Nutritional Access

ANTISEPTIC, ANTIBIOTIC AND ANTIFUNGAL LOCKS IN HOME PARENTERAL NUTRITION PATIENTS

F. Joly (FR)
Antiseptic, antibiotic and antifungal locks in home parenteral nutrition patients

Pr Francisca Joly
Beaujon Hospital, University Paris VII
Venous access?
Epidemiology of Infectious and Noninfectious Catheter Complications in Patients Receiving Home Parenteral Nutrition: A Systematic Review and Meta-Analysis

Ruth A. Reitzel, PhD; Joel Rosenblatt, PhD; Anne-Marie Chafrari, MD; and Issam I. Raad, MD

- Catheter related-bloodstream infection (CRBSI):
  - 0.19 to 13.64/1000 catheter days (0.85)
Epidemiology of catheter complications in HPN

- Thirty-two studies

- A total of 2788 microbial pathogens
  - 1478 (53%) gram-positive,
  - 736 (26%) gram-negative
  - 322 (12%) yeast

- Among the speciated organisms:
  - *Staphylococcus* (coagulase negative) (24%
  - *Staphylococcus aureus* (10%)
  - isolated. *Klebsiella* spp. (5.7%)
  - *Escherichia coli* (3.1%)
  - unspeciated *Candida* (5.8%)
  - *Candida albicans* (3.5%)

Reitzel RA, JPEN 2019
We need strategies to prevent biofilm formation

- Biofilm is a community of bacteria that are attached to a substratum or surface. Bacteria in biofilm are embedded in extracellular polymeric matrix produced by the bacteria.
- It was estimated that S. aureus and S. epidermidis caused about 40%–50% of prosthetic heart valve infections, and 50%–70% catheter biofilm infections

*Meng et al; Int. J. Mol. Sci. 2013*
In case of catheter related bloodstream infection
Place of antibiotic locks

- High concentration of antibiotics
  - 100-1000 x CMI
- Activity on biofilms
- Bactericidal activity

Total volume: 2-5 mL
Prolonged contact 8-24h?
Change < 48h?

Fortun JF, J Antimicrob Chemother 2006
Rijnders BJ, J Antimicrob Chemother 2005
Mermel LA, Clin Infect Dis 2009
Usable locks in case of sepsis
But how to prepare? Which concentration?

<table>
<thead>
<tr>
<th>Gram+</th>
<th>Gram-</th>
<th>Yeast ...?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Ciprofloxacin</td>
<td>AmB liposomale</td>
</tr>
<tr>
<td>Teicoplanine</td>
<td>Amikacine</td>
<td>Echinocandines</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Ceftazidime</td>
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<tr>
<td>Gentamicine</td>
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<td>Ciprofloxacin</td>
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<td></td>
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<tr>
<td>Cefazoline</td>
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<td></td>
</tr>
<tr>
<td>Minocycline</td>
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</table>
Ethanol lock salvage therapy
Curative treatment

Blackwood RA, JPIDS 2017
- 70% ethanol lock,
- Dwell-time: 2h. to 24h., every 24h for 14 days after the first negative blood culture
- 15 paediatric patients (7 on HPN) who have failed standard treatment
- 12 bacteria, 9 fungi
- Salvage rate: 86.7% (13/15)
- No relapse for a 2-month period

• Raad I, Antimicrobial agents and Chemotherapy 2016
  - Minocycline- EDTA- 25% ethanol lock,
  - 2h dwell-time, every day, 7 times (5 consecutive days and 2 x 1 week) + systemic antibiotic therapy (11 days)
  - Retrospective study vs. a control group (30 vs 60 adult patients: historical group who had their CVC removed and a new CVC inserted)
  - Relapse: 0 vs 3 (ns)
  - Patients with the lock intervention received a shorter duration of systemic antibiotic therapy than that of the control patients (median, 11 days versus 16 days, respectively; P < 0.0001), and they were able to retain their CVCs for a median of 74 days after the onset of bacteremia.
Long-term central venous catheter (CVC) – or port (P) – related bacteremia or fungemia

Complicated

- Tunnel infection, port abscess
  - Remove CVC/P & treat with antibiotics for 7-10 days

- Septic thrombosis, endocarditis, osteomyelitis
  - Remove CVC/P & treat with antibiotics for 4-6 weeks; 6-8 weeks for osteomyelitis

- Coagulase-negative staphylococcus
  - May retain CVC/P & use systemic antibiotic for 10-14 days + 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

Staphylococcus aureus

- Remove the infected catheter and then treat with 4-6 weeks of antimicrobial therapy unless the patient has exceptions listed in Recommendation 81

Enterococcus

- May retain CVC/P & use systemic antibiotic for 7-14 days + 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

Gram-negative bacilli

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

Candida spp.

