

**“Prevention of complications”**

11.15 - 11.30 Lock solutions: physicochemical properties *Bertrand Souweine (Clermont-Ferrand, France)*

# **Background**

**Lock strategy for preventing endoluminal CRBSI in selected patients**

**Most antimicrobial lock solutions have no anticoagulant properties**

**There is concern regarding the physicochemical properties of the lock solutions including their**

**stability**

**biological activity**

**impact on catheter integrity**

# **Antibiotics may be incompatible with heparin due to precipitation in solution**

**A precipitate appears when mixing heparin with**

**Vancomycin at concentrations  $\geq 10$  mg/mL (1)**

**Gentamicin at concentrations  $\geq 10$  mg/mL (2)**

**Ciprofloxacin at concentrations  $\geq 2$  mg/mL (3)**

**Concentrated ethanol**

1) Vercaigne LM, *Pharmacotherapy* 2000

2) Khrishnasami Z, *Kidney Int* 2001

3) Jim LK, *Ann Pharmacother* 1993

# In vitro stability of lock solutions combining ABs with heparin up to 72 hours at 37°C

Type of lock solution	Volume of solution <i>mL</i>				
	Vanc <sup>a</sup>	Gent <sup>b</sup>	Cefaz <sup>c</sup>	Heparin <sup>d</sup>	NS
Vancomycin/gentamicin	1.0	0.5	—	0.5	—
Vancomycin	1.0	—	—	0.5	0.5
Gentamicin	—	0.5	—	0.5	1.0
Cefazolin	—	—	1.0	0.5	0.5
Cefazolin/gentamicin	—	0.5	1.0	0.5	—

**Heparin 2500 U/mL can be mixed with vancomycin 2.5 mg/mL, gentamicin 1 mg/mL, and cefazolin 5 mg/mL without visual precipitation**

## Testing grid summary for visual precipitations of ciprofloxacin anticoagulant solutions at 25°C and 37°C

Ciprofloxacin (mg/mL)	Heparin (U/mL)					Citrate
	10	100	1000	5000	10 000	40 mg/ml
0	0	0	0	0	0	0
0.1	0	0	0	0	0	0
0.2	+	+	0	0	0	0
0.4	+	+	+	0	0	0
0.6	+	+	+	0	0	0
0.8	+	+	+	+	3d	0
1.0	+	+	+	+	+	NA

0, no precipitate; +, visible precipitate; 3d, precipitated after 3 days.

**Lower concentrations of heparin resulted in lock precipitation**

**Ciprofloxacin diluted in heparin must be at a concentration <0.2 mg/mL**

**No precipitation was observed when combining ciprofloxacin with 4% citrate**

# Stability of cefazolin 10 mg/mL alone and mixed with heparin 5000 U/mL stored in glass and in PU catheters at 37°C for 72 hours

Table 1. Stability of Cefazolin, Cefazolin-Heparin in Glass, and Cefazolin-Heparin in Central Venous Catheters over 72 Hours

Hours	Cefazolin 10 mg/ml (8 test tubes)			Cefazolin 10 mg/ml and Heparin 5000 U/ml (6 test tubes)				Cefazolin 10 mg/ml and Heparin 5000 U/ml (6 catheters)					
	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	% <sup>c</sup>	p Value <sup>d</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	% <sup>e</sup>	p Value <sup>f</sup>
0	0.876 ± 0.004			0.876 ± 0.004					0.865 ± 0.007				
48	0.853 ± 0.002	-2.6	<0.05	0.822 ± 0.007	-6.2	<0.05	-3.6	<0.001	0.645 ± 0.017	-25.3	<0.001	-21.5	<0.0001
72	0.817 ± 0.007	-6.7	<0.05	0.797 ± 0.002	-9.0	<0.05	-2.4	<0.05	0.628 ± 0.006	-27.4	<0.001	-21.2	<0.0001

