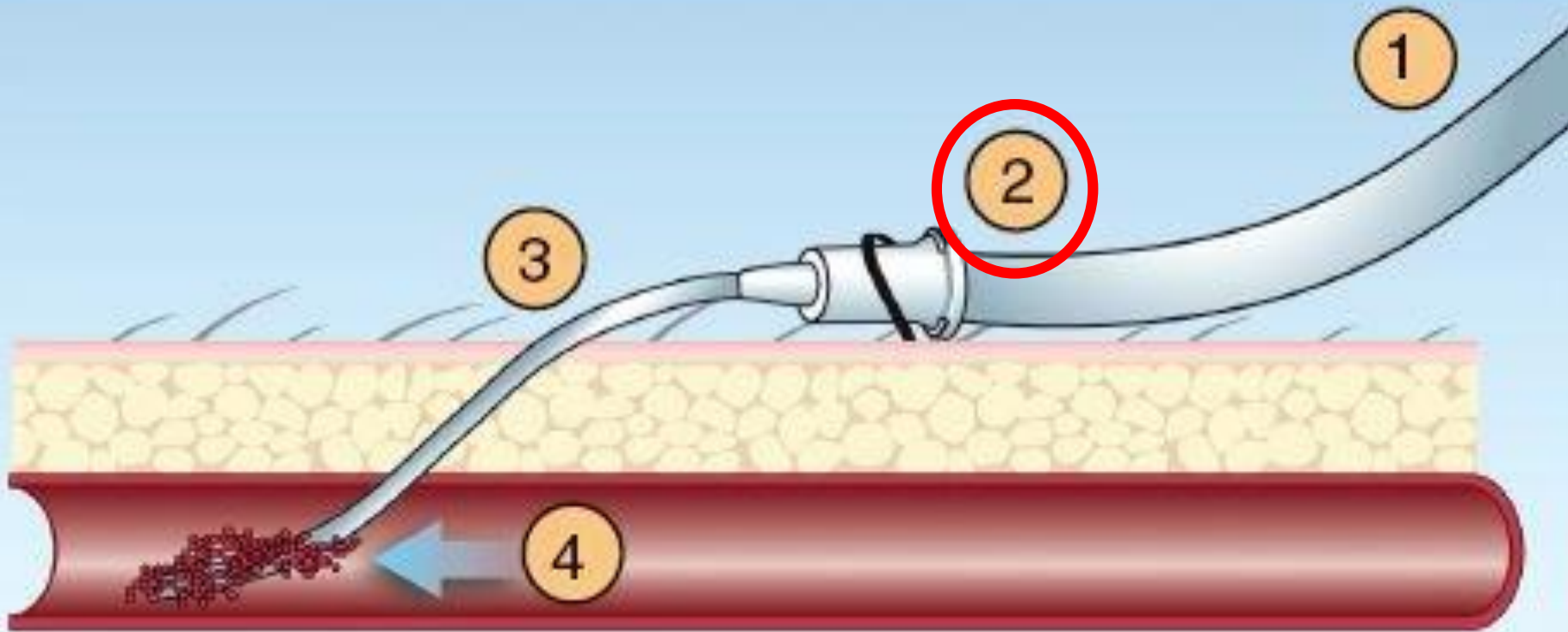
May retain CVC/P & use antibiotic lock therapy for 7-14 days
 Remove CVC/P if there is clinical deterioration persisting or relapsing bacteremia, work-up for complicated infection and treat accordingly

Remove CVC/P & treat for 7-14 days
 For CVC/P salvage, use systemic & antibiotic lock therapy for 10-14 days; if no response, remove CVC/P, rule out endocarditis or suppurative thrombophlebitis, and if not present treat with antibiotic for 10-14 days

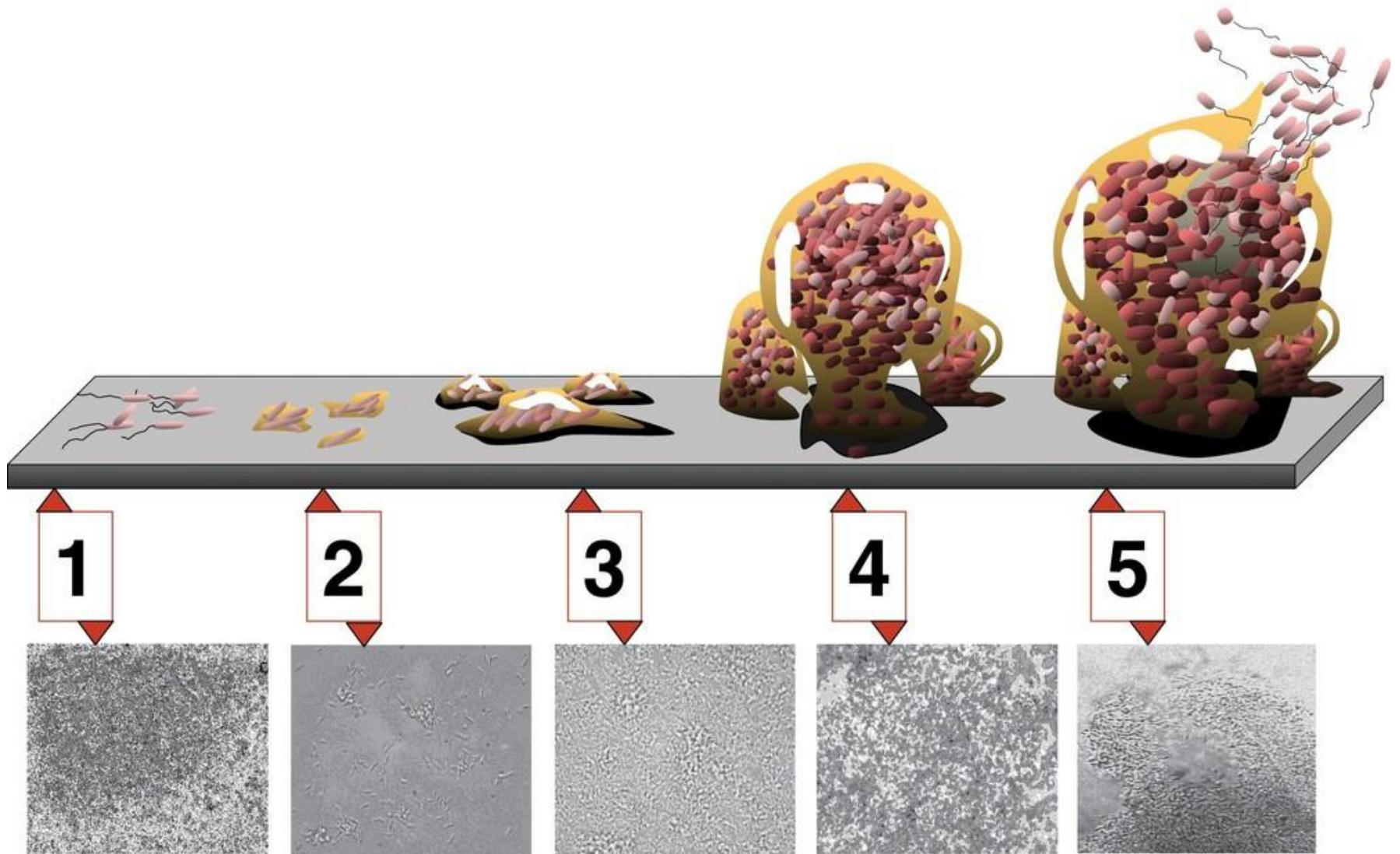
Remove CVC/P & treat with antifungal therapy for 14 days after the first negative blood culture

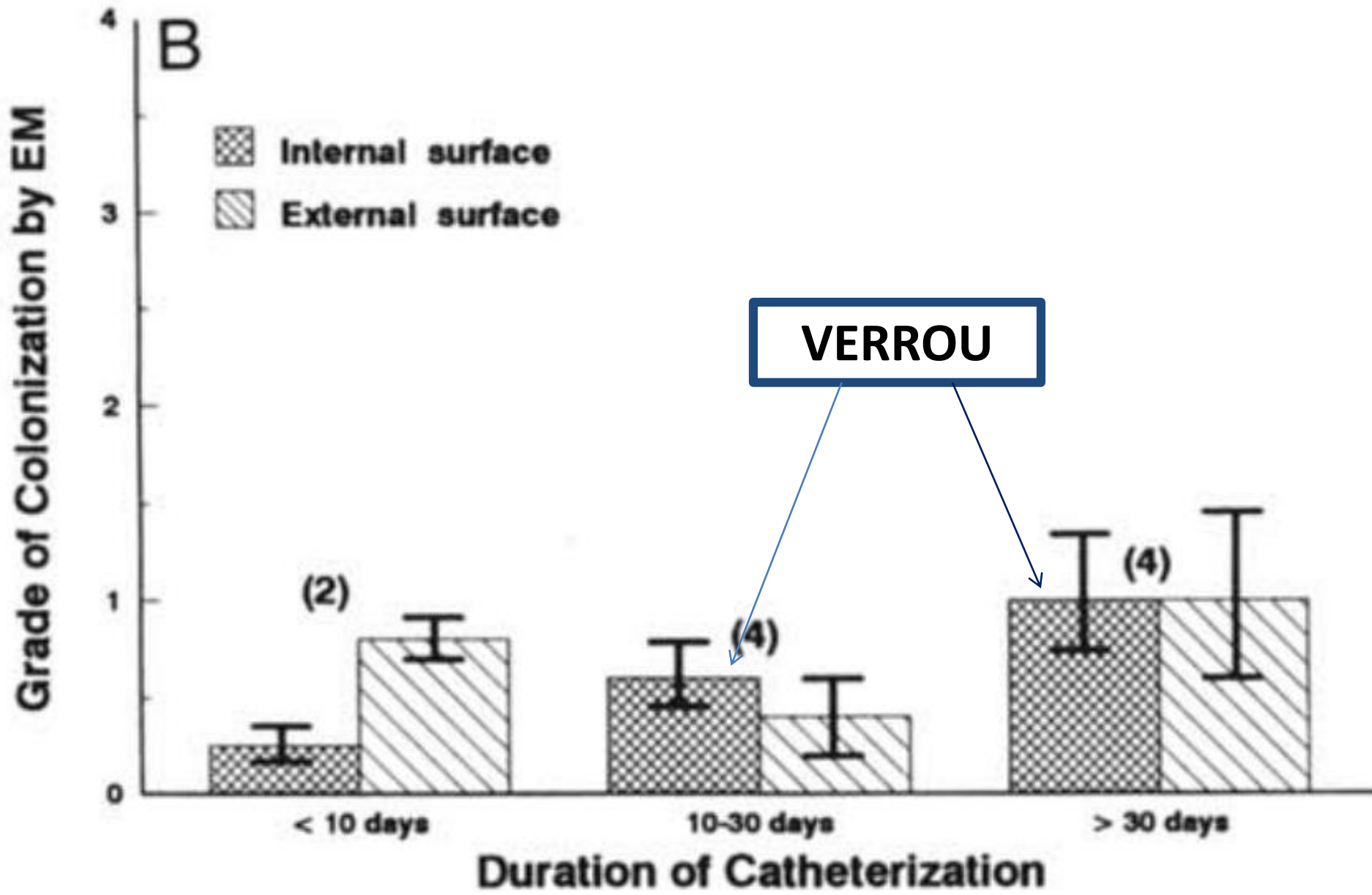
IDSA guidelines 2009

Colonisation des cathéters veineux centraux



Formation du biofilm





VERROUS ANTIBIOTIQUES CURATIFS

Verrous antibiotiques curatifs

0148-6071/88/1202-0185\$02.00/0

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Antibiotic-Lock Technique: A New Approach to Optimal Therapy for Catheter-Related Sepsis in Home-Parenteral Nutrition Patients*

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AND JEAN-JACQUES BERNIER, M.D.**

From INSERM U.290 et Clinique Gastroentérologique, Centre agréé de Nutrition Parentéral à Domicile, Hôpital Saint-Lazare, Paris, France

Verrous amikacine, vancomycine ou minocycline
2 ml, 12h/24h pendant 12 à 16 jours
Sauvetage du cathéter 91% (20/22)

