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The effect of taurolidine on the time-to-positivity of blood cultures

C.H. van den Bosch [a,*,1], J.E.P. Moree [a,b,1], S. Peeters [b], M. Lankheet [b], A.F.W. van der Steeg [a], M.H.W.A. Wijnen [a], M.D. van de Wetering [a], J.T. van der Bruggen [b]

[a] Princess Máxima Centre for Paediatric Oncology, Heidelberglaan 25, 3584 CS, Utrecht, The Netherlands
[b] Department of Medical Microbiology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands

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SUMMARY

Background: Taurolidine containing lock solutions (TL) are a promising method for the prevention of central line associated bloodstream infections. Per accident, the TL may not always be aspirated from the central venous catheter (CVC) before blood cultures are obtained. The TL could, unintentionally, end up in a blood culture vial, possibly altering the results. The aim of this study was to investigate the effect of the TLs on the detection of microbial growth in blood culture vials.

Methods: Different lock solutions (taurolidine-citrate-heparin (TCHL), taurolidine, heparin, citrate or NaCl) were added to BD BACTEC™ blood culture vials (Plus Aerobic/F, Lytic/10 Anaerobic/F or Peds Plus/F) before spiking with *Staphylococcus aureus* (ATCC 29213 or a clinical strain) or *Escherichia coli* (ATCC 25922 or a clinical strain) in the presence and absence of blood. Subsequently, blood culture vials were incubated in the BD BACTEC FX instrument with Time-to-positivity (TTP) as primary outcome. In addition, the effect of the TCHL on a variety of other micro-organisms was tested.

Discussion: In the presence of taurolidine, the TTP was considerably delayed or vials even remained negative as compared to vials containing heparin, citrate or NaCl. This effect was dose-dependent. The delayed TTP was much less pronounced in the presence of blood, but still notable.

Conclusion: This study stresses the clinical importance of discarding TLs from the CVC before obtaining a blood culture.

Abbreviations: TL, Taurolidine containing lock solutions; CVC, Central venous catheter; TCHL, Taurolidine-citrate-heparin; TTP, Time-to-positivity; CLABSI, Central line associated bloodstream infections; MIC, Minimal inhibitory concentration; UMCU, University Medical Centre Utrecht; ATCC, American type culture collection; CFU, Colony forming units.

* Corresponding author. Address: Heidelberglaan 25, 3584 CS, Utrecht, The Netherlands. Tel.: +31 088 9727272; fax: +31 088 9725009.
E-mail address: C.H.vandenBosch-4@prinsesmaximacentrum.nl (C.H. van den Bosch).

[1] C.B. and J.M. equally contributed to this manuscript.

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Background

Central venous catheters (CVCs) play an important role in the treatment of paediatric oncology patients. Central line associated bloodstream infections (CLABSIs) are common in this patient group, with reported incidence rates of 1.51—1.63 per 1000 catheter days [1,2]. CLABSIs have a large impact on the quality of life of patients due to hospital admissions, removal of the CVC, postponement of treatment, intensive care unit admissions and in some cases even death [1,2]. Research investigating preventative methods is therefore crucial.