The concentration of cefazolin was determined by HPLC

# Antibiotic-Heparin Lock: In Vitro Antibiotic Stability Combined with Heparin in a Central Venous Catheter

Hours	Vancomycin 10 mg/ml (6 test tubes)			Vancomycin 10 mg/ml and Heparin 5000 U/ml (6 test tubes)				Vancomycin 10 mg/ml and Heparin 5000 U/ml (6 catheters)					
	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	% <sup>c</sup>	p Value <sup>d</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>e</sup>	% <sup>c</sup>	p Value <sup>f</sup>
0	0.889 ± 0.002			0.889 ± 0.001					0.936 ± 0.003				
48	0.909 ± 0.007	2.3	<0.05	0.886 ± 0.008	-0.3	NS	-11.4	<0.05	0.691 ± 0.007	-26.2	<0.001	-22.0	<0.0001
72	0.883 ± 0.001	-0.7	NS	0.904 ± 0.007	1.7	<0.05	0.4	<0.05	0.658 ± 0.012	-29.7	<0.001	-27.2	<0.0001
Hours	Ceftazidime 10 mg/ml (8 test tubes)			Ceftazidime 10 mg/ml and Heparin 5000 U/ml (6 test tubes)				Ceftazidime 10 mg/ml and Heparin 5000 U/ml (6 catheters)					
	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>b</sup>	% <sup>c</sup>	p Value <sup>d</sup>	Absorbance (mean ± SD)	% <sup>a</sup>	p Value <sup>e</sup>	% <sup>c</sup>	p Value <sup>f</sup>
0	0.896 ± 0.003			0.896 ± 0.004					0.825 ± 0.017				
48	0.809 ± 0.005	-9.8	<0.05	0.802 ± 0.009	-10.6	NS	-0.87	NS	0.562 ± 0.005	-31.9	<0.001	-29.9	<0.0001
72	0.776 ± 0.003	-13.4	<0.05	0.781 ± 0.014	-12.9	NS	0.64	NS	0.493 ± 0.006	-40.2	<0.001	-36.9	<0.0001
Hrs	Gentamicin 5 mg/ml (4 test tubes)			Gentamicin 5 mg/ml and Heparin 5000 U/ml (4 test tubes)				Gentamicin 5 mg/ml and Heparin 5000 U/ml (6 catheters)					
	Area ± SD	% <sup>a</sup>	p Value <sup>b</sup>	Area ± SD	% <sup>a</sup>	p Value <sup>b</sup>	% <sup>c</sup>	p Value <sup>d</sup>	Area ± SD	% <sup>a</sup>	p Value <sup>e</sup>	% <sup>c</sup>	p Value <sup>f</sup>
	C1a	C1, C2		C1a	C1, C2				C1a	C1, C2			
0	5.0 ± 0.2	5.0 ± 0.1		5.0 ± 0.1	5.0 ± 0.1				5.0 ± 0.5	5.0 ± 0.5			
48	5.3 ± 0.1	5.3 ± 0.1	6.0 <0.05	5.3 ± 0.3	5.0 ± 0.2	3.0 NS	-3.8	<0.05	4.5 ± 0.2	4.5 ± 0.2	-10 <0.001	-11.8	<0.01
72	5.2 ± 0.1	5.1 ± 0.1	3.0 <0.05	5.6 ± 0.1	5.4 ± 0.1	10 <0.05	7.8	<0.05	4.6 ± 0.3	4.6 ± 0.3	-8 <0.001	-14.5	<0.0001

The ABs concentrations were determined by HPLC

# **Stability of AB, AB-heparin stored in glass and in PU catheters at 37°C for 72 hrs**

**In this case, the residual AB concentration (half of the initial concentration) was sufficient for antibiofilm activity**

**The interaction between AB/heparin solution and catheter surface may be greater with other lock solutions and materials**

**Whether this effect has to be taken into account for calculating the appropriate dosages of ABs and heparin in AB/heparin lock solutions is unknown**

# In vitro stability of vancomycin 1 and 3 mg/mL mixed with 4% citrate, stored in PVC syringes at 4°C and 23°C or in PU catheters at 37°C over 72 hours

Table 1 Percent remaining of vancomycin during storage<sup>a</sup>

Storage temperature	23 °C	4 °C	23 °C	4 °C	37 °C	37 °C	37 °C	37 °C
Solution	4% citrate	4% citrate	4% citrate	4% citrate	4% citrate	4% citrate	4% citrate	4% citrate
Container	5 mL PVC syringe	5 mL PVC syringe	5 mL PVC syringe	5 mL PVC syringe	Hemostar catheter	Hemostar catheter	CardioMed catheter	CardioMed catheter
Nominal concentration (mg/mL)	1	1	3	3	1	3	1	3
Initial concentration (mg/mL)	0.97 ± 0.04	0.94 ± 0.17	2.84 ± 0.42	2.82 ± 0.06	1.19 ± 0.00	2.81 ± 0.00	1.04 ± 0.00	2.63 ± 0.00
Study day								
1	98.024	96.891	96.583	99.169	92.243	96.594	99.669	102.537
3	97.138	96.953	92.268	97.019	98.076	95.297	102.669	104.857
Time to achieve a 10% change in concentration (days) <sup>b</sup>	10.9	10.5	3.8	10.0	52.2	6.4	9.7	6.7

The stability of vancomycin was assessed by its concentration determined using the liquid chromatography technique

On day 3, >92% of the initial vancomycin concentration remained in all containers at both concentrations