Messing *J Parenter Enteral Nutr.* 1988

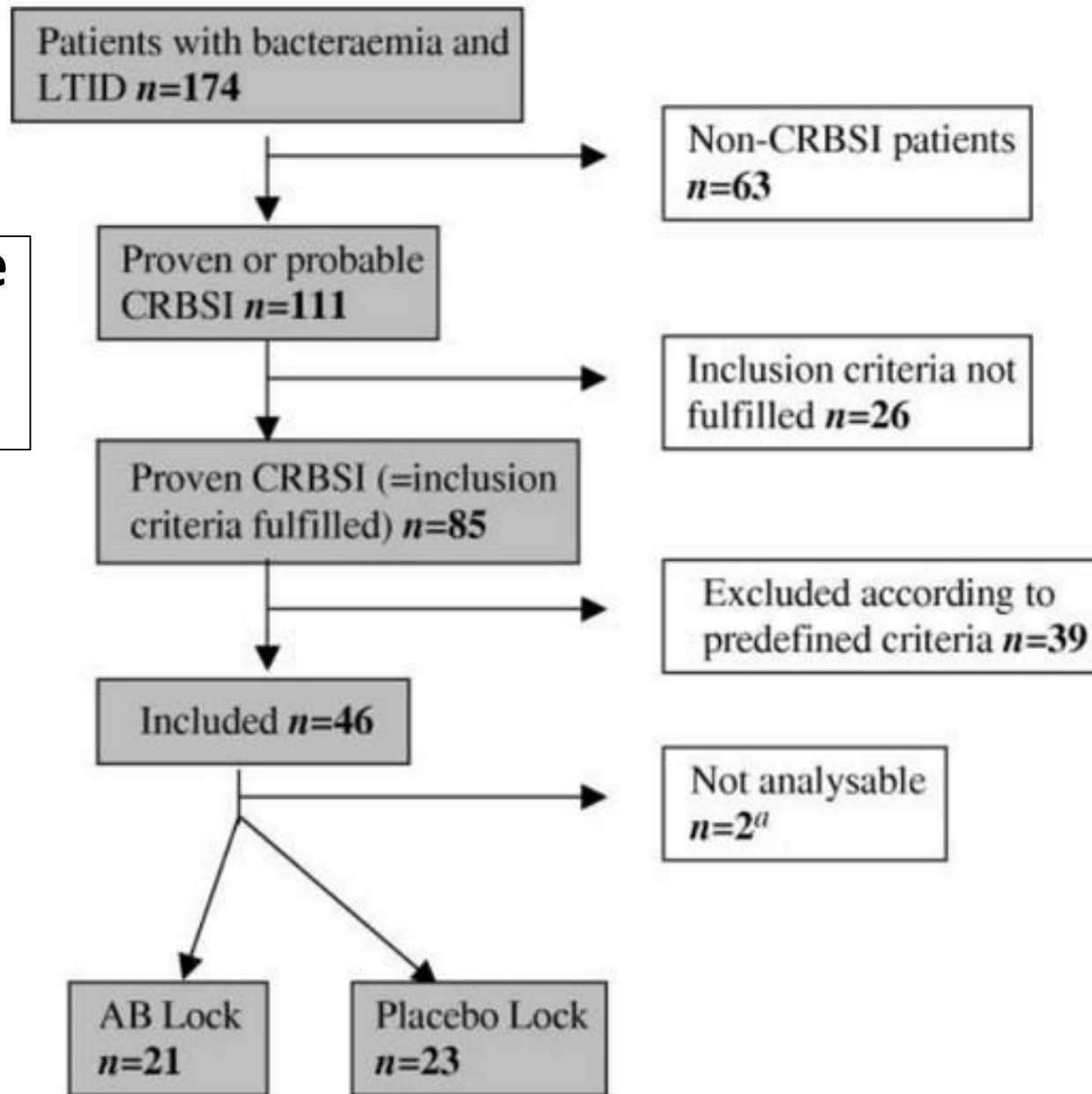
Verrous antibiotiques curatifs étudiés en clinique

Gram positifs	Gram négatifs	CG+ et BG-	Candida spp
Vancomycine	Amikacine	Vancomycine +ciprofloxacine	Amphotéricine B liposomale
Téicoplanine	Gentamicine	Vancomycine +ceftazidime	Ethanol 70%
Céfazoline	Ceftazidime	Ethanol 70%	
Daptomycine	Ciprofloxacine		
Ethanol 70%	Levofloxacine		
	Ethanol 70%		

**Verrou antibiotique
curatif
un essai randomisé**

Verrou

vanco 0,5 mg/ml
ou cefta 0,5 mg/ml
> 8h/24h
pendant 7 à 14j



Verrou antibiotique curatif un essai randomisé

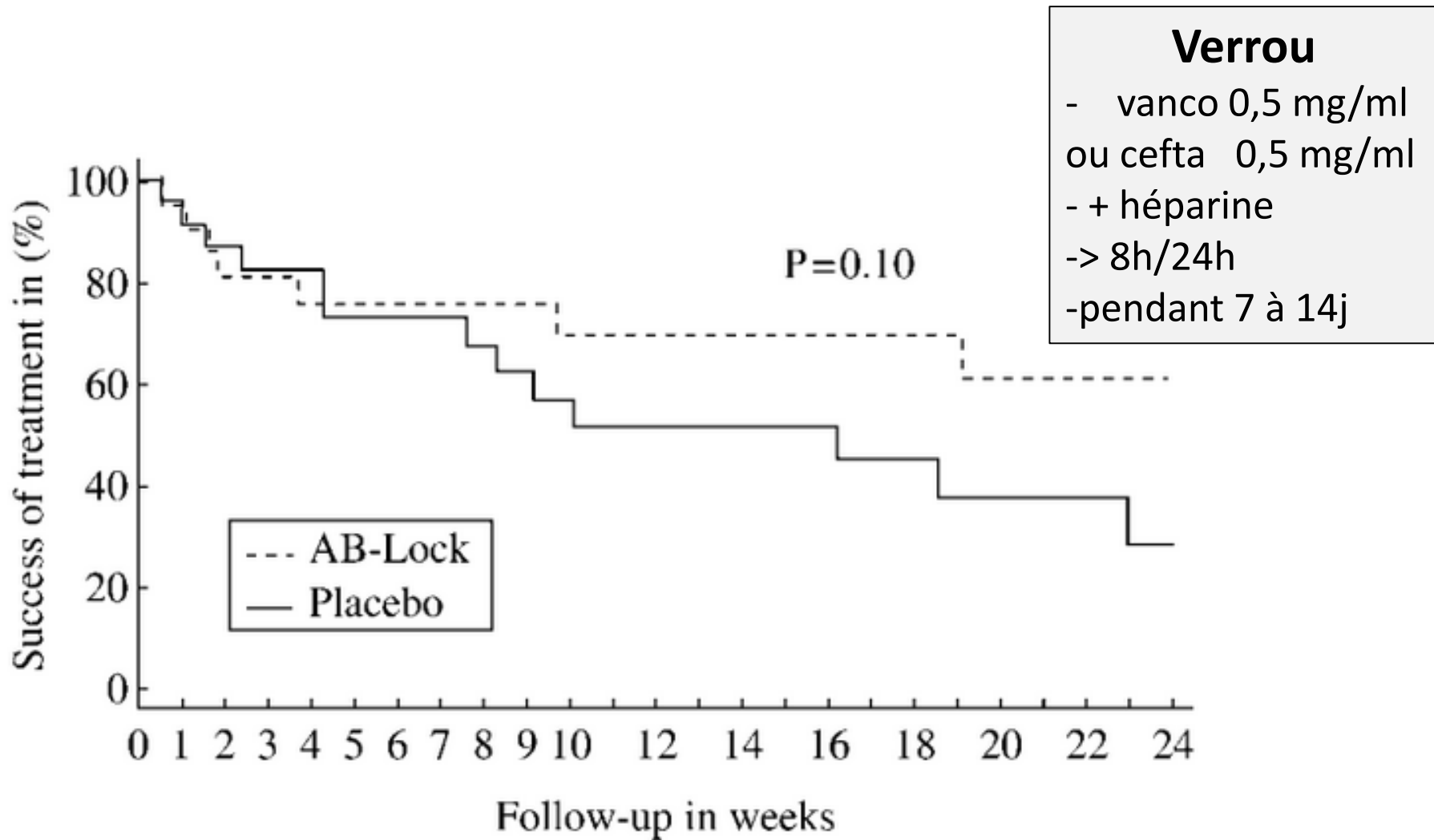


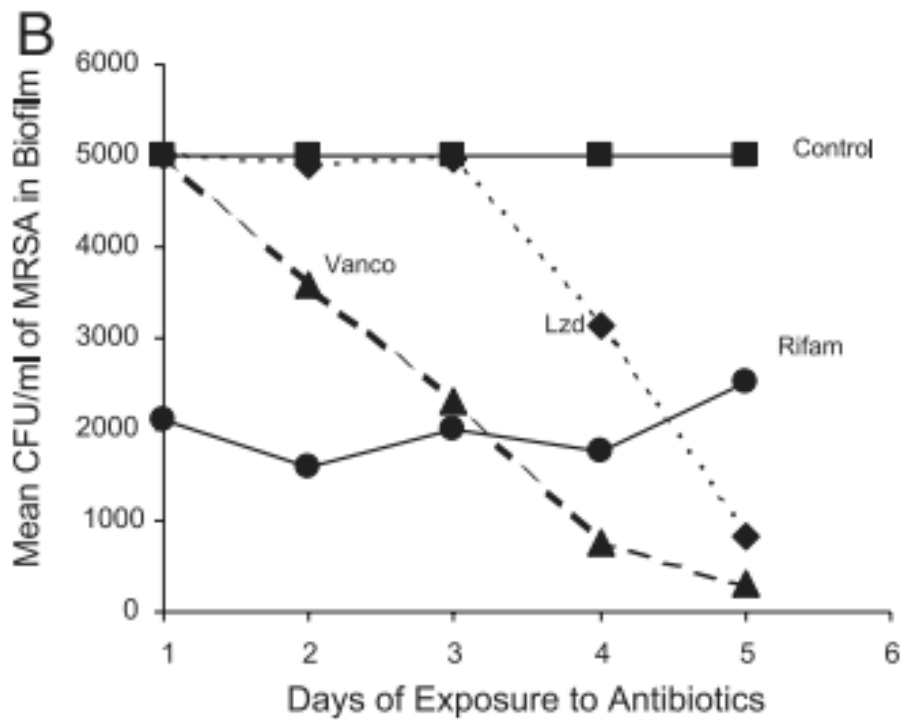
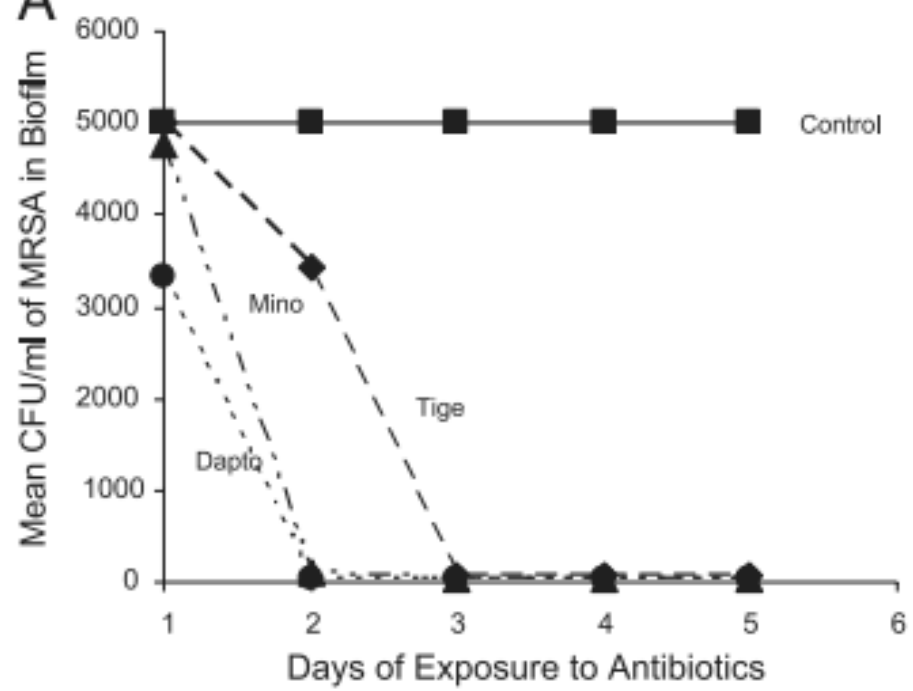
Figure 2. Kaplan–Meier survival analysis of time to treatment failure.