In between treatments, the lumen of the CVC is filled with a lock solution. Currently, heparin or NaCl locks, are the standard of care [3]. The use of antimicrobial locks (with or without the addition of an anticoagulant such as citrate and/or heparin) has been suggested as a promising method for the prevention of CLABSIs in paediatric oncology patients [4,5]. Taurolidine is one of the most promising antimicrobial lock solutions available since it is effective against Gram-positive bacteria, Gram-negative bacteria, and yeasts/fungi, microbial resistance has not been reported, it is available in combination with an anticoagulant, and side-effects are rare and mild [4,6]. Multiple in vitro studies investigated the susceptibility of various microbial strains to taurolidine. These studies found that most micro-organisms (Gram-negative bacteria and Gram-positive bacteria) were inhibited at a range of 250—2000 mg/L taurolidine, whereas *Candida albicans* was inhibited at a range of 2048—4096 mg/L [7—10]. It is thought that the active components of taurolidine are derivatives that arise after it breaks down in aqueous solutions [7]. Suggested explanations for the mechanism of action are the irreversible binding of its methyl groups to the microbial cell wall and a chemical interaction with endotoxins and exotoxins that are produced by the bacteria [7—10]. These mechanisms could affect microbial adhesion to surfaces and inhibit microbial pathogenicity [7,8]. Clinical studies also show promising results in various patient groups, including paediatric oncology patients, with a pooled CVC-related bloodstream infection incidence rate ratio of 0.30 (95%CI 0.19—0.46), in favour of taurolidine containing locks (TL) as compared to non-antimicrobial locks [6,9].

The summary of product characteristics of TLs advise to aspirate and discard the TLs before a blood culture is obtained, since it might alter the blood culture results if it enters the blood culture vial. However, per accident, the TLs may not always be discarded first and could thereby unintentionally end up in the blood culture vial. The presence of 1.0—1.5 ml (the expected intraluminal volume of the CVC) of 1.35% taurolidine in a blood culture vial could reach concentrations up to 500 μg/ml, exceeding the minimal inhibitory concentration $(MIC)_{50}$ for many microorganisms [9,10]. Potentially, this might lead to a delay in the Time to positivity (TTP) or even false-negative blood cultures. This could have serious clinical (i.e., delay of adequate treatment) and research (i.e., overestimation of the efficacy of the TLs) implications. However, as far as we know, no studies are available investigating this hypothesis and the extent of this possible effect. The aim of this study is therefore to investigate the effect of TLs on the detection of microbial growth in blood culture vials if not discarded.

Methods

The experiments were performed at the Medical Microbiology Department of the University Medical Centre Utrecht (UMCU), the Netherlands, in collaboration with the Princess Máxima Centre for Paediatric Oncology, the Netherlands. Three experiments under various conditions (with/without blood, various microorganisms in amounts of 10 or 100 colony forming units (CFU), various blood culture vial types and with the addition of TCHL in various concentrations, heparin or NaCl) were performed, details described below. Due to resource restrictions regarding donor blood, the first two experiments (different conditions tested in uniplicate, using 30 and 60 blood culture vials in total) were performed without the presence of blood in the vials to observe if the hypothesis, that TLs have an effect on microbial growth in blood culture vials, is true. Additionally, in the last experiment (48 vials), blood was added to mimic the clinical setting and investigate the size of the impact on the clinical setting.

Microbial strains and spiking

The microbial strains used for the experiments were chosen based on their potential pathogenicity and high prevalence in paediatric oncology patients [2]. The following American Type Culture Collection (ATCC) strains and paediatric oncologic patient isolates were used: *Escherichia coli* (ATCC 25922 and a patient blood culture isolate), *Staphylococcus aureus* (ATCC 29213 and a patient blood culture isolate); *Staphylococcus epidermidis* (ATCC 49134), *Enterococcus faecalis* (ATCC 29212), and *Candida albicans* (ATCC 10231).

The microbial strains used were thawed, cultured for 24h, and their identity was confirmed with the matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) Biotyper® sirius CA system (Bruker Daltonik GmbH, Bremen, Germany), before use. 0.5 McFarland suspensions were serially diluted with NaCl 0.9% and the blood culture vials were spiked with 1 ml suspension containing 10 or 100 CFU). This number of CFU per vial approximates the number of CFU per blood culture vial clinically, considering 3—8 ml of blood is drawn from paediatric patients during a bacteraemia episode [11]. To check the actual number of CFU administered, microbial suspensions were plated on Mueller-Hinton agar (MHA) for bacteria and malt extract plates for yeast and CFUs were counted by visual inspection after overnight incubation at 37°C.