Uncomplicated (Fig. 2)

Mermel et al, Clin Infect Dis 2009
Not possible for local infection

- Emergency
- Remove the CVC
For primary and/or secondary prevention: catheter locks?
SHORT REPORT

Taurolidine lock: The key to prevention of recurrent catheter-related bloodstream infections

Brian Jurewitsch*, Khursheed N. Jeejeebhoy

Digestive Diseases Program, St. Michael's Hospital, University of Toronto, 30 Bond St., Toronto, Ont., Canada M5B 1W8

Received 19 January 2005: accepted 8 February 2005

Interact with components of bacterial cell walls resulting in irreparable injury
Anti-adherence properties

Heparin Lock
Intraluminal biofilm
after 24 h

Heparin lock Intraluminal biofilm
after 7 months
*S. Epidermidis*

Taurolidine-citrate lock
no biofilm
After 5 months

*Taurolidin, a new concept for the antimicrobial therapy of surgical infection, Browne MK, 1985*
Original Article

Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in patients on home parenteral nutrition: A heparin-controlled prospective trial

Tanya M. Bisseling\textsuperscript{a}, Martine C. Willems\textsuperscript{b}, Michelle W. Versleijen\textsuperscript{a}, Jan C. Hendriks\textsuperscript{c}, Renate K. Vissers\textsuperscript{a}, Geert J. Wanten\textsuperscript{a,}\textsuperscript{*}

\textsuperscript{a} Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, PO BOX 9101, 6500 HB Nijmegen, The Netherlands
\textsuperscript{b} Department of Vascular Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
\textsuperscript{c} Department of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Open label RCT: Taurolidinie 2% vs low dose Heparin

30 HPN patients with proven CRBSI
30 patients had treatment of infection
30 patients were proven infection-free
12 had new device
18 had old device

14 patients assigned to heparin
10 developed re-CRBSI
4 did not develop a re-CRBSI
cross over to taurolidinie
1 re-CRBSI

16 patients assigned to taurolidinie
1 developed a re-CRBSI
15 did not develop a re-CRBSI
1 patient refused to cross over

Bisseling, Clin Nutr 2010
Open label RCT: Infection-free survival

Bisseling, Clin Nutr 2010
Randomised clinical trial: 2% tauroloidine versus 0.9% saline locking in patients on home parenteral nutrition

Y. Wouters¹ | M. Theilla² | P. Singer² | S. Tribler³ | P. B. Jeppesen³ | L. Pironi⁴ | L. Vinter-Jensen⁵ | H. H. Rasmussen⁵ | F. Rahman⁶ | G. J. A. Wanten¹

- HPN > 2 infusions per week
- Expected HPN duration > 1 year
- 2 groups
  - New catheter group (without biofilm):
    - New patient on HPN or new catheter
  - Pre-existing catheter (catheter > 6 months): high risk group?
    - HPN > 1 an
124 patients screened

19 excluded:
10 refused to participate
9 did not meet inclusion criteria

105 randomized

53 taurolidine
1 excluded:
1 lost all study medication due to a fire at home

52 included

52 saline
2 excluded:
1 had an acute respiratory distress syndrome
1 had a perforation of colon

50 included

Wouters Y, AP&T 2018
Results: primary outcome

<table>
<thead>
<tr>
<th></th>
<th>Taurolidine (n=52)</th>
<th>Saline (n=50)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRBSI – no. (%)</td>
<td>5 (10)</td>
<td>18 (36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total treatment days</td>
<td>15,318</td>
<td>12,493</td>
<td></td>
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</tr>
</tbody>
</table>

Taurolidine decreased CRBSI risk >4x

Wouters Y, AP&T 2018
124 patients

New catheter group

Tauroldine 2% 36

3 infections 0,29 /1000 catheterdays

RR: 0,2 (IC: 0,04-0,71) P=0,009

Saline 35

13 infections 1,49 /1000 catheterdays

Pre existing catheter

High risk group

Tauroldine 2% 16

2 infections 0,39 /1000 catheterdays

RR: 0,3 (IC: 0,03-1,82) P = 0,25

Saline 15

5 infections 1,32 /1000 catheterdays

Wouters Y, AP&T 2018
Original Communication


Cecile Lambe, MD1; Catherine Poisson1; Cecile Talbotec, MD1; and Olivier Goulet, MD, PhD1,2