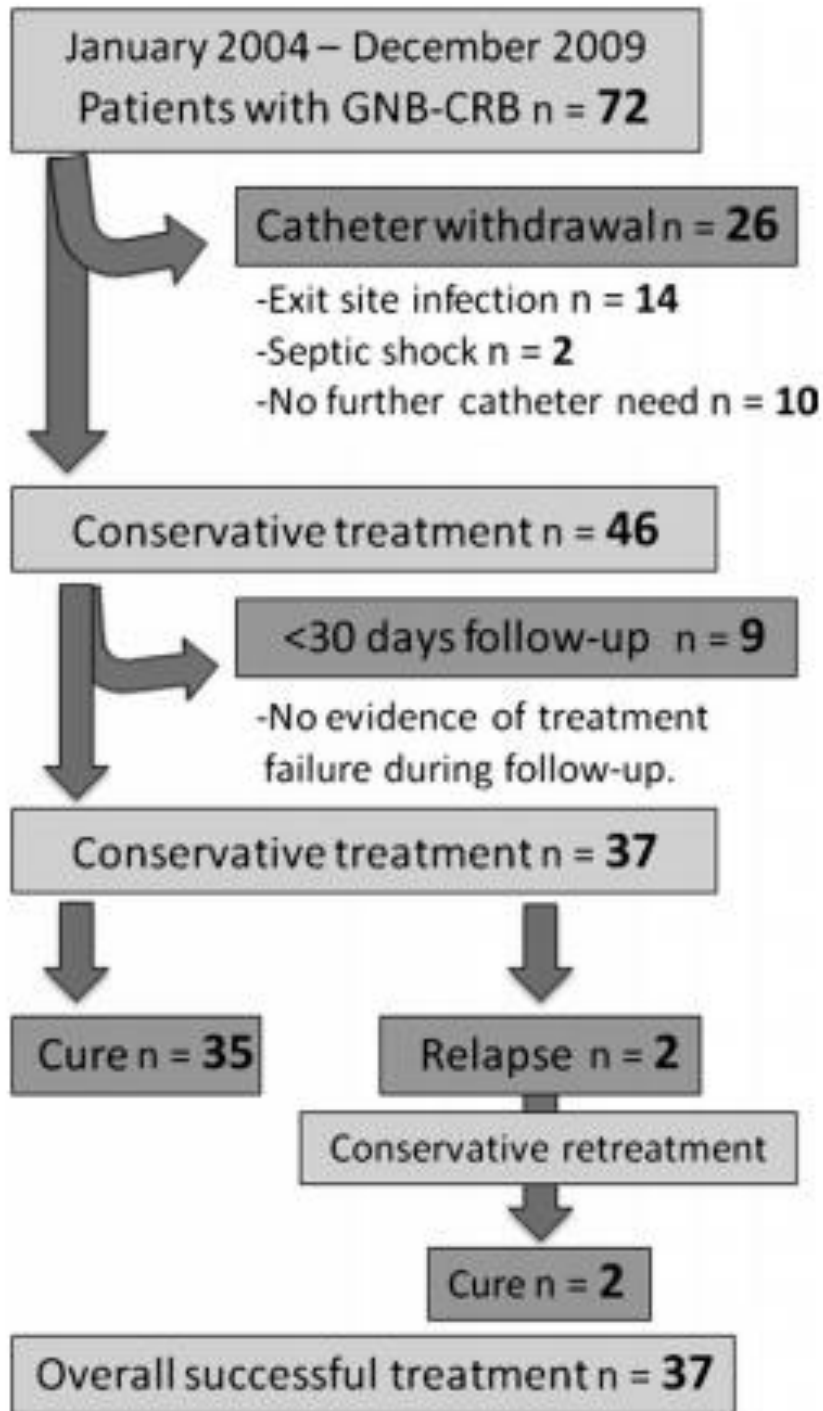
Age in years, median (range)	61.5 (35–75)
Gender (male), no. (%)	4 (50)
Underlying disease	
Solid neoplasia, no. (%)	6 (75)
Hematological neoplasia, no. (%)	1 (12.5)
Short bowel syndrome, no. (%)	1 (12.5)
Type of catheter (port-a-cath/Hickman/Groshong)	6/1/1
Clinical presentation, no. (%)	
Fever	8 (100)
Microorganisms	
MRSE ^a , no.	5
MSSE ^b , no.	1
<i>Enterococcus faecium</i> , no.	1
Polymicrobial infection ^c , no.	1
ALT ^d duration in days, mean (range)	13 (7–16)
Outcome	
Success, no. (%)	6 (75)
Time to microbiological response in days, mean (range)	2 (1–6)
Failure, no. (%)	2 (25)

Verrous curatifs à la Daptomycine en sauvetage

Verrous
Dapto 5mg/ml
dans Ringer Lactate
12h/24h
7 à 16j

In Vitro

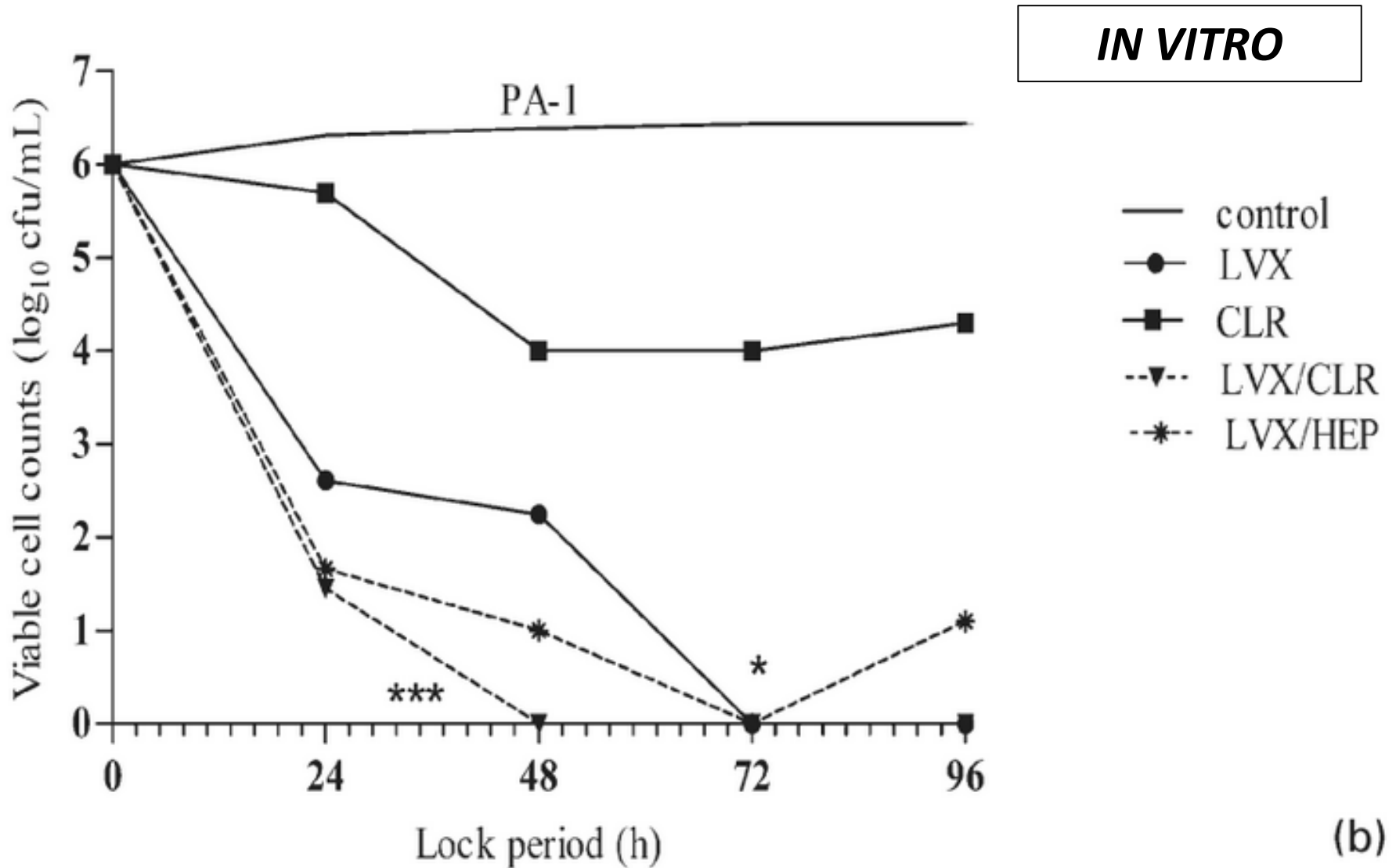




Effectiveness of Antibiotic-Lock Therapy for Long-term Catheter-Related Bacteremia Due to Gram-Negative Bacilli: A Prospective Observational Study

Verrous
Ciprofloxacin 2000 mg/l
ou Amikacine 2000 mg/l
24h/24h
14 jours

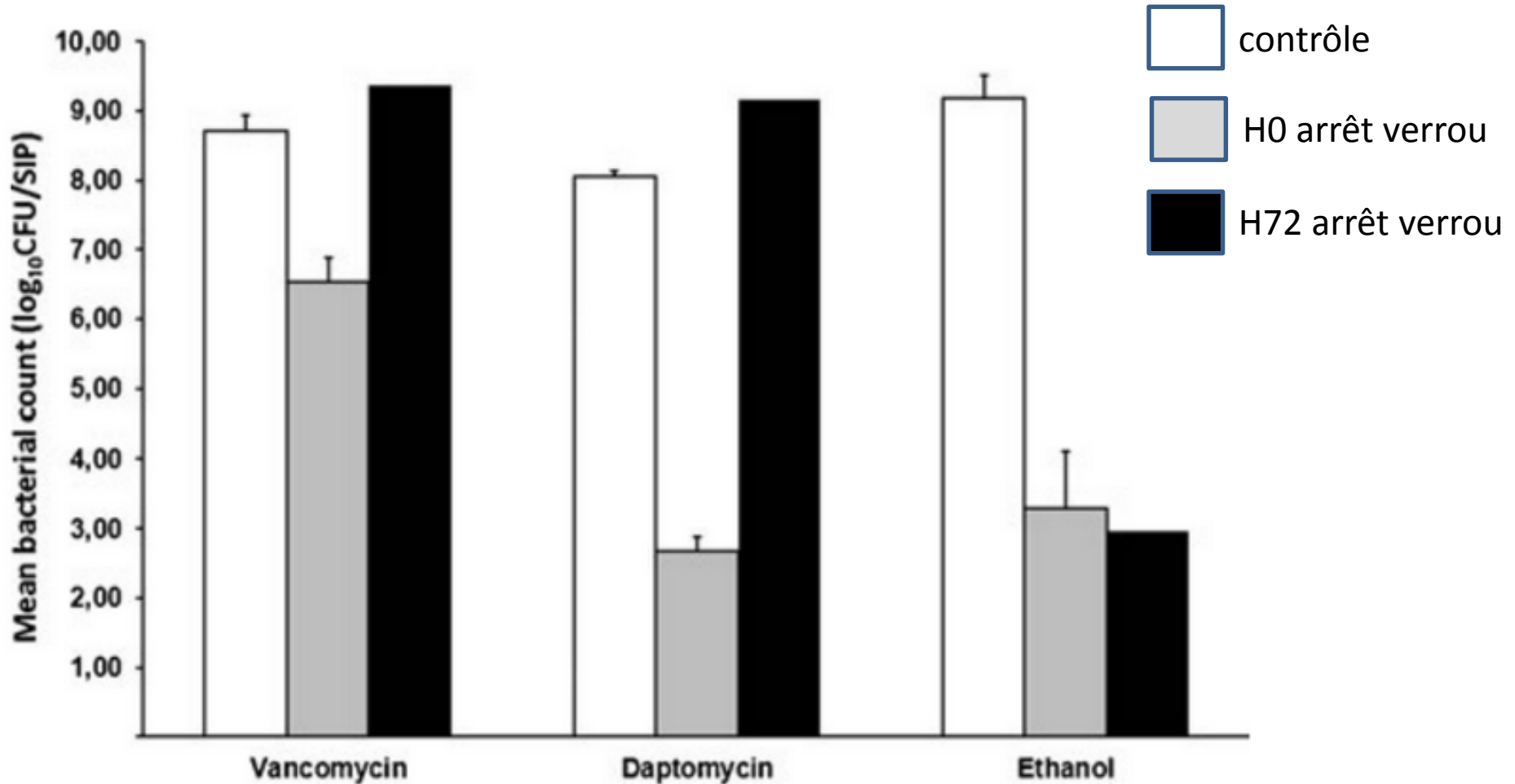
Verrou anti Pyo



Verrous à l'éthanol

IN VITRO


Verrou
24h à 37°C



Verrous à l'éthanol en curatif

Etude Clinique

Short-Dwell Ethanol Lock Therapy in Children Is Associated With Increased Clearance of Central Line- Associated Bloodstream Infections

Clinical Pediatrics
50(10) 943-951
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DOI: 10.1177/0009922811409568
<http://cpj.sagepub.com>


59 patients / 80 infections
1 seul Verrou d'Ethanol 70% de 24h
Guérison clinique 3 mois 69/80 (86%)

McGrath *Clin Pediatr* 2011

Verrou d'éthanol en sauvetage

Organism	Catheter (Lumen)	Treatment Success
<i>Klebsiella pneumoniae</i>	Broviac (2)	Yes
<i>Serratia marcescens</i> , <i>Candida lusitanae</i> , <i>Candida parapsilosis</i>	Broviac (1)	No
<i>Enterobacter cloacae</i>	Broviac (1)	Yes
<i>Candida albicans</i>	Broviac (3)	Yes
<i>Cryptococcus neoformans</i>	Port (2)	Yes
CNS	Broviac (2)	No
CNS	Broviac (1)	Yes
MRSA	Port (2)	Yes
<i>C albicans</i> <i>Enterococcus faecium</i> CNS	Broviac (2)	Yes
<i>E faecalis</i>	Broviac (1)	Yes
<i>C albicans</i> , <i>E faecalis</i>	Broviac (1)	Yes
<i>E faecalis</i>	Broviac (2)	Yes
<i>C albican</i> , <i>S marcescens</i>	Broviac (1)	Yes
<i>C albicans</i>	Broviac (2)	Yes
<i>C parapsilosis</i>	Broviac (1)	Yes

**Etude prospective
Alimentation
Parenterale**

Ethanol 70%

Verrous antifungiques

IN VITRO

	Biofilms jeunes	Biofilms matures
Caspo 5 mg/l	76,8	80,4
Caspo 25 mg/l	78,6	81,5
Mica 5 mg/l	77,7	78,7
Mica 15 mg/l	65,4	75,9
Posaco 10 mg/l	49,7	48,4
L-Amb 200mg/l	91	87,5
L-Amb 1000mg/l	88,5	87,5

Pourcentage d'inhibition de l'activité métabolique de *Candida albicans*
durée verrou 12h ; délai post-verrou 48h.

