



# BD PosiFlush™ 4% Sodium Citrate Lock Solution

## Clinical evidence compendium

A summary of the clinical evidence supporting the use of 4% sodium citrate lock solution



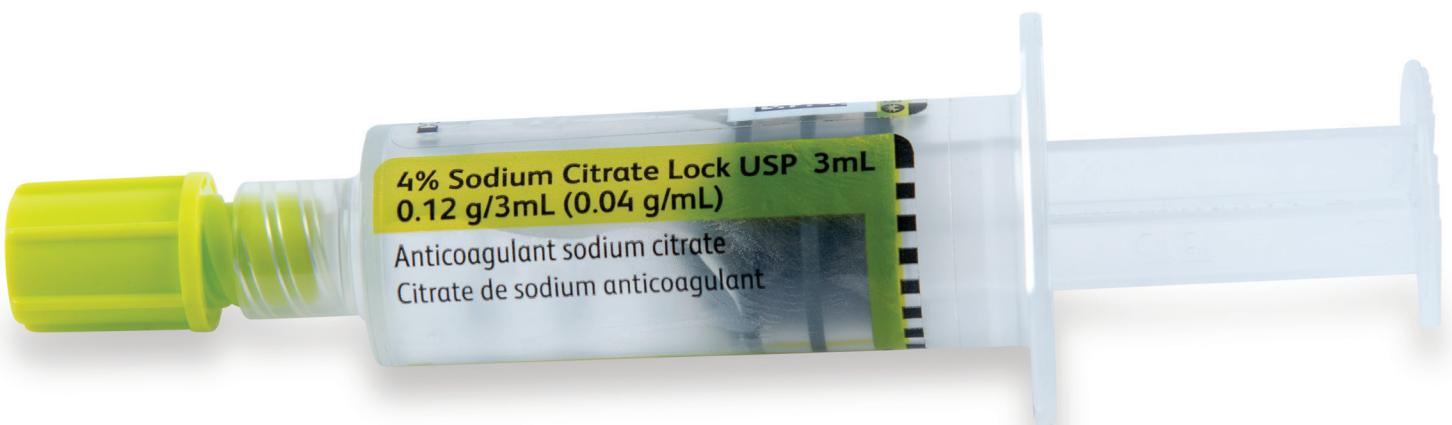
# BD PosiFlush™ 4% Sodium Citrate Pre-Filled Lock Syringes

Maximize catheter patency. Minimize risk of adverse events.

Maintaining catheter patency and preventing catheter-related bloodstream infections (CRBSIs) are central goals in vascular access management. BD PosiFlush™ pre-filled syringes are uniquely designed to standardize and enhance best clinical practice for improved patient outcomes and greater clinical efficiency. With a full range of flushing and locking solutions, including a new 4% sodium citrate lock solution, BD PosiFlush pre-filled syringes provide clinicians with the right tools to meet their clinical needs.

Recommended by clinical practice guidelines as an alternative to heparin,<sup>1</sup> 4% sodium citrate provides equivalent catheter patency while offering an improved safety profile, reduction in the risk of CRBSIs and prevention of biofilm formation—all at a lower cost.

This evidence summary was compiled to facilitate access to current literature relevant to the BD PosiFlush 4% sodium citrate pre-filled lock syringe. All studies in this compendium were identified via a literature search and are provided as a courtesy. BD is not liable for any inaccuracies therein.



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# Trisodium citrate 4%—an alternative to heparin capping of haemodialysis catheters<sup>2</sup>



## Study authors:

Lok CE, Appleton D, Bhola C, Khoo B, Richardson RMA.



## Patient population:

250 chronic hemodialysis (HD) patients with a permanent, cuffed internal jugular CVC



## Journal and publication date:

Nephrology Dialysis Transplant, 2007.