Lock solutions

The blood culture vials were filled with 1.5 ml (the approximate intraluminal volume of the CVC) of taurolidine 1.35%, citrate 4.0% and heparin 100 IU/ml lock (TCHL) (TauroLock-Hep100™, TauroPharm GmbH, Waldbüttelbrunn, Germany), 1.5 ml taurolidine 1.35% (obtained by dilution with NaCl 0.9% from NutriLock™, TauroPharm GmbH, Waldbüttelbrunn, Germany, which contains taurolidine 4%), citrate 4.0% (Citra-Lock™, Citra-Gen®, Oss, the Netherlands), heparin 100 IU/ml, or NaCl 0.9%. For some experiments, TCHL was diluted 3.16-fold and 10-fold with NaCl 0.9% before 1.5 ml was added to the blood culture vials.

Table I
Time to positivity of blood culture vials spiked with 100 CFU *Staphylococcus* aureus (ATCC 29213) and *Escherichia coli* (ATCC 25922) and with 1.5 ml TCHL, taurolidine 1.35%, citrate 4%, heparin 100 IU/ml, or NaCl 0.9%, without blood

	Staphylococcus aureus (ATCC 29213)			*Escherichia coli* (ATCC 25922)		
	PB	AE	AN	PB	AE	AN
TCHL	Negative	Negative	2:02:44	Negative	Negative	0:14:56
Taurolidine	Negative	Negative	2:07:13	Negative	Negative	0:12:54
Citrate	0:15:39	0:20:39	0:13:08	0:09:55	0:10:25	0:09:34
Heparin	0:14:08	0:14:38	0:13:28	0:09:55	0:10:34	0:09:23
NaCl	0:13:08	0:14:38	0:13:07	0:10:06	0:10:15	0:09:24

CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, AN; Lytic/10 Anaerobic vials, PB; Peds Plus/F vial, TCHL; Taurolidine-Citrate-Heparin Lock.
The CFUs counted for the quantity check (target 100 CFU) were 124 and 121 for *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 25922), respectively.

Blood

Blood from healthy donors from the Mini Donor Service (University Medical Centre Utrecht, Utrecht, the Netherlands) was used for the experiments. Donors gave their explicit consent for the use of their blood for research purposes. The blood culture vials were filled with 2 ml (Peds Plus/F vial) or 8 ml (Plus Aerobic/F vial) of blood.

BD BACTEC™ FX system

The blood culture vials used were the BD BACTEC™ Plus Aerobic/F, Lytic/10 Anaerobic/F, and PEDS Plus/F (Becton, Dickinson and Company, Franklin Lakes, New Jersey, United States of America). First, the blood (if applicable, depending on the experiment) and lock solutions were added to the blood culture vials. It should be noted that, for the experiments without blood, the vials contained a lower overall volume and thereby higher lock concentration (i.e., 30—40 mL media solution depending on the vial type, 1.0 mL spike solution and 1.5 mL lock solution), since the blood (2—8 mL depending on the vial type) was not added. Subsequently, microbial suspensions were added, immediately followed by placement of the vials in the BD BACTEC™ FX instrument for incubation at 35°C for a maximum of five days (bacteria) or seven days (yeasts). Vials detected as positive by the instrument were taken from the machine, the TTP was noted and the content was subcultured on agar to confirm that the blood culture became positive with the micro-organism used for spiking. Vials that remained negative after five or seven days were also subcultured for 48 hours. The vials were confirmed negative if there was no growth detected.

Outcome measurements

The primary outcome was the TTP of the spiked blood culture vials in the presence of the TCHL or taurolidine-only versus citrate-only, heparin-only or NaCl-only, with and without blood.