• 193 children with intestinal failure 2008-2014
  – 95 short bowel syndrome
  – 22 long segment Hirschsprung disease,
  – 32 congenital enteropathy,
  – 24 chronic intestinal pseudo obstruction,
  – 10 immune deficiency, 4 IBD, 6 other causes

• After a CRBSI Start after antibiotic treatment of 14 days and after sterile blood cultures
  • Taurolidine 1.35% + citrate 4%, 0.4ml to 0.6 ml
  • Parents/carers specific training for the lock technique by HPN center specialized nurses/instillation-withdrawal
Results

• From October 2011 to December 2014, Taurolidine-citrate locks have been used in 40 patients.

• 5 infections occurred in 5 patients/40
  – 2 infections with *Staphylococcus aureus* (treatment discontinuation?)
  – 1 infection with *Pseudomonas aeruginosa* (vomiting)
  – 1 infection with *Serratia Marcescens*
  – 1 infection with *Staphylococcus Capitis*

• On 2 observation periods on these patients:
  – Without TL: 4.16 infections/1000 catheter-days (29547 days)
  – With TL: 0.25 infections/1000 catheter-days (19688 days) P<0.0001

*Lambe C, JPEN 2018*
Survival 18 months without infection  92% vs. 61%

\[ \text{% of patients out of infection} \]

- Taurolidine-citrate
- No Taurolidine-citrate

\[ P=0.01 \]

Lambe C, JPEN 2018
Taurolidine lock solutions as primary or secondary prevention treatment

- Taurolidine as catheter lock solution reduces risk for CRBSI in adult and children HPN patients

- Favorable safety and cost profile

- Supports routine use of Taurolidine locking for CRBSI prevention in HPN care
Systematic Review and Meta-Analysis of the Utilization of Ethanol Locks in Pediatric Patients With Intestinal Failure

Riad Rahhal, MD,MS¹, Maisam A. Abu-El-Haija, MD², Lin Fei, PhD²,³, Dawn Ebach, MD¹, Sarah Orkin, MD⁴, Elizabeth Kiscaden, MLIS,AHIP⁵, and Conrad R. Cole, MD,MPH²

- 9 retrospective studies: 2008-2017 - 131 patients
- 70% ethanol vs heparin lock
- Daily therapy (except 1), minimum 2 hours, 7/9 aspirating ethanol
<table>
<thead>
<tr>
<th>Source (Year)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al (2010)</td>
<td>23</td>
</tr>
<tr>
<td>Cober et al (2011)</td>
<td>15</td>
</tr>
<tr>
<td>Wales et al (2011)</td>
<td>10</td>
</tr>
<tr>
<td>Pieroni et al (2013)</td>
<td>14</td>
</tr>
<tr>
<td>Ardua et al (2015)</td>
<td>14</td>
</tr>
<tr>
<td>Mezoff et al (2016)</td>
<td>30</td>
</tr>
<tr>
<td>Mokha et al (2017)</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Favors Heparin Locks</th>
<th>Favors Ethanol Locks</th>
<th>Mean Diff. [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouw et al, 2008</td>
<td></td>
<td></td>
<td>7.76 [0.66, 14.86]</td>
</tr>
<tr>
<td>Jones et al, 2010</td>
<td></td>
<td></td>
<td>7.80 [4.00, 11.60]</td>
</tr>
<tr>
<td>Cober et al, 2011</td>
<td></td>
<td></td>
<td>6.70 [3.52, 9.88]</td>
</tr>
<tr>
<td>Pieroni et al, 2013</td>
<td></td>
<td></td>
<td>7.10 [3.81, 10.39]</td>
</tr>
<tr>
<td>Abu-El-Haija et al,2014</td>
<td></td>
<td></td>
<td>8.90 [-0.63, 18.43]</td>
</tr>
<tr>
<td>Ardua et al, 2015</td>
<td></td>
<td></td>
<td>6.37 [2.78, 9.96]</td>
</tr>
<tr>
<td>Mezoff et al, 2015</td>
<td></td>
<td></td>
<td>1.70 [-1.65, 5.05]</td>
</tr>
<tr>
<td>Mokha et al, 2016</td>
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<td></td>
<td>5.97 [-0.77, 12.71]</td>
</tr>
</tbody>
</table>

Total: 6.27 [4.89, 7.66]
Ethanol locks for the prevention of catheter-related bloodstream infection: a meta-analysis of randomized control trials