**No significant interaction was observed between the vancomycin / citrate solution and the catheter surface.**

# In vitro stability of gentamicin 2.5 mg/mL and 4% citrate stored in PU catheters at 37°C over a 96-hour period

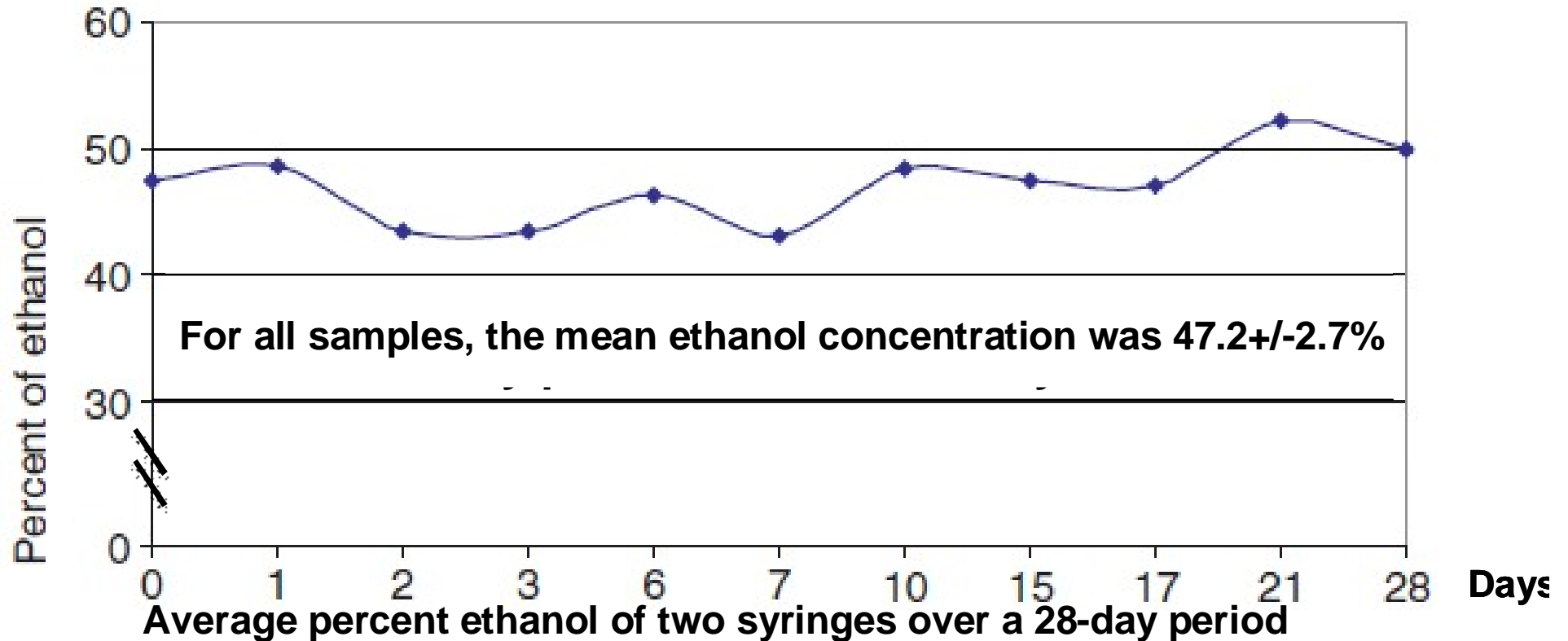
**Table: Percent remaining during storage**

<b>Hour</b>	<b>Gentamicin 2.5mg/mL</b>	<b>Sodium citrate 40 mg/mL</b>
<b>0</b>	<b>99.36+/-1.24</b>	<b>100.8+/-0.95</b>
<b>24</b>	<b>104.8+/-3.32</b>	<b>102.6+/-1.55</b>
<b>48</b>	<b>101.6+/-0.62</b>	<b>102.7+/-1.71</b>
<b>72</b>	<b>103.4+/-0.67</b>	<b>104.1+/-1.07</b>
<b>96</b>	<b>102.4+/-1.03</b>	<b>102.9+/-1.25</b>
	<b>P=0.2769</b>	<b>P=0.5556</b>

The stability of the mixture was assessed by the concentrations of gentamicin and sodium citrate determined by HPLC assays

Adapted from Battistella M, *Hemo Int* 2010

# Stability of 50% ethanol solution (v/v) in polypropylene syringes stored at room temperature, not protected from light, over a 28-day period



The mean ethanol concentrations ranged from 43% to 52% over the 28 day period. These variations were unlikely to be of clinical relevance

# Testing grid summary for visual precipitations of ethanol heparin solutions stored inside glass at 25°C and 37°C for 72 hours

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Ethanol (v/v)	Sodium heparin 3000 U/mL	Enoxaparin 400 IU/mL
30%	0	0
40%	0	0
50%	+	+
60%	++	++
70%	++	++

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Physical incompatibility was defined as the presence of any visible precipitation or cloudiness.

When ethanol at a concentration >40% was diluted in heparin 3000 U/mL or in enoxaparin 400 IU/mL a precipitate formed immediately.

