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Pyrogenic reactions in haemodialysis patients linked to contaminated citrate lock

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To the Editor,

Chronic haemodialysis (HD) is a life-sustaining therapy for >3 million patients worldwide with kidney failure [1]. A substantial proportion of these patients rely on central venous catheters (CVCs), which remain associated with high risks of malfunction, thrombosis, and catheter-related bloodstream infection [2–6]. To prevent these complications, low-concentration (<5%) citrate lock solutions are widely used as an alternative to heparin due to their efficacy, lower bleeding risk, lack of interference with coagulation assays, and cost-effectiveness [2–7]. While previous outbreaks of pyrogenic reactions in HD patients have historically been linked to microbial or endotoxin contamination of the water or dialysate distribution systems, or inadequate dialyser reprocessing [8–10], no published reports have specifically implicated CVC lock solutions as the source of pyrogenic reactions. Although generally regarded as safe, we report the first documented cluster of pyrogenic reactions in HD patients linked to endotoxin contamination of prefilled citrate lock syringes.

Between 12 April and 6 May 2025, seven of 149 chronic HD patients treated at the University Hospitals Namur (CHU UCL Namur, Belgium) experienced a total of 11 pyrogenic reaction episodes shortly after the completion of their dialysis session. Symptoms, which consistently developed within 1 post-dialysis, were characterized by chills, generalized malaise, and, in some instances, fever, rigours, nausea, cyanotic and cold extremities, hypotension, and tachycardia (Table 1, Supplementary Methods). All affected patients used tunnelled CVCs, while no case occurred among patients with an arteriovenous fistula. Six patients had a split-tip CVC in the jugular vein, and one had a symmetrical-tip CVC in the right femoral vein. The diagnostic procedures used during these reactions included monitoring systemic inflammation and obtaining blood cultures. C-reactive protein levels transiently increased (23–150 mg/l), whereas blood cultures remained negative in all 10 episodes tested. Empirical antibiotic therapy was administered to four patients at the discretion of the attending physician, based on individual clinical assessment and each patient's infection history. The choice of antibacterial agent targeted the most likely pathogens (predominantly *Staphylococcus species* and Gram-negative bacilli), with preference given to agents compatible with post-dialysis administration (e.g. cefazolin, ceftazidime, vancomycin). Patients experienced rapid clinical improvement, with symptoms resolving spontaneously within 24–48 hours, irrespective of empirical antimicrobial therapy. Two required hospitalization for severe chills and hypotension but recovered fully. No cases were observed among patients on home HD or those treated at two affiliated self-care dialysis units.

The distinct temporal pattern (symptom onset after rather than during dialysis, rapid spontaneous resolution), restriction to CVC users, systemic inflammatory response, and consistently negative blood cultures strongly suggested acute endotoxin exposure from contaminated catheter lock solutions rather than catheter-related bloodstream infections, or exposure from contaminated water or dialysate. During the observation period, three different batches (2502149, 2500245, and 2502173) of 4% citrate lock syringes (2.5 ml prefilled) were in use in the in-centre HD unit. On 9 May 2025, we discontinued the use of 4% citrate lock syringes and alerted the distributor. No new suspected cases have been reported since. Regulatory authorities and Sciensano, the Belgian national reference laboratory, were also notified, and independent testing was initiated.

Laboratory analyses were performed independently by Sciensano (Belgium) and the Paul-Ehrlich Institute (Germany), both accredited Official Medicines Control Laboratories operating under ISO/IEC 17025 and European Pharmacopoeia standards. Samples from several batches of the citrate lock solution and from the dialysis water system were tested using both the monocyte activation test and two complementary endotoxin assays: the kinetic Limulus amoebocyte lysate and recombinant Factor C methods (Supplementary Methods).

Endotoxin contamination was confirmed in two syringes from batch 2502149, with concentrations ranging from 526 to 1040 endotoxin units per ml (EU/ml) (Table 2). All other tested citrate batches and dialysis water samples were negative. Intra-batch heterogeneity was noted, as not all syringes from the same lot were contaminated. These findings conclusively identified batch 2502149 as the source of the outbreak. The contaminated syringes were immediately quarantined. Water samples

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Table 1: Clinical presentation of cases.

Pt	Age(years)	Gender	Kidney disease	Dialysis vintage (months)	CVC location and characteristics	Lock volume per lumen* (ml)	Episode	Chills	Fever	Hospitalization	CRP (mg/l)
1	74	F	Renovascular	40	Right internal jugular, 14.5F, 23 cm	1.7	1	Yes			37
							2	Yes			36
2	87	M	Diabetes	22	Right internal jugular, 14.5F, 23 cm	1.7	1	Yes			26
							2	Yes	38.5°C		23
3	89	F	Unknown	62	Right internal jugular, 14.5F, 23 cm	1.7	1	Yes			65
							2	Yes			110
4	70	M	IgAN	200	Right internal jugular, 14.5F, 23 cm	1.7	1	Yes			64
5	84	F	Unknown	88	Right femoral, 14.5F, 55 cm	3.1	1	Yes	38.0°C	Yes	20
							2	Yes	39.1°C	Yes	150
6	60	M	Unknown	27	Left internal jugular, 14.5F, 27 cm	1.9	1	Yes		Yes	104
7	62	M	Diabetes	26	Right internal jugular, 14.5F, 23 cm	1.7	1	Yes			

*According to manufacturer. Pt, patient; yrs, years; CRP, C-reactive protein; F, female; M, male; neg., negative; IgAN, immunoglobulin A nephropathy.

collected from the dialysis circuit were confirmed to be endotoxin free.