Results

As shown in Table I, Peds Plus/F and Plus Aerobic/F blood culture vials spiked with 100 CFU *S. aureus* (ATCC 29213) or *E. coli* (ATCC 25922) and containing taurolidine (TCHL or taurolidine-only), remained negative after 5 days of incubation. The TTP of the Lytic/10 Anaerobic vials was delayed for 37—42 hours (*S. aureus*) and 3—5 hours (*E. coli*) as compared to vials containing citrate, heparin or NaCl. The TTP between vials containing TCHL and taurolidine-only was comparable. Also, the TTP of vials containing citrate, heparin and NaCl appeared comparable. In the following experiments, we continued only with the TCHL, since TTP was comparable to taurolidine-only, and since this is the most researched lock solution in paediatric oncology patients. The TCHL was compared to heparin and NaCl locks since these are currently the standard of care in most hospitals [4—6].

The inhibitory effect of the TCHL could also be found when Plus Aerobic/F or Lytic/10 Anaerobic vials were spiked with 10 CFU or 100 CFU of other micro-organisms, Table II. Plus Aerobic/F vials spiked with *S. epidermidis* (ATCC 49134), also remained negative in the presence of TCHL, similar to *S. aureus* ATCC (29213) and *E. coli* (ATCC 25922). TCHL prolonged the TTP in vials spiked with *E. faecalis* (ATCC 29212). On the other hand, TCHL had almost no effect on the TTP of *C. albicans* (ATCC 10231) in Plus Aerobic/F vials. Moreover, *C. albicans* did not grow at all in Lytic/10 Anaerobic/F vials under all study conditions tested.

Next, blood was added to the blood culture vials in order to represent blood cultures in a clinical setting more closely. In addition to the ATCC strains, two clinical strains were used for spiking (100 CFU/vial), i.e. *S. aureus* and *E. coli* blood culture isolates from paediatric oncology patients. Also, 3.16 fold and 10-fold dilutions of TCHL were tested (representing a TCHL volume of approximately 470 μl and 150 μl per vial, respectively). Without blood, the results with undiluted TCHL were essentially similar to the previous experiments, i.e., blood culture vials remaining negative or showing a marked delay in TTP in the presence of TCHL for both *S. aureus* and *E. coli* [Table III]. A 10-fold dilution of TCHL still affected the TTP in vials spiked with *S. aureus* with a delay ranging from around 4—19 hours. The TTP in vials spiked with *E. coli* was much less affected by a 10-fold dilution of TCHL, with a delay of <1 hour. A higher dose (3.16-fold dilution of TCHL) modestly affected the TTP of vials containing *E. coli* with a delay of around 1—2 hours. Notably, the effect of the TCHL on the TTP was mitigated, but still demonstrated, in the presence of blood, both in Plus Aerobic/F vials (containing 8 ml of blood) and Peds Plus vials (containing 2 ml of blood). Most vials eventually became positive, also in the presence of the highest dose of TCHL (i.e. 1.5 ml of undiluted TCHL), with the exception of the Plus Aerobic/F vial spiked with the *S. aureus* patient isolate that

Table II
Time to positivity of blood culture vials spiked with 100 and 10 CFU of various micro-organisms and with 1.5 ml TCHL, heparin 100 IU/m or NaCl 0.9%, without blood

Staphylococcus epidermidis (ATCC 49134)					*Escherichia coli* (ATCC 25922)				
	10 CFU		100 CFU			10 CFU		100 CFU	
	AE	AN	AE	AN		AE	AN	AE	AN
TCHL	Negative	1:17:55	Negative	1:19:23	TCHL	Negative	0:14:32	Negative	0:13:50
Heparin	1:22:18	0:22:01	1:18:53	0:18:47	Heparin	0:12:42	0:11:01	0:11:40	0:10:10
NaCl	1:18:44	0:22:10	1:18:23	0:19:07	NaCl	0:12:41	0:12:11	0:11:40	0:11:20
***Enterococcus faecalis* (ATCC 29212)**					***Staphylococcus aureus* (ATCC 29213)**				
	10 CFU		100 CFU			10 CFU		100 CFU	
	AE	AN	AE	AN		AE	AN	AE	AN
TCHL	3:07:25	0:22:49	1:18:52	0:22:58	TCHL	Negative	2:01:47	Negative	2:00:46
Heparin	0:12:16	0:11:46	0:10:33	0:10:22	Heparin	0:13:39	0:16:09	0:14:28	0:11:58
NaCl	0:12:06	0:11:56	0:10:22	0:10:22	NaCl	0:17:08	0:13:58	0:15:07	0:11:47
***Candida albicans* (ATCC 10231)**									
	10 CFU		100 CFU						
	AE	AN	AE	AN					
TCHL	1:04:11	Negative	1:01:13	Negative					
Heparin	1:03:10	Negative	1:00:12	Negative					
NaCl	1:03:10	Negative	1:00:11	Negative					

CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, AN; Lytic/F Anaerobic vials, TCHL; Taurolidine-Citrate-Heparin Lock.
The CFUs counted for the quantity check (target 100 CFU) were 51, 180, 36, 256 and 240 for *Staphylococcus epidermidis* (ATCC 49134), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC) 29213 and *Candida albicans* (ATCC 10231), respectively.

remained negative after five days of incubation. A dose-dependent delay in TTP was observed in all settings ranging from $<$ 1 hour to several days [Table III].

For all experiments, subcultures of positive vials only showed the spiked micro-organisms and subcultures of negative vials did not show growth. The conditions that were repeated across the three experiments for *Staphylococcus aureus* and *Escherichia coli* ATCC isolates, showed comparable results.

Discussion

The presence of taurolidine in blood culture vials seems to affect the growth of various microorganisms, with vials remaining negative or delaying the TTP. The higher the concentration of taurolidine in the blood culture, the larger the effect. Blood mitigates this inhibitory effect, but does not fully counteract it. Still, delays of hours were observed in vials with blood in combination with a 3.16-fold TCHL dilution (approximately 470 µl TCHL per blood culture vial). In addition, delays of multiple days were observed if a complete (i.e. 1.5 ml) non-diluted taurolidine lock was added to the vial. Possible explanations for the mitigation by blood are that blood creates a better environment for microbial growth, that taurolidine binds to albumin or other components in blood or that the derivatives of taurolidine (e.g., formation of radicals) are neutralized by blood. Nonetheless, even a TTP delay of hours can have important clinical implications, since adequate antimicrobial therapy might be postponed in seriously ill patients. Moreover, not all laboratories are open 24/7 and a positive blood culture with a delayed TTP around closing hours could be noticed only the next day. All blood cultures containing blood eventually did became positive except for one. This suggests that the potential impact of taurolidine (accidentally present in blood culture vials when not discarded) on the results of research projects investigating taurolidine locks to prevent CLABSI may be less prominent.

All vials used in the experiments contain a non-ionic adsorbing resin and a cationic exchange resin, designed to bind antimicrobial agents. The cationic exchange resin binds positively charged antimicrobial agents, whereas the non-ionic adsorbing resin binds most antimicrobial agents through interaction with hydrophobic regions [12]. It is unknown whether these resins bind and inactivate taurolidine, but our experiments show that taurolidine still inhibits microbial growth in the presence of the resins. Possible explanations might be that the resins do not bind taurolidine, do not inactivate taurolidine, or that too much taurolidine is present for the resins to bind/inactivate all taurolidine completely. An alternative explanation of the observed inhibitory effect of taurolidine in this study could be that taurolidine interferes with the detection itself, i.e. CO_2 related fluorescence of the sensor in the vials. However, this seems unlikely because 1) the detection of *Candida albicans* was hardly affected by taurolidine and 2) subculture of the negative vials did not show any growth, suggesting inhibition of microbial growth, rather than interference with detection is the mechanism of action. Limitations of this study were that only five micro-organisms were investigated (of which only two in the presence of blood), that the taurolidine susceptibility was not tested for the different micro-organisms, blood came from healthy non-paediatric oncology patients, and only one blood culture system and its corresponding vials were tested.