# In vitro stability of gentamicin at concentrations $\geq 1$ mg/mL diluted in heparin 2500 U/mL determined by bioassay.

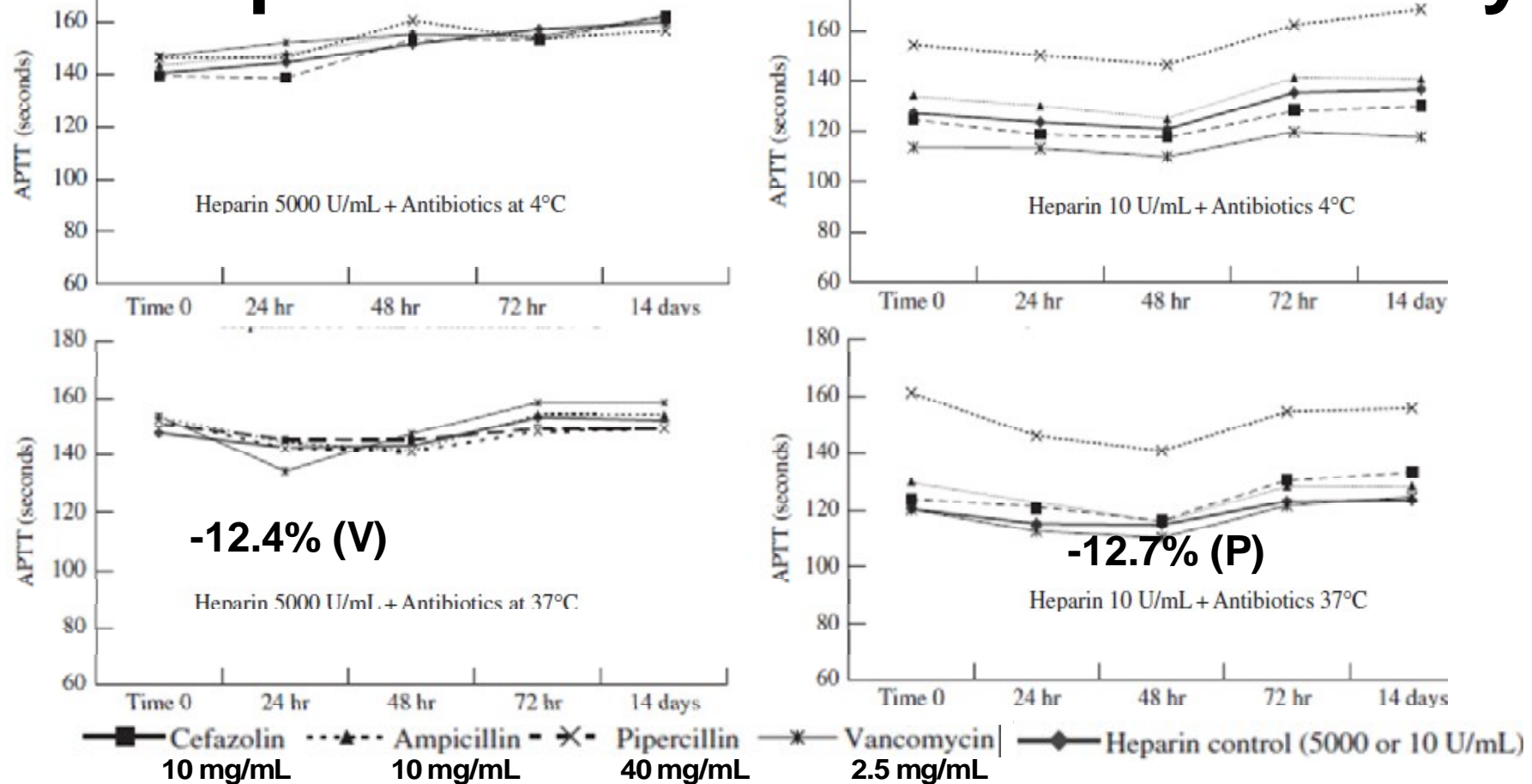
**Table 1.** In vitro compatibility and antimicrobial activity of gentamicin with heparin

	Gentamicin concentration $\mu\text{g/mL}$					
	0	1	4	32	128	1000
No heparin	$0.57 \pm 0.04$	$0.28 \pm 0.02$	$0.14 \pm 0.01$	$-0.06 \pm 0$	$-0.06 \pm 0$	$-0.06 \pm 0$
Heparin	$0.16 \pm 0.01$	$0.15 \pm 0.01$	$0.15 \pm 0.01$	$0.11 \pm 0$	$0.06 \pm 0.02$	$-0.06 \pm 0$

The values in the Table are absorbance ( $\pm$  SD) at OD 600 nm. Using the broth macrodilution technique, sodium heparin was added to vials containing various concentrations of gentamicin. A standardized suspension of *E. coli* was added to each tube to obtain a final concentration of  $4.5 \times 10^5$  CFU/mL. The final heparin concentration was 2500 U/mL in all vials. After a 48 hour incubation at 37°C, the visible turbidity was determined as the absorbance measured at OD 600 nm. The MIC was defined as the lowest concentration at which no bacterial growth occurred, as evidenced by the absence of turbidity (absorbance = 0). In the absence of gentamicin, heparin partially inhibited bacterial growth. Heparin partially inhibited the antimicrobial effect of gentamicin, but this inhibition was overcome at a gentamicin concentration of 1 mg/mL.

**The final concentration of gentamicin diluted in heparin 2500 U/mL must not be  $<1$  mg/mL**

# Biological activity of heparin in AB/heparin solutions stored for 14 days



The largest drops in APTT from baseline were <13% and only transiently observed

These variations are unlikely to be of clinical relevance

**Similar results on the stability of the anticoagulant effect of heparin diluted in ABs have been reported with**

- **Benzylopenicillin,**
- **Methicillin,**
- **Cefepime,**
- **Ceftazidime,**
- **Ciprofloxacin,**
- **Meropenem,**
- **Teicoplanin,**
- **Trovafloxacin,**
- **Tobramycin**

# **Take home messages**

**The stability of antimicrobial / anticoagulant lock solutions depends on the concentrations of the components**

**AB / heparin solutions could have lower stability than AB / 4% citrate solutions**

**Diluting antibiotics in heparin has no clinically significant effect on the biological activity of heparin**

**Catheter integrity after lock instillation  
and particularly after ethanol lock is  
another topic of interest**



ELSEVIER

## LETTERS TO THE EDITOR

Complications of the ethanol-lock technique in the treatment of central venous catheter sepsis

To the Editor

In these cases, 3 ml of 100% ethanol was locked into the catheter lumens for 24 h. The catheters quickly became occluded and precipitated material was clearly visible upon line aspiration. Pithie et al.<sup>1</sup> reported flushing such catheters, without any adverse effect, however, concerns must be raised regarding the possible complications of introducing such precipitants into the blood stream.

ethanol o

alcohol-based antiseptic or disinfectant use on or in central venous catheters made of polyurethane has been strongly discouraged by the manufacturers.