## Primary outcome:

Number of catheter exchanges per 1,000 catheter-days



## Study location:

Canada



## Secondary outcomes:

Rate of TPA use/1,000 catheter-days, rate of access-associated hospitalizations, time to catheter exchange, time to TPA requirement, cost



## Study design:

Prospective cohort study of the clinical efficacy, safety and cost of 4% sodium citrate vs heparin. The study compared rates of central venous catheter (CVC) exchange, thrombolytic use (*tissue plasminogen activator [TPA]*) and access-associated hospitalizations during two study periods:




- Heparin 5,000 U/lumen (*manually filled 0.5 mL of 10,000 U/mL heparin*) June 1, 2003–February 15, 2004
- 4% sodium citrate 5 mL (*manually filled*) March 15–November 15, 2004



## Study conclusion:

4% sodium citrate solution has equivalent or better outcomes with regard to catheter exchange, TPA use and access-associated hospitalizations compared to heparin locks. It is a safer and less expensive alternative.

# Efficacy

	Outcome	4% sodium citrate	Heparin	p value
<b>Patency</b> 	Rate of CVC exchange per 1,000 days	1.65	2.98	$p = 0.01$
	% patients requiring CVC exchange	67%	83%	$p = 0.006$
	TPA rate per 1,000 CVC days	3.3	5.49	$p = 0.002$
	Hospitalization rate per 1,000 CVC days	0.28	0.59	$p = 0.49$
	Average days of hospitalization	3.34	8.62	$p = 0.02$
<b>CRBSI</b> 	Catheter-related bacteremia rate per 1,000 CVC days*	0.2	1.7	$p < 0.0001$
<b>Cost</b> 	Cost of preparing and administering locking	\$0.72 CDN	\$1.68 CDN	N/A

\* Policy was to apply polyantibiotic ointment to catheter exit sites.

## Cost implications:

- In a program that uses **100 catheters**, cost savings could be **\$10K–\$14K per year**
- **Cost savings are \$0.63–\$0.96/lock** depending upon whether it is commercially available or pharmacy prepared pre-filled syringes respectively
- **Pharmacy convenience:** After 4% sodium citrate is drawn up into a 5 mL polyvinyl chloride syringe, it is chemically stable (*up to 10% loss in the original concentration*) for at least 28 days stored at room temperature

# Citrate 4% versus heparin and the reduction of thrombosis study (CHARTS)<sup>3</sup>



## Study authors:

MacRae JM, Dojcinovic I, Djurdjev O, et al.



## Patient population:

61 HD patients with tunnelled, cuffed HD catheters



## Journal and publication date:

Clinical Journal of the American Society of Nephrology, 2008.



## Primary outcome:

Development of catheter dysfunction (CD) (defined as a blood pump speed <250 mL/min or the use of tissue plasminogen activator) and catheter-associated bacteremia (CAB)



## Study location:

Canada



## Secondary outcomes:

Development of an exit-site infection or bleeding complications (either local or systemic)



## Study design:

Prospective, randomized, non-blinded pilot study comparing 4% sodium citrate (prefilled syringe) vs heparin 5,000 U/mL (manually filled) as locking agents after HD






## Study conclusion:

The preliminary findings from the pilot study demonstrate that 4% citrate is effective in maintaining catheter patency and does not appear to have any increased incidence of infections.

Because citrate is significantly cheaper and has a more favourable side effect profile than heparin, it can be considered a potentially better locking agent in HD catheters.

# Efficacy

	Outcome	4% sodium citrate	Heparin	p value	
<b>Patency</b> 	<b>Catheter dysfunction episodes</b>	<b>40.6%</b>	44.8%	<i>p</i> = 0.799	
	<b>TPA use*</b>	<b>40.6%</b>	44.8%	<i>p</i> = 0.799	
	<b>Catheter removal</b>	<b>65.5%</b>	51.7%	N/A	
	<b>Reasons for catheter removal:</b>				
	Dysfunction	<b>25%</b>	17.2%	N/A	
	Infection	<b>9.3%</b>	10.3%	N/A	
	Transfer to graft/fistula	<b>28.1%</b>	24.1%	N/A	
	<b>Catheter survival days</b>	<b>15</b>	16	<i>p</i> = 0.867	
	<b>Bacteremia-free catheter survival days</b>	<b>133</b>	175	<i>p</i> = 0.930	
	<b>Time to combined primary outcome (CD or CAB) (days)</b>	<b>54</b>	55	<i>p</i> = 0.912	
<b>CRBSI</b> 	<b>CAB episodes (rate per 1,000 catheter-days)</b>	<b>5 (2.2)</b>	6 (3.3)	<i>p</i> = 0.743	
	<b>CAB episodes preceded by exit-site infections</b>	<b>0/5</b>	1/6	<i>p</i> = 0.743	
<b>Safety</b> 	<b>Systemic bleeding events</b>	<b>7</b>	21	<i>p</i> = <b>0.035</b>	
	<b>Local bleeding events</b>	<b>18</b>	16	<i>p</i> = 1.0	
	<b>Overall bleeding episodes</b>	<b>25</b>	37	<i>p</i> = 0.48	
	<b>Total patients with a bleeding event<sup>†</sup></b>	<b>14</b>	20	<i>p</i> = <b>0.048</b>	