This study underlines the importance of discarding taurolidine after aspiration from the CVC before blood cultures are obtained. In our opinion, clinical guidelines and method

Table III
Time to positivity of spiked blood cultures vials spiked with *Staphylococcus aureus* (ATCC 29213 and patient isolate) or *Escherichia coli* (ATCC 25922 and patient isolate) with and without blood and different concentrations of TCHL or NaCl

Staphylococcus aureus (ATCC 29213)				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	1:11:27	1:12:40	Negative	3:17:40
TCHL 3.16x	0:14:26	0:17:08	2:10:36	1:04:09
TCHL 10x	0:12:24	0:13:38	0:23:04	0:16:38
NaCl	0:11:56	0:12:49	0:14:06	0:12:07
***Staphylococcus aureus* (patient isolate)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	Negative	3:15:18	Negative	Negative
TCHL 3.16x	0:19:14	0:23:11	Negative	2:13:36
TCHL 10x	0:13:16	0:15:10	1:18:43	1:00:45
NaCl	0:12:58	0:12:37	0:23:05	0:15:09
***Escherichia coli* (ATCC 25922)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	0:17:03	0:17:05	Negative	Negative
TCHL 3.16x	0:11:04	0:11:23	0:12:35	0:11:15
TCHL 10x	0:10:26	0:10:46	0:10:56	0:10:26
NaCl	0:10:18	0:10:17	0:10:38	0:09:58
***Escherichia coli* (patient isolate)**				
	Blood		No blood	
	AE	PB	AE	PB
TCHL	0:16:20	2:10:21	Negative	Negative
TCHL 3.16x	0:10:47	0:10:17	0:12:17	0:10:46
TCHL 10x	0:09:58	0:09:37	0:10:37	0:09:58
NaCl	0:10:09	0:09:48	0:10:18	0:09:29

PB; Peds Plus/F, CFU; Colony Forming Units, TTP; Time To Positivity (days:hours:minutes), AE; Plus Aerobic/F vials, TCHL; Taurolidine-Citrate-Heparin Lock.
The CFUs counted for the quantity check (target 100 CFU) were 94, 312, 101, 76 and 75 for *Staphylococcus aureus* (ATCC 29213 AE), *Staphylococcus aureus* (ATCC 29213 PB), *Staphylococcus aureus* (patient isolate AE and PB), *Escherichia coli* (ATCC 25922 AE and PB), and *Escherichia coli* (patient isolate AE and PB), respectively.

sections of trials focussing on the efficacy of TLs should specifically state this and may encourage to register that the TLs are discarded before a blood culture is taken. If this is not done correctly, it can have an important impact on the treatment of patients.

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Transparency declaration

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical statement

Ethical approval by a medical ethics committee was not required for this study since participants were not subject to procedures performed for this study. The blood used in this study was delivered by the Mini Donor Service of the University Medical Center Utrecht. Patients give their explicit informed consent at the Mini Donor Service to use their blood for medical research in general, not for this study specifically.

Author contributions

Conceptualization (C.B., J.M., J.B.), data curation (C.B., J.M., M.L., S.P., J.B.), formal analysis (C.B., J.M.), funding acquisition (not applicable), investigation (C.B., J.M., M.L., S.P., J.B.), methodology (C.B., J.M., J.B.), project administration (C.B., J.M., M.L., S.P.), resources (C.B., J.M., J.B.), software (M.L., S.P.), supervision (J.B., A.S., M.W., M.vdW.), validation (C.B., J.M., M.L., S.P., J.B.), visualization (C.B., J.M., J.B.), roles/writing — original draft (C.B., J.B., J.M.), writing — review & editing (J.B., A.S., M.W., M.vdW.), all authors reviewed and edited the manuscript and approved the final version of the manuscript.

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