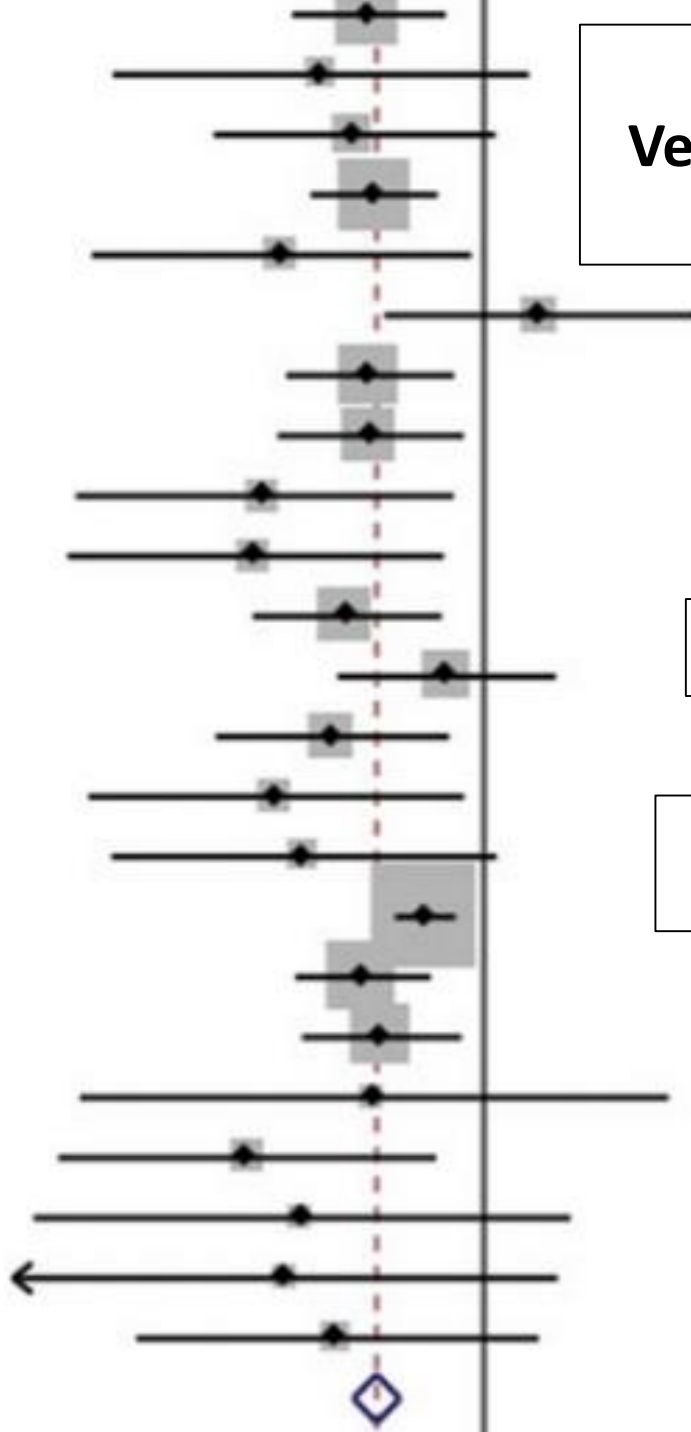
Candidémies sur cathéters

- Verrous actifs sur *Candida spp*
 - Verrous antibiotiques : inhibent formation du biofilm à *Candida*
 - Verrous Taurolidine : ne stérilisent pas le biofilm à *Candida*
 - Verrous antifongiques: ne stérilisent pas le biofilm à *Candida*
 - Verrous éthanol > 40% ++: stérilise biofilm *Candida* en 30mn
- Utilisation exceptionnelle des verrous en curatif
 - Règle = ablation du cathéter car échecs > 50% et risque vital
 - Si sauvetage : fond d'œil, écho cœur, hémocultures répétées
 - Verrou éthanol >40%

Sidrim Int J Antimic agents 2015
Cateau *Med Sciences* 2012
Oncu *Clin Nutr* 2014

Verrous antibiotiques préventifs

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 om HD patients
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Verrous préventifs

RR = 0,31

12 verrous
Évitent 1 infection

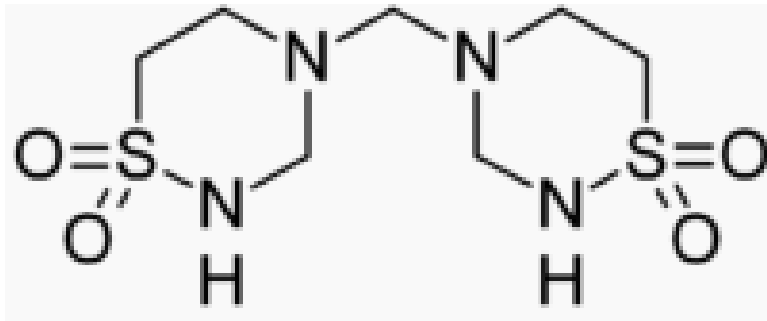
**Zacharioudakis
CID 2014**

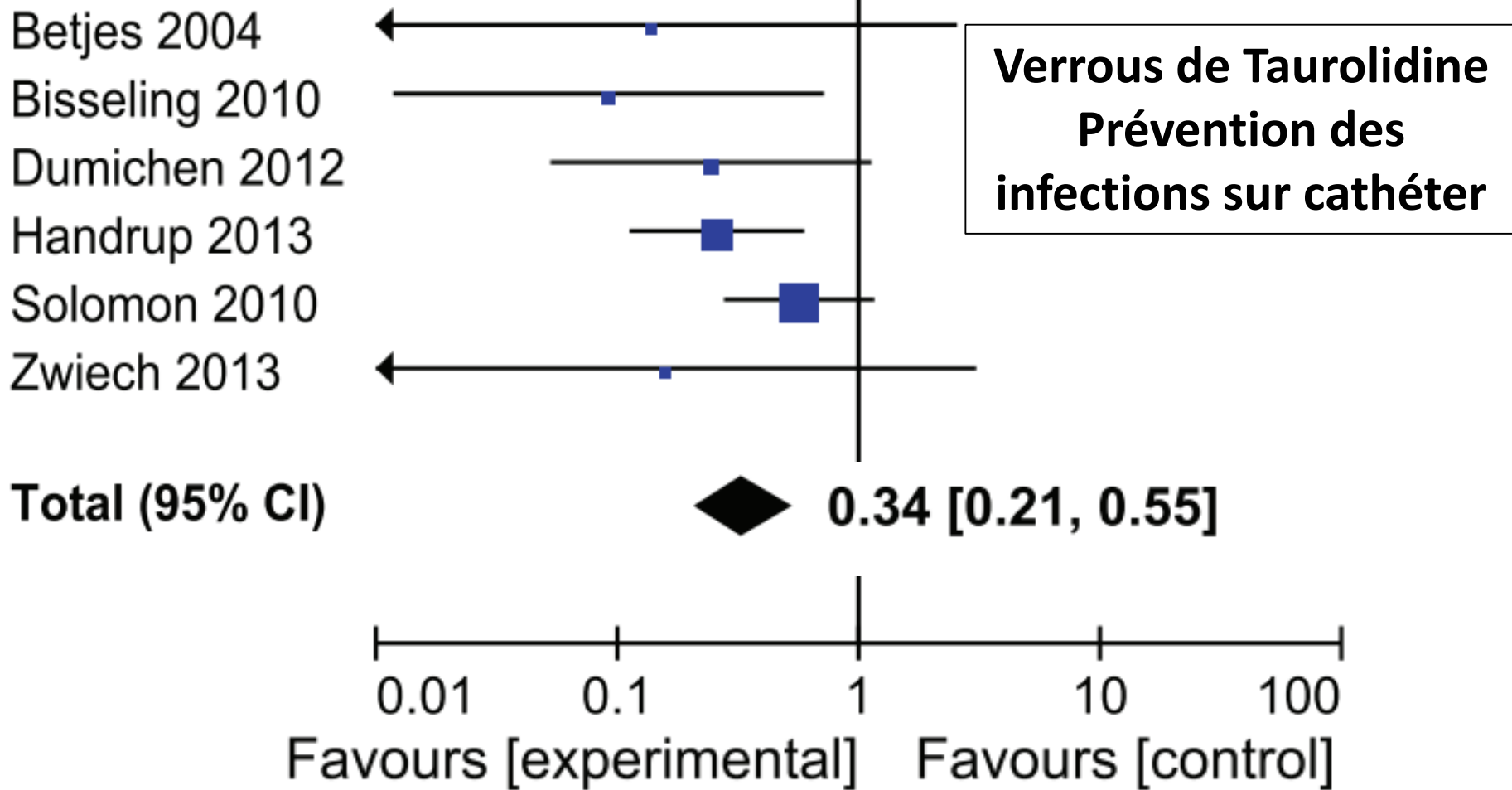
Overall (I-squared = 12.3%, P = .293)

2013	Pediatric cancer	113	Taurolidine, citrate, heparin	0.4/1.4
2012	HD	49	Ethanol, heparin	0.28/1.64
2012	Pediatric cancer	71	Taurolidine, citrate	0.3/1.24
2012	HD	303	Gentamicin, citrate	0.28/0.91
2012	HD	135	Vancomycin, heparin	0.61/5.48
			Linezolid, heparin	0/5.48
2012	HD	56	NaCl 26%, heparin	1.19/0.65
2011	HD	416	Sodium citrate, methylene blue, methylparaben, propylparaben	0.24/0.82
2011	HD	225	Tissue plasminogen activator, heparin	0.4/1.37
2010	TPN	30	Taurolidine	0.19/2.02
2009	HD	140	Gentamicin, heparin	0.06/0.67
2009	Critically ill neonates	97	Amikacin, heparin	4.5/19.9
2008	HD	61	Citrate	2.2/3.3
2008	Hematology patients	64	Ethanol	5.99/31.2
2007	Critically ill neonates	103	Fusidic acid, Heparin	2.2/21.1
2006	HD	120	Cefazolin, gentamicin, heparin	0.44/3.12
2005	HD	208	Cefotaxime, heparin	1.65/3.13
2005	HD	291	Citrate	1.1/4.1
2005	Critically ill neonates	90	Vancomycin, heparin	8.2/24.9
2005	HD	60	Minocycline, EDTA	0/0.47
2004	HD	50	Gentamicin, heparin	0.31/4.05
2004	HD	76	Taurolidine, citrate	0/2.12
2002	HD	83	Gentamicin, citrate	0/1.14
2002	HD	55	Gentamicin, tricitrasol	0.62/3.05

Verrous préventifs

Verrous préventifs à la Taurolidine





! Risque d'occlusion du cathéter par thrombose

Taurolidine



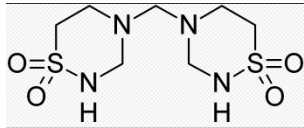
TauroLock UM 25000

Urokinase
25.000IU
+ Taurolidine
+ Citrate (4%)

Composition of evaluated catheter lock solutions according to the manufacturers.

	Manufacturer	Taurolidine (%)	Citrate (%)	Heparin (IU/mL)
Taurosept [®]	Geistlich	2	—	—
Taurolock [®]	TauroPharm	1.34	4	—
Taurolock-Hep [®]	TauroPharm	1.34	4	500
Heparin [®]	Pharmacy Radboud University Medical Center	—	—	500
Citrate	—	—	4	—