Ethanol is thought to adversely affect some polyurethane catheters producing micro-cracking, potentially leading to premature catheter failure.

## **Ethanol impairs coagulation and fibrinolysis in whole blood: a study performed with rotational thromboelastometry**

Martin Engström<sup>a</sup>, Ulf Schött<sup>b</sup> and Peter Reinstrup<sup>a</sup>



ELSEVIER

LETTERS TO THE EDITOR

Complications of the ethanol-lock technique in the treatment of central venous catheter sepsis

To the Editor

In these cases, 3 ml of 100% ethanol was flushed into the catheter lumens for 24 h. The catheters quickly became occluded and the ethanol lock was clearly visible upon line inspection. The reported flushing caused no adverse effect. We are regarding this as a warning regarding the use of such procedures.

alcohol-based antiseptics on or in central venous polyurethane catheters by the manufacturer.

**Many manufacturers of intravascular devices have advised against exposure of their catheter to alcohol for fear of structural degradation.**

Ethanol is thought to adversely affect some polyurethane catheters producing micro-cracking, potentially leading to premature catheter failure.

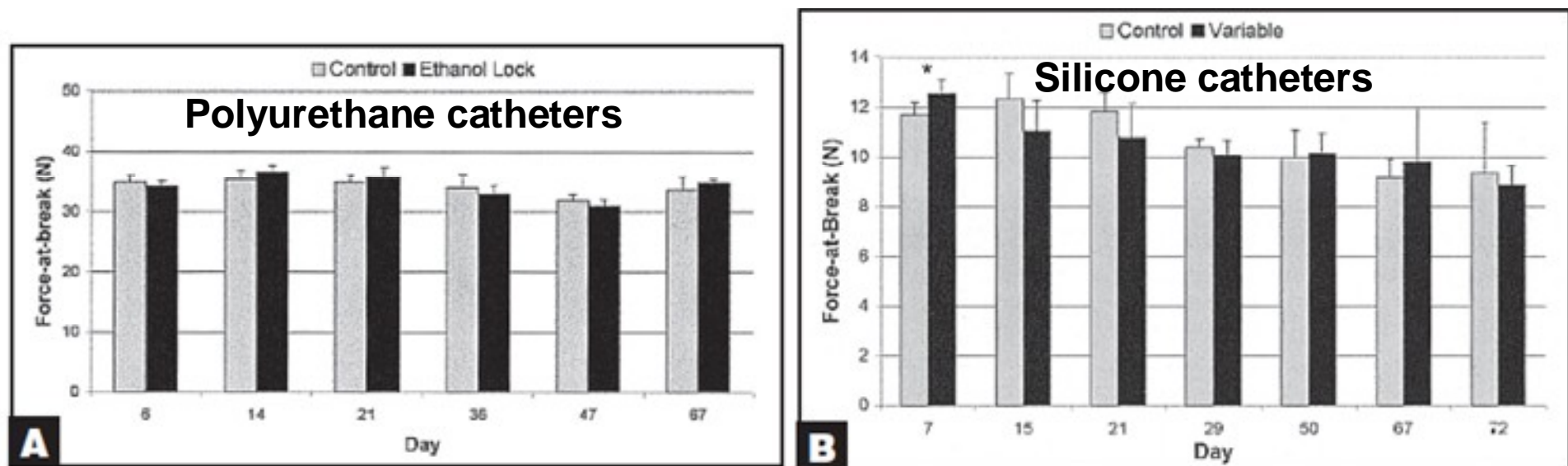
**Effect of ethanol on coagulation and fibrinolysis in whole blood: a study performed with rotational thromboelastometry**

Manfred Ström<sup>a</sup>, Ulf Schött<sup>b</sup> and Peter Reinstrup<sup>a</sup>

# Mechanical properties of polyurethane and silicon catheters exposed to a 70% ethanol solution for up to 10 weeks

PU catheters were single lumen peripherally inserted central catheters

Mechanical tests on the catheters included, force at break, elongation at failure, failure stress, maximum strain, modulus of elasticity, modulus of toughness, and wall thickness



There was only a slight reduction in the modulus of elasticity for both types of catheters and a minor increase in the wall area for PU catheters.