To the best of our knowledge, this is the first documented case series linking pyrogenic reactions in chronic HD patients to endotoxin contamination of prefilled citrate lock syringes. Endotoxins are the major contributors to pyrogenic response caused by contaminated pharmaceutical products formulation ingredients, and medical devices [11]. The consistent onset of symptoms post-dialysis and the restriction of the outbreak only to CVC users strongly distinguished this event from dialysate contamination, which typically results in reactions during the session and affects a broader patient population [8–10]. The early suspicion and rapid confirmation of endotoxin exposure were vital for patient safety, allowing us to prevent further adverse reactions and avoid unnecessary diagnostic workups, potential hospital admissions, and unwarranted antibiotic use. The mechanism for systemic exposure is the well-documented 'spill-over' of lock solutions into the systemic circulation, a phenomenon known to occur within seconds of instillation in CVCs [10, 12–14]. Given that the threshold pyrogenic dose for intravenous endotoxin is approximately 5 EU/kg/h [15], and the measured concentration of the contaminant was up to 1040 EU/ml, the exposure was sufficient to trigger a significant systemic inflammatory response. The two patients who required temporary hospitalization due to the severity of their symptoms (fever in one, severe chills and hypotension in both) were those with the largest catheter lock volumes (up to 3.3 ml instilled in the patient with a femoral catheter), suggesting a dose-dependent systemic exposure. The risk and extent of spill-over may be further intensified by specific catheter characteristics and patient factors. In particular, femoral catheters have been associated with a high risk of lock solution migration into the systemic circulation, which may further be increased by physical activity and the bending of the catheter when the patient is sitting [16]. Furthermore, the unit's practice of instilling an additional 0.2 ml per lumen beyond the manufacturer-specified CVC volume, originally intended to compensate for spill-over, likely intensified the systemic exposure by directly increasing the volume of contaminated solution delivered into the circulation. The incidence of reactions among CVC users in our unit (9%) probably reflects the simultaneous use of multiple batches of citrate syringes, of which only one was contaminated, along with intra-batch variability, which suggests sporadic contamination during manufacturing or filling. Both national and European authorities were informed, and pharmacovigilance investigations are ongoing to determine the source and scope of contamination.

The strength of evidence lies in the consistent clinical phenotype, clear epidemiologic restriction to CVC users, immediate disappearance of cases after discontinuing the suspect batch, and independent confirmation of endotoxin contamination by two official laboratories using validated assays. We also acknowledge limitations including the retrospective and single-centre design, as well as the lack of complete traceability regarding the specific batch of citrate lock solution administered to each individual patient.

In summary, we report the first cluster of pyrogenic reactions in chronic HD patients caused by endotoxin-contaminated prefilled citrate lock syringes. This unique observation calls for reinforcement of quality control and pharmacovigilance measures for medical devices used in HD, particularly catheter lock solutions. Clinicians should consider endotoxin contamination from catheter lock solutions in the differential diagnosis when evaluating chills and systemic inflammation in the CVC-dependent HD population and blood cultures remain sterile.

Table 2: Endotoxin detection.

Samples		MAT assay (EE/ml)[b]	LAL assay (EU/ml)[c]	rFC assay (EU/ml)[d]
Dialysis water[a]	In-centre HD, loop 1, start	<0.1	n.d.	n.d.
	In-centre HD, loop 1, return	<0.1	n.d.	n.d.
	In-centre HD, loop 2, start	<0.1	n.d.	n.d.
	In-centre HD, loop 2, return	<0.1	n.d.	n.d.
	Self-care HD, start	<0.1	n.d.	n.d.
	Self-care HD, return	<0.1	n.d.	n.d.
Lot #149	Syringe 1	773	718	526
	Syringe 2	738	1040	785
	Syringe 3	<0.1	<1	<5
	Syringe 4	<0.1	<1	<5
Lot #173		<0.1	<1	<5
Lot #045		<0.1	<1	<5
Lot #196		<0.1	n.d.	n.d.
Lot #141		<0.1	n.d.	n.d.
Lot #236		<0.1	n.d.	n.d.

[a]Samples were collected at the start and return points of every dialysis water distribution loop.
[b]The obtained values are calculated values based on an endotoxin dose–response curve of peripheral blood mononuclear cells. The coefficient of variation (CV%) obtained for syringe 1 and 2 were <15%.
[c]The obtained CV% were <6%.
[d]The obtained CV% were <15%.
MAT, monocyte activation test; LAL, Limulus amoebocyte lysate; rFC, recombinant Factor C; EEU, endotoxin equivalent units; n.d., not determined.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

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AUTHORS' CONTRIBUTIONS

C.C., H.G., S.L., F.S., M.T., L.G., C.D., and J.M. took clinical care of the patients. A.S., I.S., C.V., and B.D. performed *in vitro* experiments to detect endotoxin in lock solutions. C.C., A.S., C.V., B.D., and J.M. wrote the first draft of the paper. All authors significantly contributed to the content and reviewed and approved the final version of the paper.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author. De-identified individual participant data that support the findings will be made available to qualified researchers for academic purposes, subject to institutional data use agreements.

CONFLICT OF INTEREST STATEMENT

J.M. reports consultancy for Alexion Pharmaceuticals, AstraZeneca, Bayer, CSL Vifor, EG Specialty Care, GSK, Novartis, Sanofi-Genzyme, and Versantis; research funding from Alexion Pharmaceuticals, AstraZeneca; speaker honoraria from Alexion Pharmaceuticals, AstraZeneca, and Novartis, and travel grants from Alexion Pharmaceuticals, AstraZeneca, CSL Vifor, Novartis, and Sanofi-Genzyme, outside the submitted work. The remaining authors declare that they have no relevant financial interests.

DISCLAIMER

This publication reflects the authors' views, and neither regulatory authorities or related national and international organizations are responsible for any use that may be made of the information contained therein.

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