Taurolidine : absence d'adaptation microbiologique

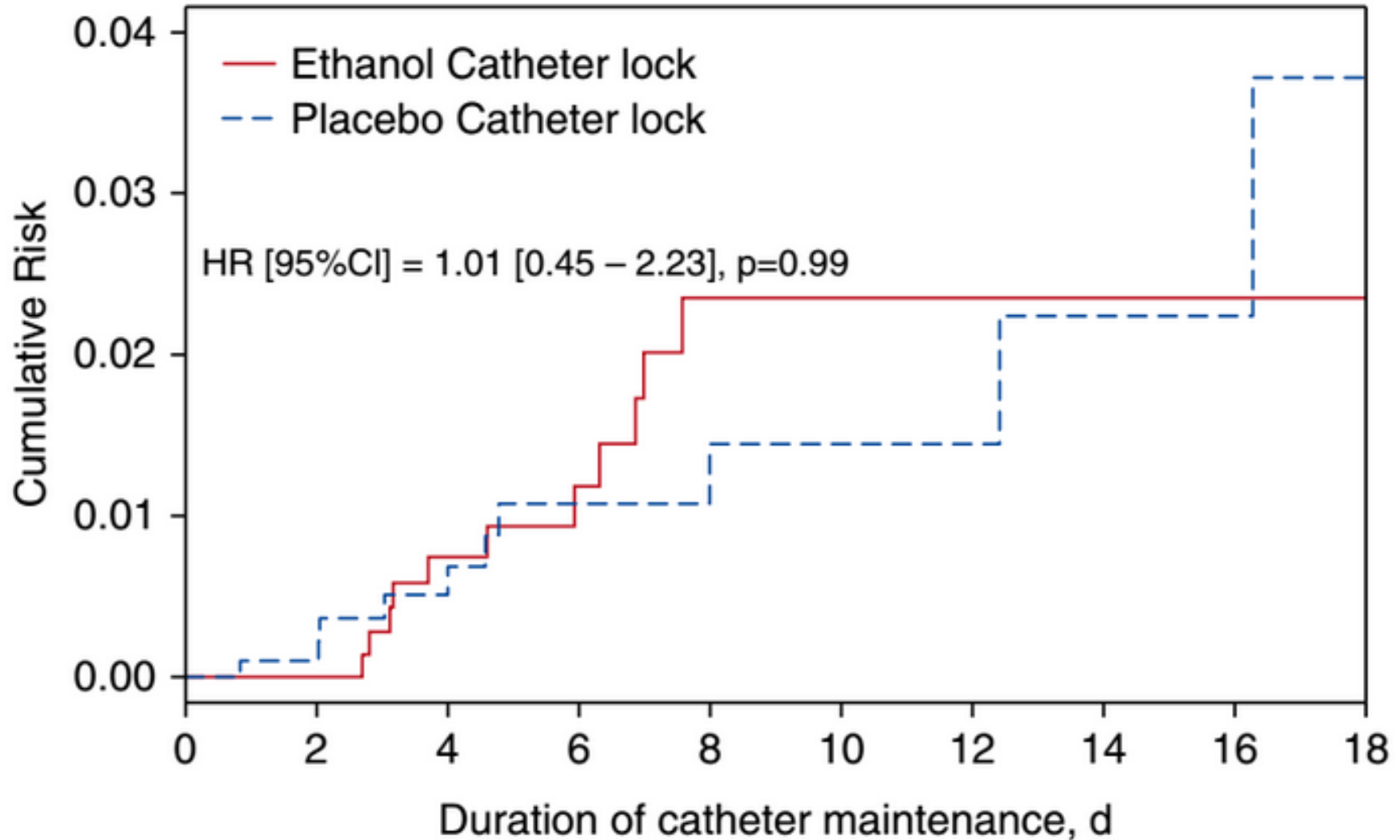


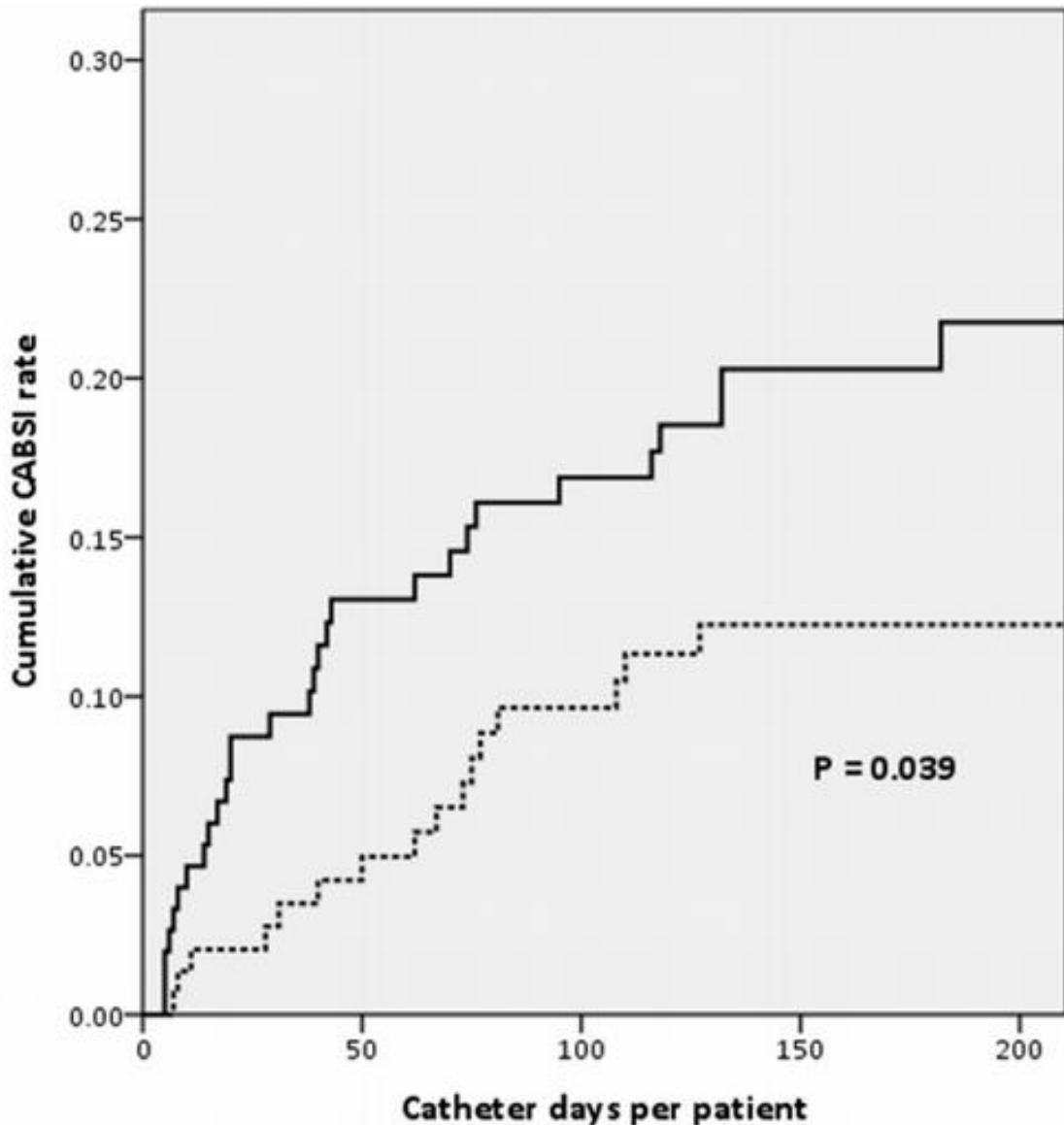
Taurolidine MIC (mg/l)

	This study			Nösner et al.	Torres-Viera et al.
	<i>n</i>	Median	Range	MIC ₅₀ ^a	MIC ₅₀
<i>Candida albicans</i>	5	2048	2048–4096	500–1000	N.D.
<i>Klebsiella pneumoniae</i>	1	256	N.A.	125–250	250
<i>Escherichia coli</i>	2	512	512–512	250–500	500
<i>Citrobacter freundii</i>	2	256–2048	256–2048	125–250	500
<i>Serratia marcescens</i>	1	512	N.A.	125–250	500
Coagulase-negative staphylococci	9	512	256–512	125–250	500
<i>Staphylococcus aureus</i>	3	512	512–512	125–250	500
<i>Enterococcus faecalis</i>	2	512–1024	512–1024	250	500
<i>Enterococcus faecium</i>	1	512	N.A.	N.D.	500
Viridans group streptococci	1	256	N.A.	60–125	250

Verrou éthanol préventif en réanimation

Un essai randomisé





TREATMENT

--- Ethanol

— Heparin

Verrou à l'éthanol
en préventif

Essai randomisé en onco-pédiatrie

307 patients

Ethanol 70% pendant 2 heures

Bactériémies liées au cathéter

0,77 vs 1,44 / 1000 cathéter-jours

P = 0.039

! Retrait de consentement pendant l'étude
Ethanol = 20 / contrôle = 8

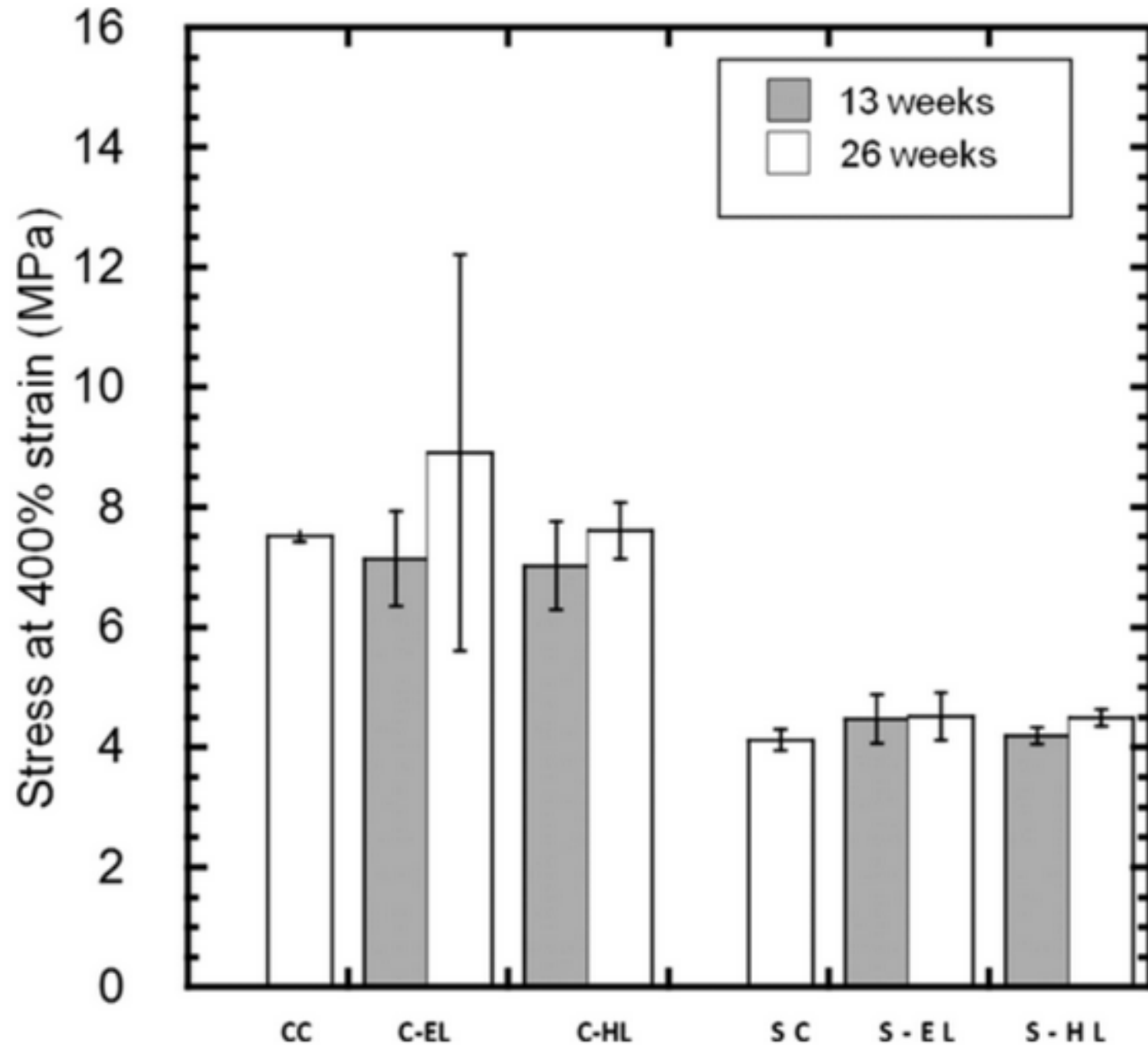
Schoot *Eur J Cancer* 2015

Verrou à l'Ethanol

Effets secondaires

- Effets systémiques
 - Effet antabuse avec métronidazole
 - Goût de vodka dans la bouche
 - Tête légère
 - Flush facial
- Altération du cathéter
 - Polyuréthane > carbothane > silicone
 - Élution de polymères (polyuréthane et carbothane)
- Occlusion du cathéter
 - Ethanol > 28% => précipitation protéines plasmatiques
- Favorise formation de biofilm à staphylocoque

Verrous à l'Ethanol : Résistance à l'élongation



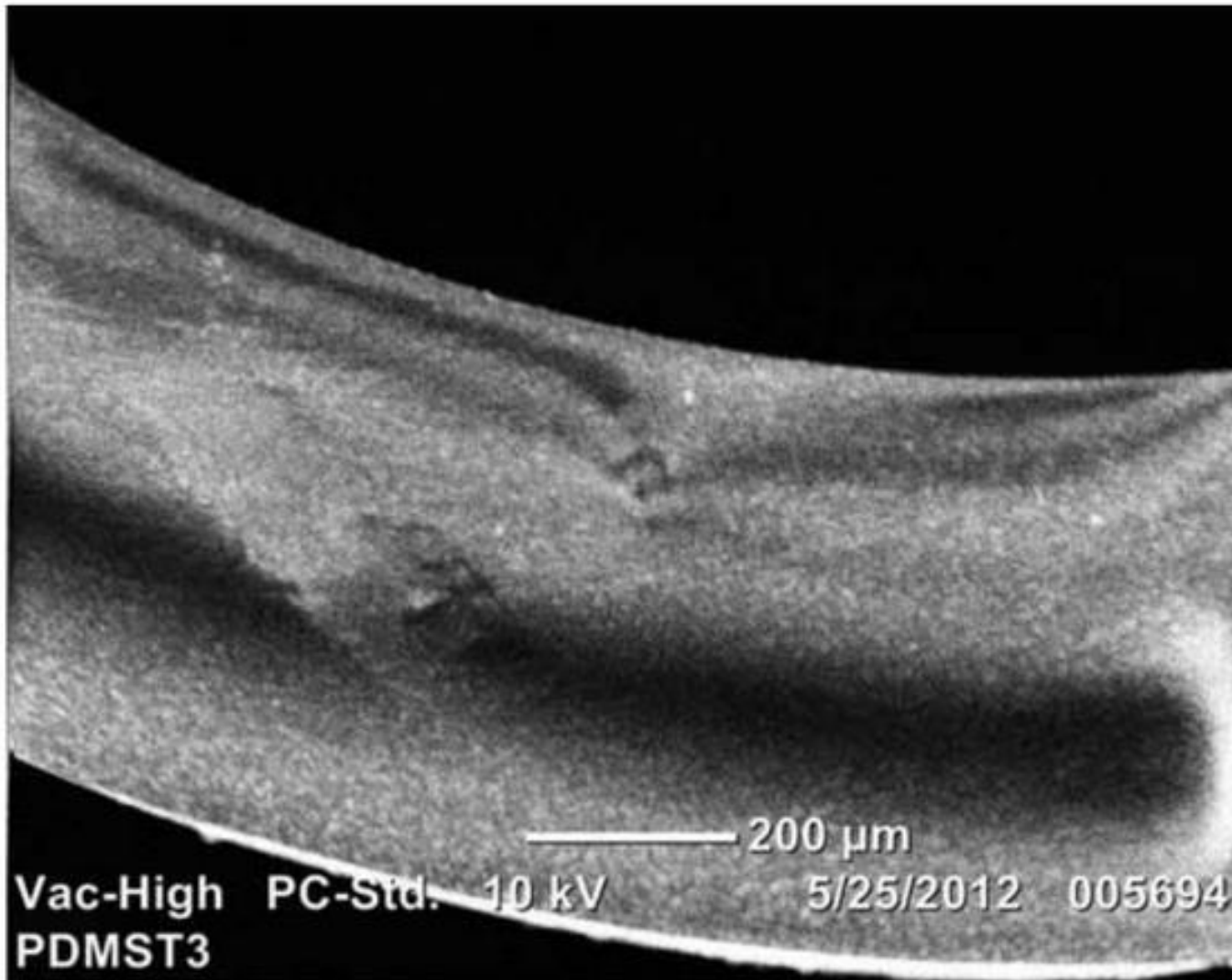
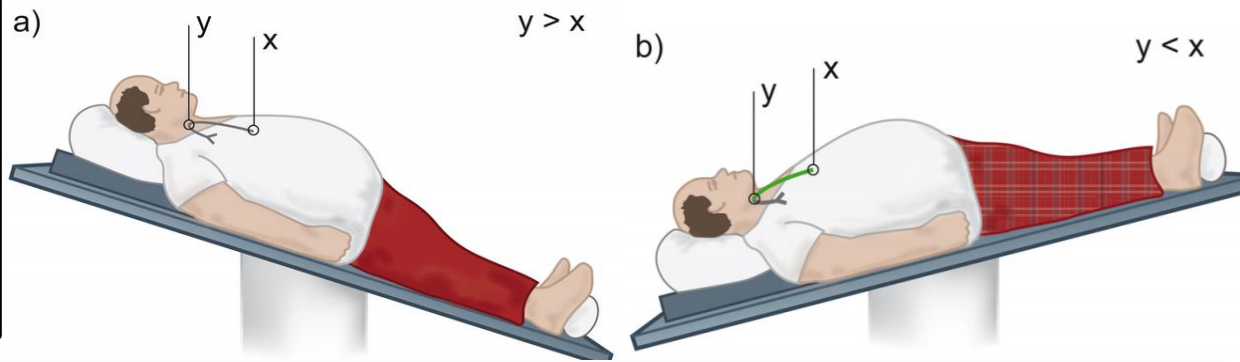