\* TPA use in the past month and in catheters dwelling <1 month led to significantly greater risk of primary outcome (bacteremia or dysfunction).

† 4% sodium citrate provides a superior safety profile vs heparin with significantly less risk of systemic and total bleeding events.

## Cost differentiation between heparin and 4% sodium citrate

Heparin components	Lumen 1	Lumen 2	4% sodium citrate components	Lumen 1
Heparin vial (10,000 U/5 mL)	\$1.10 CDN	\$1.10 CDN	4% citrate prefilled syringe (single pack)	\$1.07 CDN
2 mL syringe (need 2)	\$0.22 CDN	\$0.22 CDN	4% citrate prefilled syringe (twin pack)	\$1.80 CDN
18G needle	\$0.02 CDN	\$0.02 CDN		
1 mL normal saline	\$0.55 CDN	\$0.55 CDN		
<b>Total cost</b>	<b>\$3.78 CDN</b>		<b>Total cost</b>	<b>\$1.89–\$2.14 CDN</b>
<b>Total yearly per patient</b>	<b>\$589.58 CDN</b>		<b>Total yearly per patient</b>	<b>\$166.92–\$280.80 CDN</b>

# Sodium citrate 4% locking solution for central venous dialysis catheters— an effective, more cost-efficient alternative to heparin<sup>4</sup>



## Study authors:

Grudzinski L, Quinan P, Kwok S, Pierratos A.



## Patient population:

307 chronic HD patients with permanent, tunneled CVCs



## Journal and publication date:

Nephrology Dialysis Transplant, 2007.



## Outcomes:

Flow-related catheter exchange rate, prevalence of international normalized ratio (INR) assay interference, bacteremia rates, TPA utilization rate and annual cost per patient (*based on 3x weekly dialysis*)



## Study location:

Canada



## Study design:

Retrospective analysis of heparin vs 4% sodium citrate comparing over two 12-month study periods:

Heparin 10,000 U/mL (*manually filled*)  
April 1, 2002–March 31, 2003

4% sodium citrate 5 mL (*manually filled*)  
April 1, 2003–March 31, 2004






## Study conclusion:

In addition to pharmaco-economic benefits, 4% sodium citrate offers several clinical advantages over heparin; avoiding heparin-related bleeding complications, improving reliability of INR assays, and providing an effective alternative for patients with suspected or confirmed heparin-induced thrombocytopenia.



# Efficacy

Outcome		4% sodium citrate		Heparin		<i>p</i> value	
		No.	No./1,000 catheter-days	No.	No./1,000 catheter-days		
<b>Patency</b> 	Rate of CVC exchange	70	1.88	56	1.81	<i>p</i> = 0.89	
	TPA utilization rate	120	3.23	127	4.10	<i>p</i> = 0.07	
<b>CRBSI</b> 	Catheter-related bacteremia rate per 1,000 CVC days	35	0.94	24	0.77	<i>p</i> = 0.36	
<b>Cost</b> 	Cost per treatment	\$0.94 CDN		\$6.46 CDN		N/A	
	Cost per TPA treatment	\$108 CDN					
	Total TPA cost	\$12,960 CDN		\$13,716 CDN		N/A	

## Cost implications:

- The actualized **annual cost savings** associated with use of 4% sodium citrate vs heparin were **\$861.12 CDN/patient** (based on a 3x weekly catheter-locking schedule)
- This reflects an **85% reduction in costs**
- The **cost savings totalled \$112,000 CDN** during the 12-month 4% sodium citrate period