**Exposure to ethanol does not appreciably alter the mechanical properties of the two types of catheters.**

# Mass spectrometry and scanning electron microscopy study of silicone tunneled dialysis catheter integrity after an exposure of 15 days to 60% ethanol solution

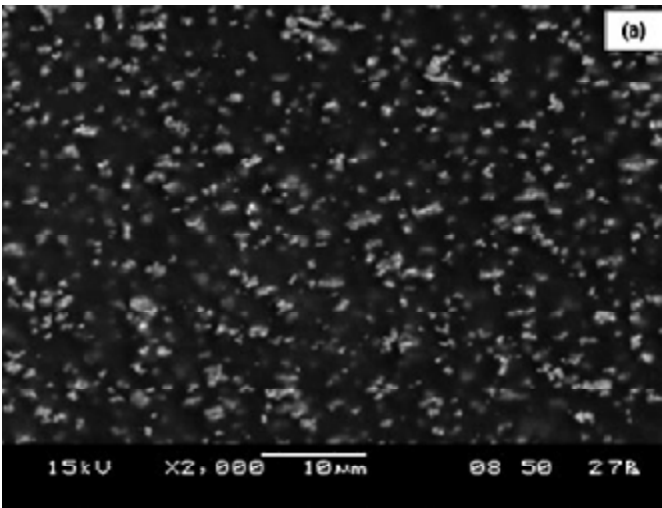
Sophie Guenu<sup>1</sup>, Anne-Elisabeth Heng<sup>2</sup>, Françoise Charbonné<sup>3</sup>, Marie-Josèphe Galmier<sup>1</sup>, Franck Charlès<sup>4</sup>, Patrice Deteix<sup>2</sup>, Bertrand Souweine<sup>2</sup> and Claire Lartigue<sup>1\*</sup>

<sup>1</sup>University of Clermont 1, Laboratoire de Chimie Analytique et Spectrométrie de Masse, UFR Pharmacie, 63001 Clermont-Ferrand, France;

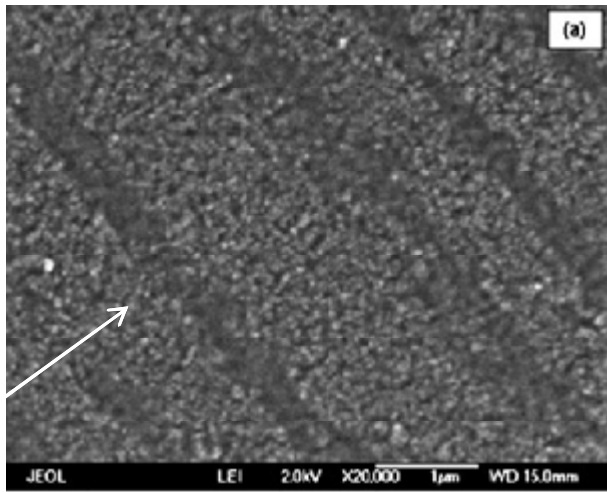
**Purpose of the study: to evaluate the ultrastructural integrity and chemical release of compounds from silicone catheters after ethanol exposure**

**The silicone catheters were immersed in three different solvents: saline, 60% ethanol, and 95% ethanol for 4 hours, 15 days, and 15 days after a first storage of 4 hours**

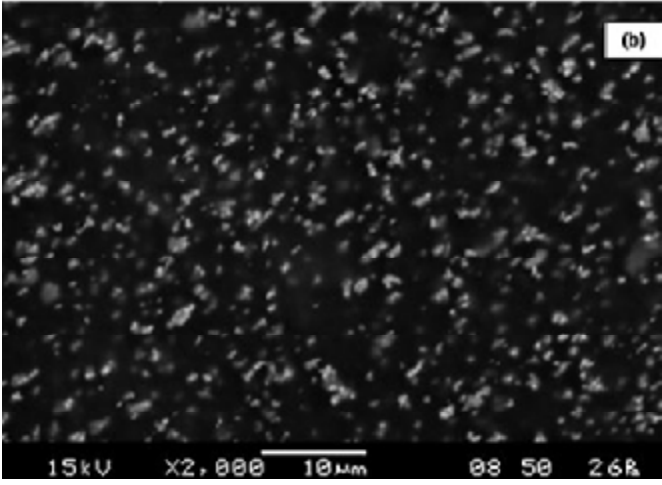
# The inner surface of the catheters was examined by scanning electron microscopy