Fig. 2 - Electron microscopy of carbothane exposed to 70% ethanol lock for 26 weeks.

L'éthanol > 28% entraîne une précipitation des protéines du plasma



Ethanol concentration of lock solution [%]	Visible precipitation ^a jugular-vertical ^b	Visible precipitation ^a jugular-recumbent ^c
70	-	+++
63	-	++
56	-	++
49	-	+
42	-	+
38.5	-	+
35	-	+
31.5	-	+
28	-	-
21	-	-
14	-	-
7	-	-

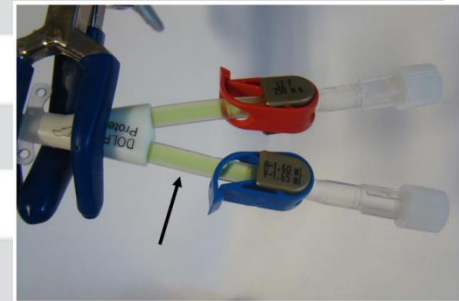
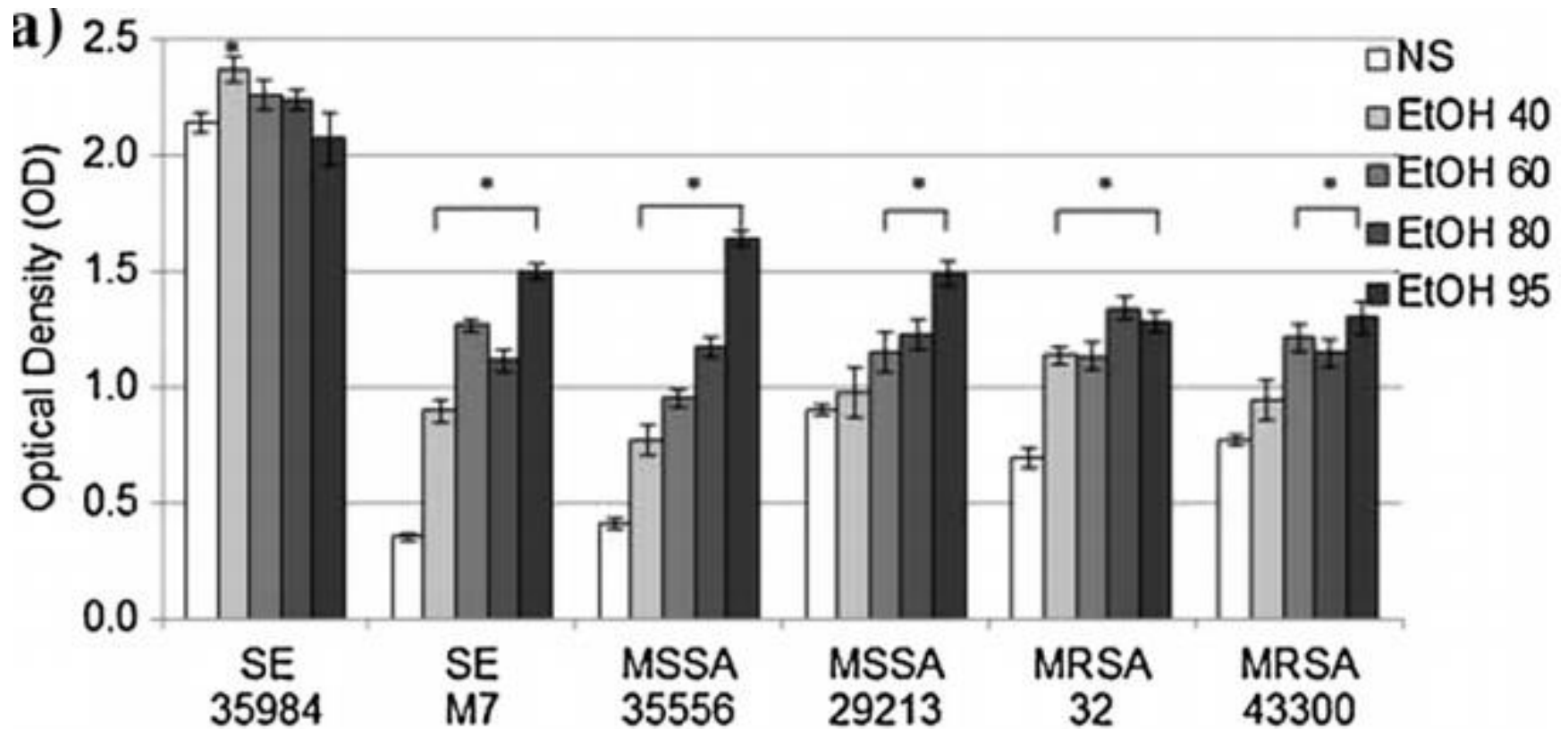


Figure 4. Catheter studies. After ethanol instillation (concentrations ranging from 7 to 70%) in upright position, a simulated jugular (or subclavian) catheter contained green colored plasma up to the clamp (see arrow) after the catheter tip was elevated into recumbent/head down tilt position. Gravity forced ethanol back to leak out of the catheter followed by plasma, or in vivo whole blood influx, respectively.

L'éthanol favorise la formation de biofilm par le Staphylocoque



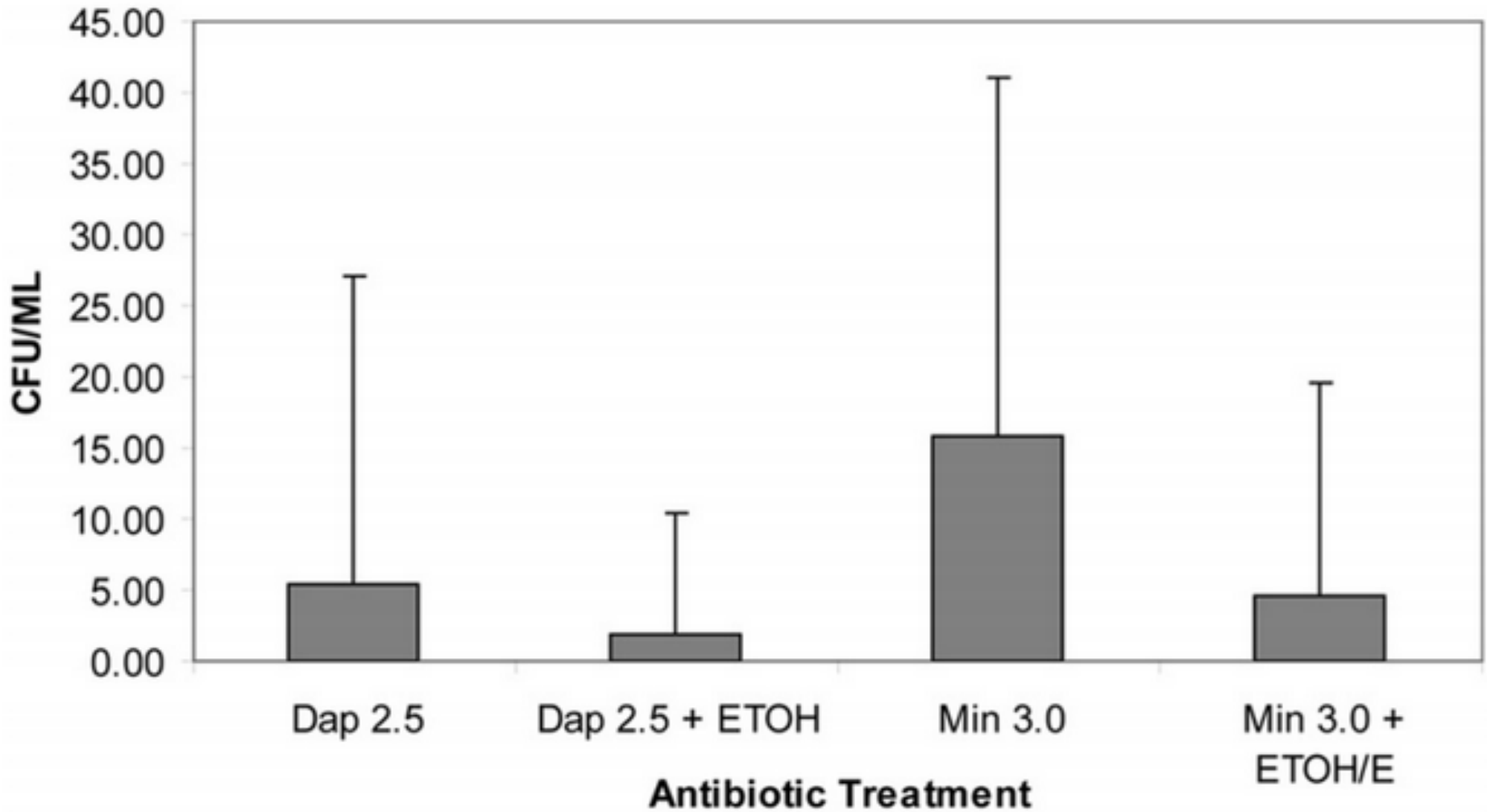
Verrou à l'éthanol

Recommandations

- N'utiliser que sur des cathéters approuvés pour l'utilisation d'éthanol par le fabricant
- Utiliser concentration, volume, durée minimum
- Ajouter produits pour diminuer l'obstruction et inhiber la formation de biofilm (citrate?)
- Réaliser des études randomisées prospectives avec des cathéters en place à différents sites anatomiques