# Sodium citrate 4% versus heparin as a lock solution in hemodialysis patients with central venous catheters<sup>5</sup>



**Study authors:**  
Yon CK, Low CL.



**Patient population:**  
85 long-term HD patients with CVC



**Journal and publication date:**  
American Journal of Health System  
Pharmacy, 2013.



**Outcomes:**  
Catheter patency, catheter-related  
infection and hospitalizations



**Study location:**  
United States



**Study design:**  
Single-centre, open-cohort study  
comparing the effect of 4% sodium  
citrate vs heparin during two  
time periods:

Heparin 5,000 U/mL (*manually filled*)  
July 2008–July 2009



4% sodium citrate 2–3 mL (*manually  
filled*) September 2009–December 2010

Patients receiving heparin who  
continued to have a CVC in September  
2009 were transitioned to 4% sodium  
citrate lock solution. New patients with  
CVCs placed after September 2009  
received 4% sodium citrate without a  
heparin period.



**Study conclusion:**  
In patients with long-term HD catheters, a 4% sodium citrate lock solution was associated with fewer catheter-related infections and similar effectiveness as an antithrombotic agent when compared with heparin 5,000 U/mL.

# Efficacy

	Outcome	4% sodium citrate	Heparin	<i>p</i> value
<b>Patency</b> 	Number of catheters exchanged or removed	18	34	<i>p</i> = 0.002
	Catheters exchanged/1,000 catheter-days	1.33	3.24	<i>p</i> = 0.002
	Number of TPA uses	40	41	<i>p</i> = 0.24
<b>CRBSI</b> 	Number of catheter-related infections	11	20	<i>p</i> = 0.026
	Number of catheter-related infections/1,000 catheter-days	0.81	1.90	<i>p</i> = 0.026
	Hospitalizations related to catheter-related infections	9	16	<i>p</i> = 0.064

## Cost implications:

- The cost associated with one catheter-related infection episode, which includes catheter exchange or removal, hospitalization and antibiotic treatment, offsets the auxiliary costs associated with using 4% sodium citrate for a year

There were 45% fewer catheter-related infections overall, and 57% fewer catheter-related infections per 1,000 catheter-days in the 4% sodium citrate group vs the heparin group

# Morphometric and biological characterization of biofilm in tunneled hemodialysis catheters<sup>6</sup>



## Study authors:

Jones SM, Ravani P, Hemmelgarn BR, Muruve D, MacRae JM.



## Patient population:

30 HD patients with tunnelled, cuffed catheters removed for either noninfectious reasons ( $n=19$ ) or bacteremia ( $n=11$ )



## Journal and publication date:

American Journal of Kidney Diseases, 2011.



## Outcomes:

Bacteria density in biofilm, catheter luminal surface covered by biofilm, biofilm thickness, exopolysaccharide content



## Study location:

Canada



## Study design:

Prospective, observational study of biofilm characteristics in patients with and without CRBSI, accounting for either 4% sodium citrate or heparin 1:1,000 locking solution



## Study conclusion:

Biofilms are present in all tunnelled catheters; however, the extent of the biofilm varied by the presence of bacteremia and type of locking solution.

All biofilm parameters were significantly higher in heparin-locked catheters.

# Efficacy

Outcome	Citrate-locked catheter in patients with CRBSI (95% CI)	Heparin-locked catheter in patients with CRBSI (95% CI)
Bacteria density (CFU/mL)	2.86 (2.67–3.04)	8.14 (7.96–8.32)
Catheter surface coverage (%)	29.19 (26.89–31.49)	64.39 (62.22–66.56)
Biofilm thickness ( $\mu\text{m}$ )	20.03 (17.86–22.21)	56.11 (54.01–58.21)
Exopolysaccharide content (%)	14.71 (12.94–16.48)	45.04 (43.35–46.74)

- All biofilm parameters were lower in catheters from patients with bacteremia when 4% sodium citrate was used as a locking agent
- All biofilm parameters were significantly higher in heparin-locked catheters from patients with bacteremia
- Catheters locked with 4% sodium citrate appeared to have a much thinner coat of biofilm and bacterial cells vs those locked with heparin



# References:

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