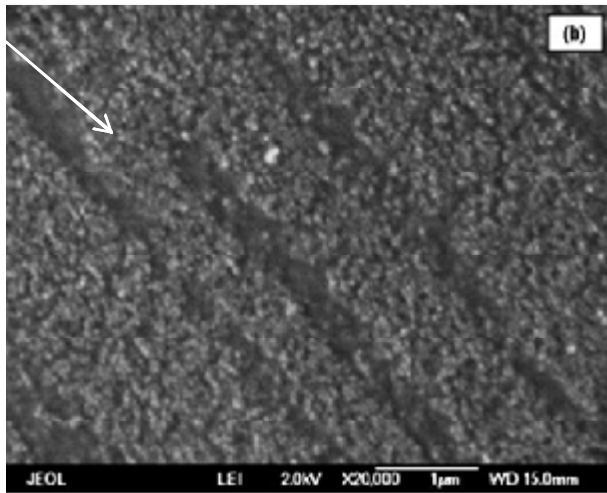
Reference catheter



Native guide-rails



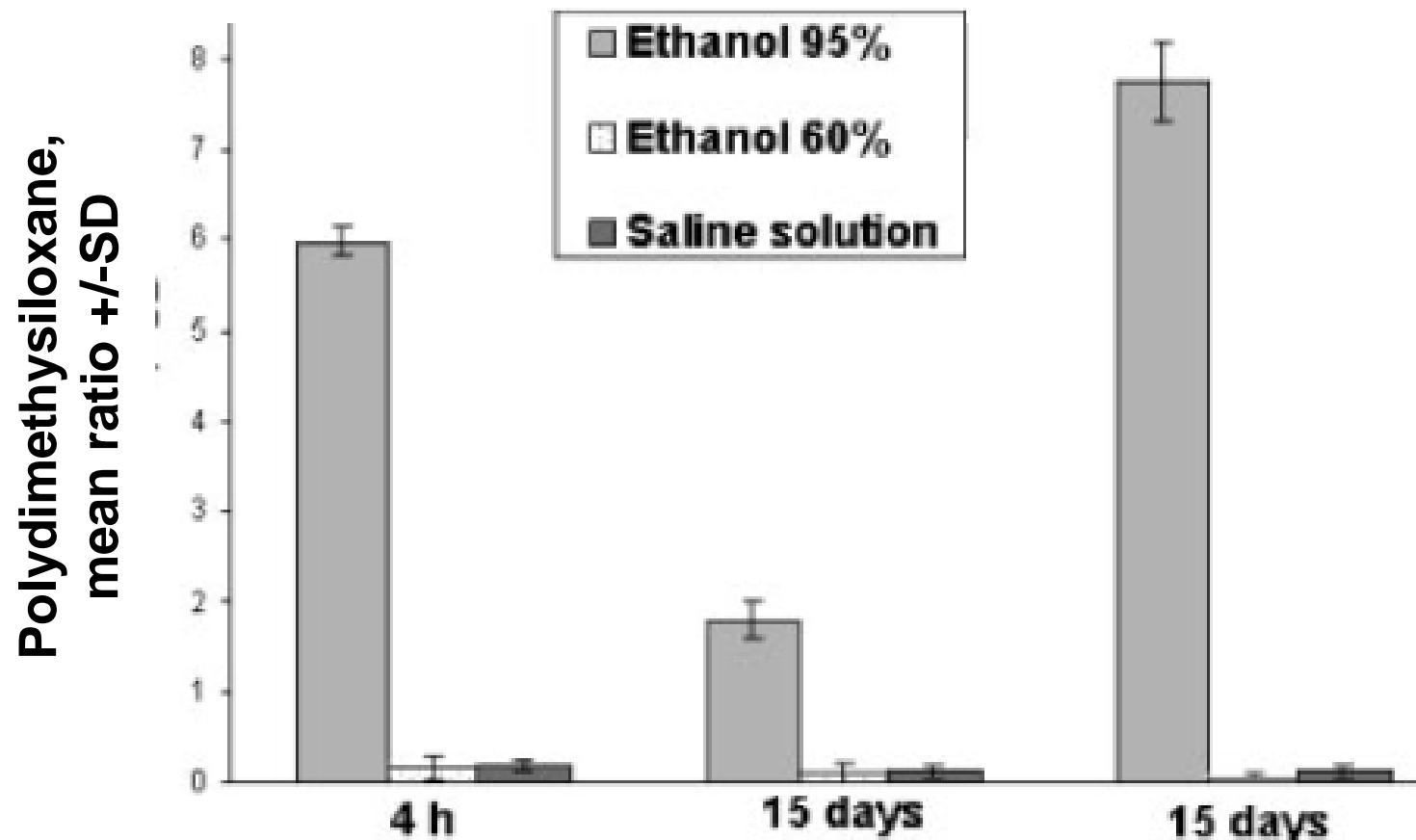
Catheter placed in 95% ethanol for 15 days



X 2,000

X 20,000

# Silicone compounds released in the storage solutions resulting from the catheter degradation



There were no differences in the amounts of silicone released in saline and in 60% ethanol whatever the exposure time

In contrast, a significant release of PDMS was observed in the 95% ethanol solution

# Mechanical properties of carbothane catheters immersed for 9 weeks in heparin 5000 U/mL, 4%TSC, and 30% ethanol / 4%TSC

Catheter Segment*	Force at Break (N)	Elongation at Break (fold increase from baseline)	Elastic Modulus (MPa)
<b>Lower portion</b>			
Heparin 5000 U/mL	191.97 ± 24.09	38.29 ± 7.14	7.05 ± 1.56
4% TSC	229.72 ± 26.76	42.42 ± 5.02	6.78 ± 1.78
30% Ethanol/4% TSC	113.26 ± 7.86* (11.5 kg)	21.97 ± 1.59*	6.66 ± 0.90
<b>Upper connection</b>			
Heparin	249.14 ± 26.01	5.09 ± 0.66	n/a
4% TSC	345.11 ± 15.78	5.89 ± 0.35	n/a
30% Ethanol/4% TSC	198.57 ± 8.73*	4.83 ± 0.25*	n/a

\*, P <0.001 between the heparin group and the TSC group;

The catheter placed in alcohol could still withstand >110 Newtons of force, many times higher than the clinically produced force during dialysis (<1N).