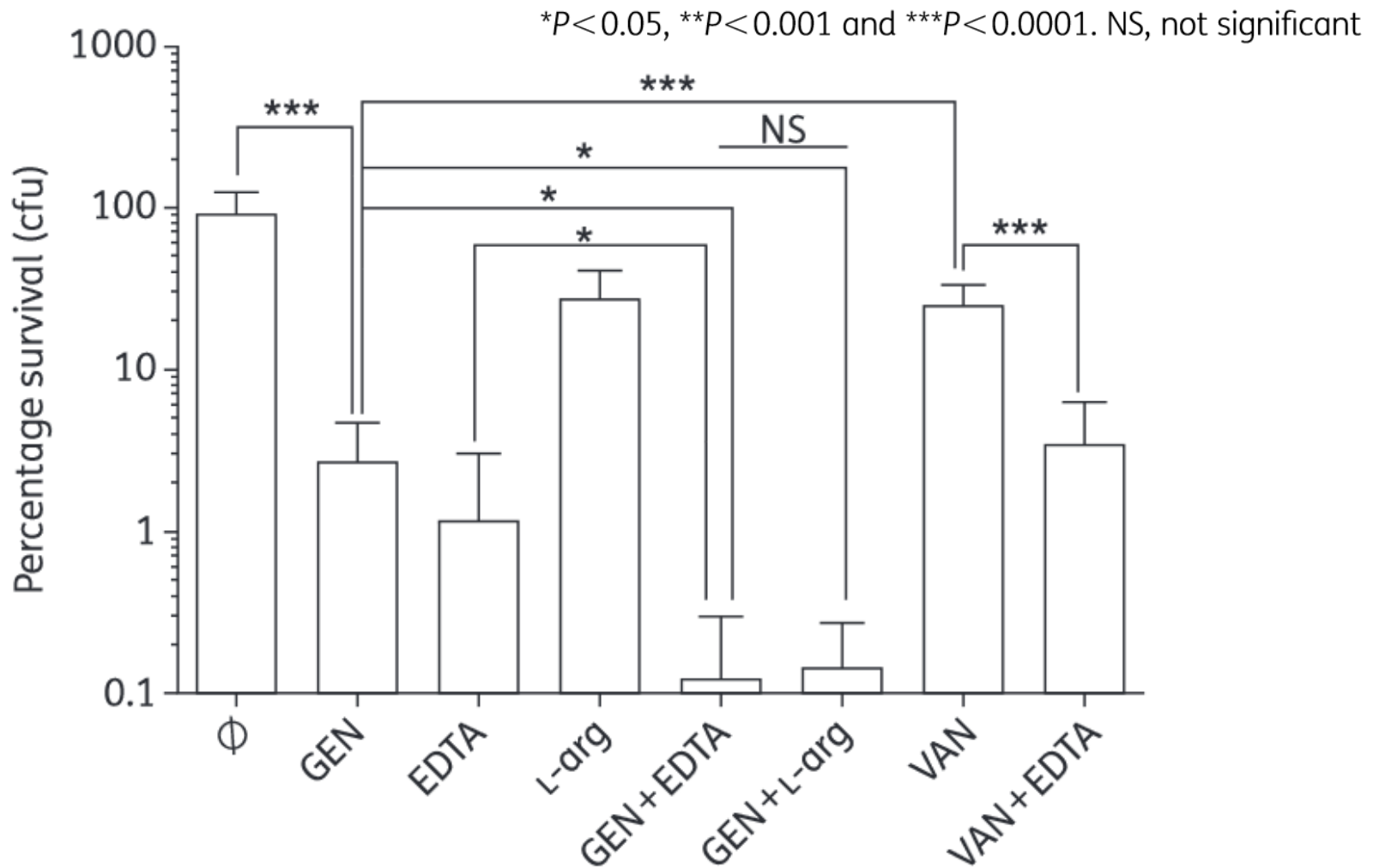
BIOFILM : Prévention ou contrôle

Approche thérapeutique	Mécanisme d'action	Application potentielle	Validé /études humaines
Agents Chélateurs	Antimicrobien; déstabilise EPS	Verrou pour enlever le biofilm	Oui
Ethanol	Antimicrobien; pénètre EPS	Verrou pour enlever le biofilm	Oui
Taurolidine-citrate	Antimicrobien	Verrou pour prévenir colonisation ou enlever biofilm	Oui
Dispersant du biofilm	Disperse cellules biofilm	Verrou pour enlever le biofilm	Non
Bactériophage	Antimicrobien; dégrade EPS	Prétraitement des cathéters pour prévenir colonisation	Non
Oxyde Nitric	Relargue NO	Prétraitement des cathéters pour prévenir colonisation	Non
GImU inhibiteur enzymatique	Antimicrobien; anti-adhésines	Prétraitement des cathéters pour prévenir colonisation	Non
Inhibiteur du RIP Quorum-Sensing	Inhibe QS nécessaire à <i>S. aureus</i> pour biofilm	Injection parentérale enlève le biofilm formé	Non