The abnormalities of the mechanical properties of the catheters placed in ethanol were not clinically relevant

# Similar results were reported in triniflex catheters placed in 30% ethanol / 4% citrate for 36 weeks.

**TABLE 1 - TENSILE TESTING RESULTS: FORCE AND ELONGATION AT BREAK OF CATHETERS EXPOSED TO SALINE OR 30% ETHANOL/4% SODIUM CITRATE**

	Force at Break (Newtons; mean $\pm$ SD)		P value	Elongation (fold increase from baseline; mean $\pm$ SD)		P value
	Saline	Ethanol/citrate		Saline	Ethanol/citrate	
Upper connection						
12 weeks	323.0 $\pm$ 12.4	212.2 $\pm$ 20.8	0.002			
24 weeks	373.8 $\pm$ 22.8	306.5 $\pm$ 21.8	0.032			
36 weeks	306.2 $\pm$ 29.5	280.4 $\pm$ 50.3	0.319			
Lower catheter segment						
12 weeks	206.1 $\pm$ 39.5	143.0 $\pm$ 24.8	0.015	34.2 $\pm$ 1.3	37.4 $\pm$ 2.0	NS
24 weeks	258.7 $\pm$ 29.7	191.0 $\pm$ 49.6	0.010	39.2 $\pm$ 0.8	34.7 $\pm$ 4.5	NS
36 weeks	164.7 $\pm$ 24.1	164.8 $\pm$ 11.9	0.998	30.0 $\pm$ 7.2	37.0 $\pm$ 3.1	NS

NS = not statistically significant

**Conclusions:** We conclude that the 30% ethanol/4% sodium citrate locking solution had an effect on the mechanical properties of the catheters investigated, but not to the degree that would preclude further in vivo investigation. Further studies are necessary to determine the safety and efficacy of this catheter locking solution. (J Vasc Access 2010; 11: 12-16)

# THE EFFECTS OF PROLONGED ETHANOL EXPOSURE ON THE MECHANICAL PROPERTIES OF POLYURETHANE AND SILICONE CATHETERS USED FOR INTRAVASCULAR ACCESS

Christopher J. Crnich, MD, MS; Jeremy A. Halfmann, BS; Wendy C. Crone, PhD; Dennis G. Maki, MD

Clinical Nephrology, Vol. 67



Effect

lock on the  
ethane

M. Vercaigne<sup>1,3</sup>

...nterscience.wiley.com) DOI: 10.1002/rcm.2837



Mass spectrometry study of...  
an e...  
...on microscopy  
... catheter integrity after  
... ethanol solution

**However none of the studies evaluating the impact of solvents on the catheter integrity have assessed the catheter hub or the place where the hub meets the catheter lumen.**

eng<sup>2</sup>, Françoise Charbonné<sup>3</sup>, Marie-Josèphe Galmier<sup>1</sup>,  
aix<sup>2</sup>, Bertrand Souweine<sup>2</sup> and Claire Lartigue<sup>1\*</sup>

The Journal of Vascular Access 2010; 11: 12-16  
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ORIGINAL ARTICLE

## Long-term effect of an ethanol/sodium citrate locking solution on the mechanical properties of hemodialysis catheters

Lavern M. Vercaigne<sup>1,2</sup>, Teresa A. Takla<sup>1</sup>, J. Raghavan<sup>3</sup>

# Prevention of Catheter-Related Bacteremia with a Daily Ethanol Lock in Patients with Tunnelled Catheters: A Randomized, Placebo-Controlled Trial

To assess the efficacy of 70% ethanol lock in hematology patients with silicone catheters

Each lumen of the CVC was locked for 15 minutes per day and flushed through with 10 mL saline

safety and tolerability aspects	Ethanol	Placebo	P
	(n = 226)	(n = 222)	
All-cause mortality	7	5	.77
Thrombosis of insertion blood vessel	9	12	.62

No difference was observed in the incidence of thrombosis between groups

One device has to be removed because of a rupture of one of the three catheter lumens in the ethanol group.

# **Conclusion**

**The stability and biological activity of lock solutions must be evaluated using valid stability indicating methods and bioassays**

**Since many treatments may alter the integrity of catheters, manufacturers would be well advised to subject their intravascular devices to formal testing**

**Silicone catheters are compatible with ethanol**

**Catheters made of copolymers are more resistant to ethanol than PU**

Clinical Practice Guidelines for the Diagnosis  
and Management of Intravascular Catheter-Related  
Infection: 2009 Update by the Infectious Diseases  
Society of America

Antibiotic and dosage	Heparin or saline, IU/mL	Reference(s)
Vancomycin, 2.5 mg/mL	2500 or 5000	[100, 275]
Vancomycin, 2.0 mg/mL	10	[275]
Vancomycin, 5.0 mg/mL <sup>a</sup>	0 or 5000	[276, 277]
Ceftazidime, 0.5 mg/mL	100	[123]
Cefazolin, 5.0 mg/mL	2500 or 5000	[100, 277]
Ciprofloxacin, 0.2 mg/mL <sup>b</sup>	5000	[130]
Gentamicin, 1.0 mg/mL	2500	[100]
Ampicillin, 10.0 mg/mL	10 or 5000	[275]
Ethanol, 70% <sup>c</sup>	0	[131]

**Final concentrations of antimicrobial lock solutions reported in IDSA guidelines for the treatment of CRBSIs.**

# **Acknowledgements**

**Claire Aumeran and Ousmane Traoré (prevention control unit)**

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