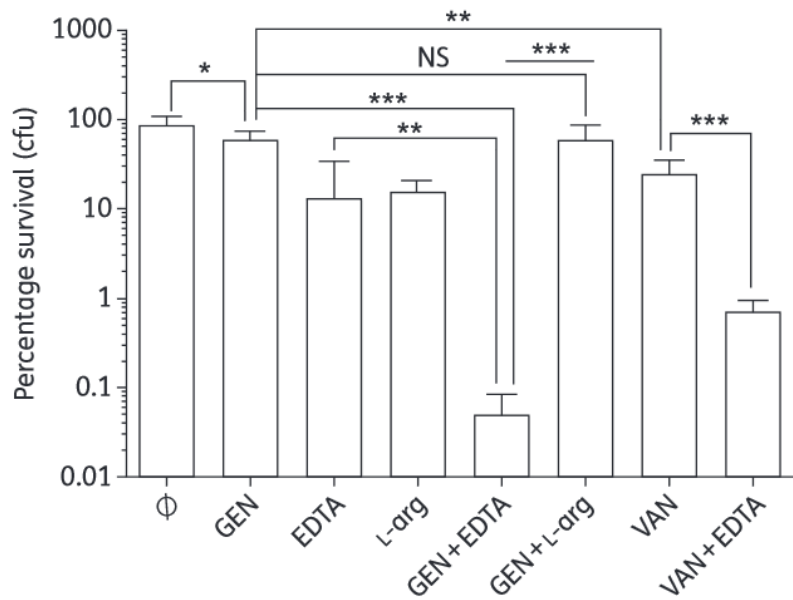
Verrous antibio + chélateur

(a) *S. aureus* strain 40

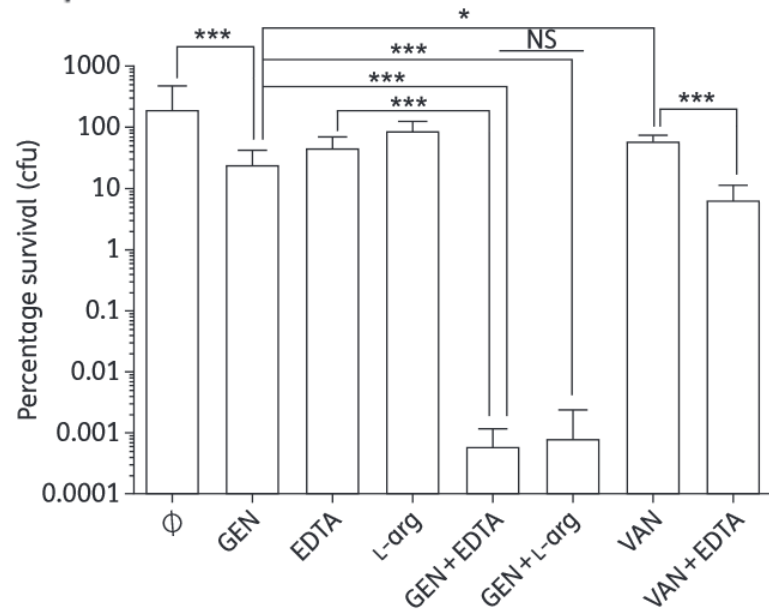


H+24

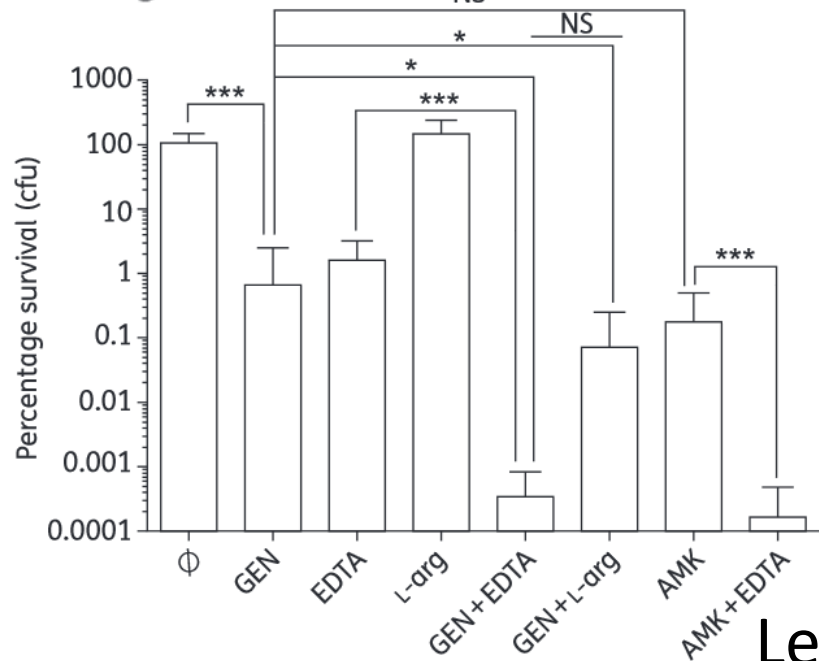
S. epidermidis strain 50



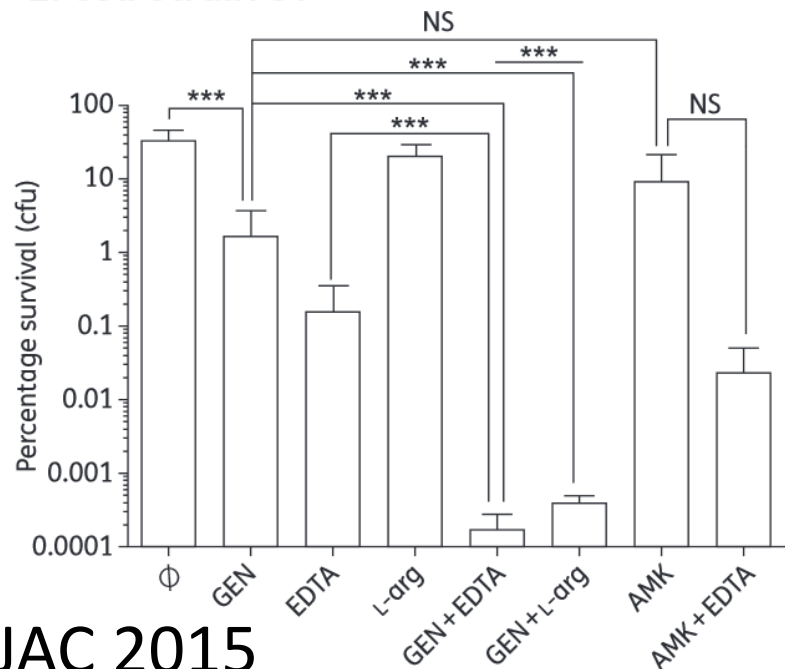
E. faecalis strain 65



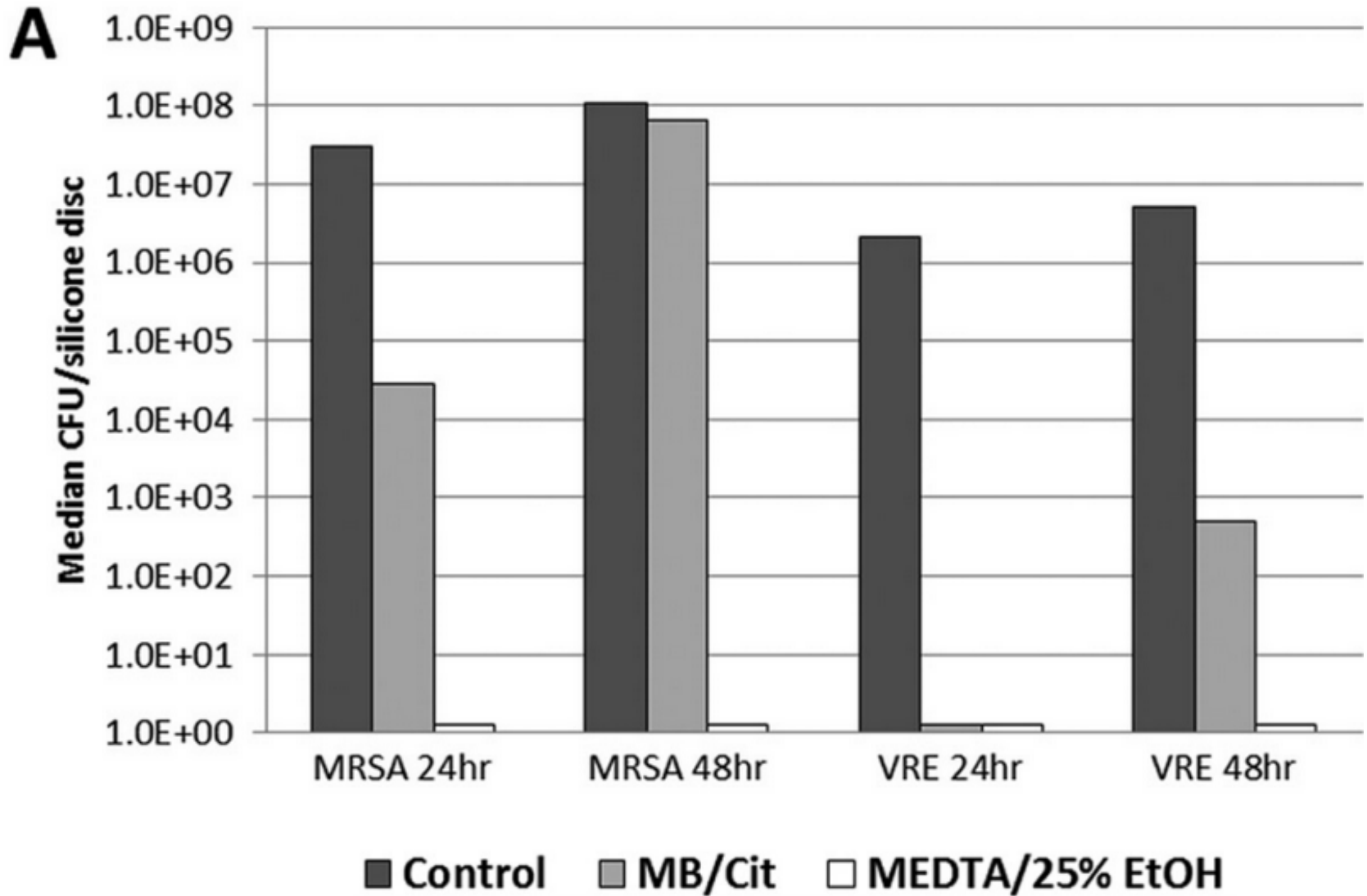
P. aeruginosa strain 32



E. coli strain 57

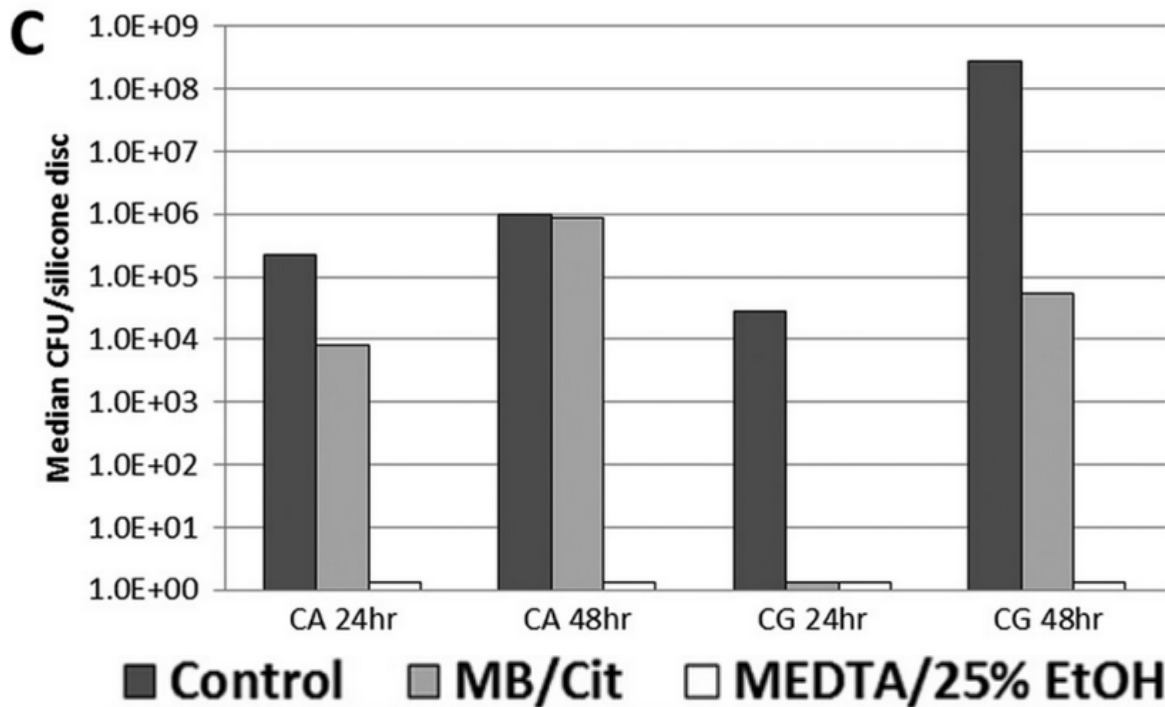
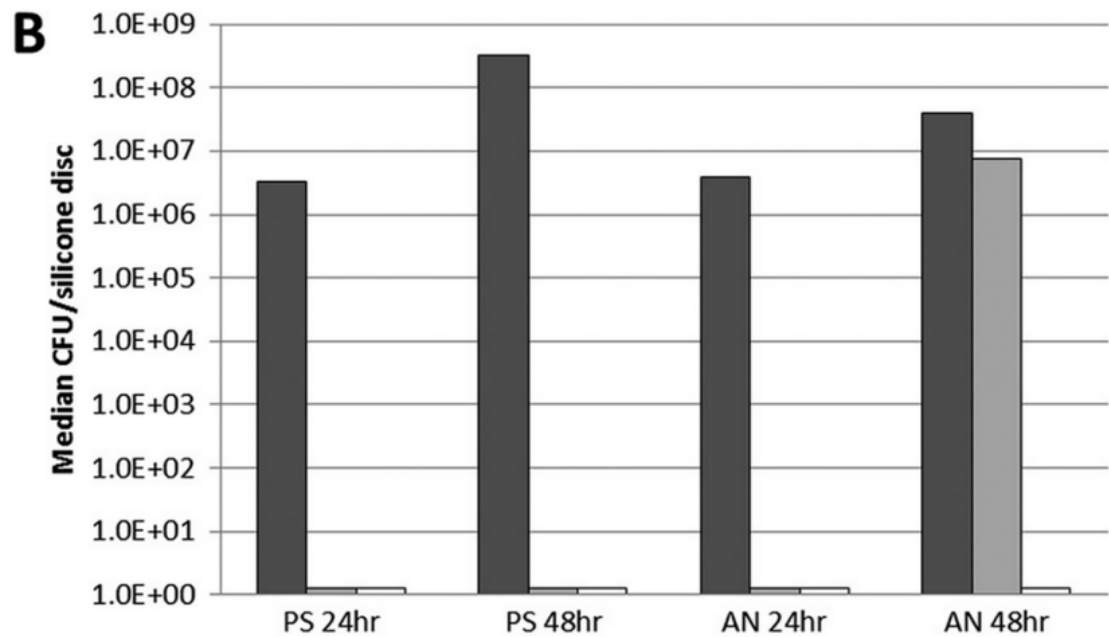


Verrou antibio + chélateur + éthanol



PS *Pseudomonas aeruginosa*

AN *Acinetobacter baumannii*



CA *Candida albicans*

CG *Candida glabrata*

Conclusion

- Utilité des verrous antimicrobiens
 - Pour les cathéters de longue durée précieux
 - En préventif, surtout si taux d'infection élevé ou en cas d'infections récidivantes :
 - Taurolidine ou éthanol > antibiotiques
 - En curatif, sauf si complications ou staph doré ou candida
 - Antibiotiques validés par des études cliniques
 - daptomycine ou éthanol en sauvetage
- Perspectives : associations antimicrobiens + antibiofilms
- Protocoles locaux

Le protocole verrou curatif (1)

I. PRINCIPES : KT précieux; intraluminal; forte concentration; validé;
associé à antibiothérapie systémique

II. INDICATIONS :

Algorithme du traitement des bactériémies sur cathéter veineux central

III. PROCEDURES :

I. Solutions verrou

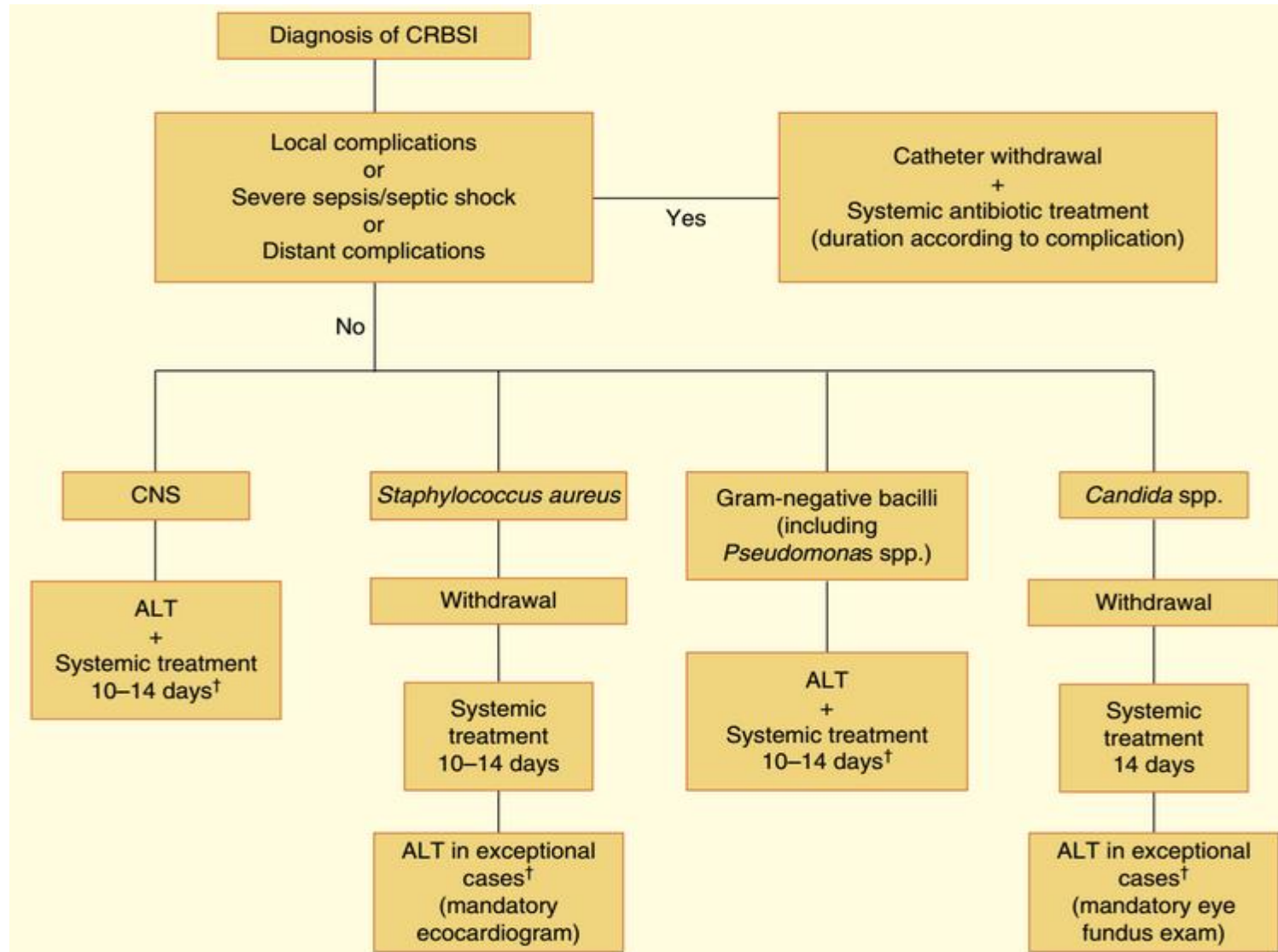
II. Préparation des solutions verrou

III. Administration

IV. Stockage et Stabilité

Le protocole verrou curatif (2)

Algorithme du traitement des bactériémies sur cathéter veineux central



Le protocole verrou curatif idéal? (3)

Solutions verrous

Antibiotique	Concentration	Indication
Vancomycine	2 mg/ml	Cocci gram positif
Amikacine	2 mg/ml	Bacilles gram négatif
Vancomycine + Amikacine	5 mg/ml + 5 mg/ml	Association Cocci gram positif et Bacilles gram négatif
Daptomycine*	5 mg/ml dans Ringer Lactate	<i>Staphylococcus aureus</i> * S. Coag nég (2e intention)
Ethanol*	70%	<i>Candida sp</i> *

* Avis infectiologique requis

Le protocole verrou curatif (4)

Préparation Verrou

Pharmacy Technician Preparation Instructions

Antibiotic Solution final concentration	Pharmacy preparation instructions
Vancomycin 2.5 mg/mL + heparin 2500 units/mL	<ol style="list-style-type: none"> 1. Dilute 500 mg of vancomycin with 10 mL of NS (50 mg/mL) 2. Remove 1 mL and further dilute with 9 mL of sodium chloride resulting in a vancomycin concentration of 5 mg/mL – Label as “solution A” 3. Draw up 1.5 mL of 5,000 units/mL heparin into a syringe and mix with 1.5 mL of solution A (vancomycin 7.5mg) for 3 mL of final solution *If a precipitate appears when mixing vancomycin with heparin, continue agitating the solution for ~10 seconds until the precipitation resolves
Cefazolin 5 mg/mL + heparin 2500 units/mL	<ol style="list-style-type: none"> 1. Dilute 500 mg cefazolin vial with 10 mL of normal saline (50mg/mL) 2. Remove 1 mL of the cefazolin 50mg/mL solution and further dilute with 4 mL of NS resulting in a cefazolin concentration of 10 mg/mL – Label as “Solution A” 3. Draw up 1.5 mL of heparin 5,000 units/mL into a syringe and mix with 1.5 mL of Solution A (cefazolin 15mg) 4. Dispense 3mL of the final solution
Ceftazidime 0.5 mg/mL +	<ol style="list-style-type: none"> 1. Dilute 1000 mg ceftazidime product with 10 mL of NS, for a

Administration Verrou

Administration Instructions:

1. Prior to installation of antibiotic lock, withdraw contents from catheter lumen
2. Flush catheter with normal saline
3. Instill antibiotic lock solution to fill catheter lumen
 - a. Refer to Table 2 for catheter volumes
 - b. Dialysis catheters have catheter volumes written on the catheter “legs”
4. Label the catheter: “DO NOT USE- Antibiotic Lock”
5. Allow lock solution to dwell for a period of time specified by the physician order
 - a. Usual treatment duration: 6-12 hours twice daily
6. After dwell time is complete, aspirate antibiotic lock solution from catheter lumen
7. Flush catheter with normal saline before using line to administer medication

Stabilité Verrou

Storage & Stability:²

Lock Solution	Stability
Vancomycin	72hr at room temp ³
Cefazolin	72hr at room temp ³
Ceftazidime	7 days at room temp ⁴