Peng Zhang, Jun-Hao Lei, Xin-Jun Su and Xing-Huan Wang

- 10 RCT – 2,760 patients
- Ethanol vs. heparin or saline
- Large heterogeneity: Oncology, hematology, hemodialysis, pediatric and adult population
- The overall pooled result indicated that ethanol locks significantly reduced the incidence of CRBI (RR 0.66, 95% CI 0.51–0.86)
- Subgroup analysis suggested that an ethanol lock significantly decreased the incidence of CRBI in patients with hematological diseases (RR 0.50, 95% CI 0.31–0.80).
86. A conservative approach with systemic and local (locks) use of antibiotics is advocated for simple infections. Catheter removal should be the first choice in case of tunnel infections or blood cultures positive for virulent bacteria; catheter removal is mandatory for port abscesses, complicated infections, persistent hemodynamic instability, or blood cultures that are positive for fungi. (Grade of evidence: moderate)

90. We suggest that catheter locking with taurolidine may be used to prevent central venous catheter-related infections. (Grade of evidence: low).

92. We do not recommend catheter locking with 70% ethanol to prevent central venous catheter-related infections, because its use is associated with systemic toxicity, catheter occlusion and catheter damage. (Grade of evidence: high)

93. We recommend in patients who repeatedly present with central venous catheter-related infections, re-education of the patient and/or caregiver and/or use of an antimicrobial catheter lock. (Grade of evidence: low)
Questions and Future

- New locks
- And/or new devices
- Personalised therapy
  - effect of dwell time
  - adaptation of line sepsis protocols related to type of venous access?
- optimization of formulation
Clinical isolates obtained during CRBSI of HPN patients were grown in the presence of catheter
locks:
- 2% taurolidine
- 1.34% taurolidine + citrate,
- 1.34% taurolidine + citrate + heparin
- Phosphate buffered saline

Biofilm formation, assessed by crystal violet staining, and growth of clinical isolates were determined by optical density measurements.
Growth of *S. aureus*

- 2% taurolidine
- 1.34% taurolidine + 4% citrate
- 1.34% taurolidine + 4% citrate + 500 IU/ml heparin
- Phosphate buffered saline (PBS, control)

Concentration of 2% taurolidine appears to be the most potent in this *in vitro* setting as compared to combination formulations with citrate and heparin with lower taurolidine concentration.

*Oltphof E, Clin Nutr 2015*
Original article

In vitro comparison of efficacy of catheter locks in the treatment of catheter related blood stream infection

Jakub Visek a, *, Lenka Ryskova b, Roman Safranek c, Martina Lasticova a, Vladimír Blaha a

- Bacterial strains of microorganisms (Staphylococcus epidermidis, Staphylococcus aureus, methicillin resistant S. aureus (MRSA), Pseudomonas aeruginosa, multidrug-resistant P. aeruginosa, Candida albicans) were used.
- The catheter was exposed to the microbes and then was incubated with a specific lock
  - ethanol 70%,
  - Taurolidine (taurolidine, citrate 4% and heparine à 100 IU/m)
  - gentamicine in concentrations 0,5, 1 and 10 mg/ml
  - vancomycine in concentrations 1, 5, and 10 mg/ml.
- The number of remaining CFU (colony forming units) was compared after incubation.
• The most effective antimicrobial lock solutions to eradicate selected pathogenic agents were ethanol and taurolidine.
• Use of antibiotics is often effective after many hours of treatment and there is a risk of inadequate therapy.
Messages

- Curative strategy
  - We need to implement specifics protocols regarding type of catheter
  - Place to perform trials
  - A place for ethanol lock?

- Prevention therapy
  - Taurolidine is largely used in HPN population
  - Place for oncology? Primary prevention vs secondary prevention?
  - Comparison between all «lock solution» in clinical practice will be complicated
  - No place for antibiotic lock solution

- Research on devices is also necessary to avoid bacterial adhesion and biofilm
Preventive taurolidine-lock studies in HPN patients

- **Klek S, JPEN 2014**
  - RCT: 2% taurolidine vs. citrate-1.35% taurolidine vs saline
  - 10 adult patients/group in HPN 12 months before, 1-year follow-up
  - Pre-study CRBSI rate: 0.82–1.1/1000CD
  - Only 1 CRBSI in citrate-1.35% taurolidine group (CRBSI rate: 0.273/1000CD)

- **Bisseling TM, Clin Nut 2010**
  - 2% taurolidine (16) vs. heparin (14) – RCT in patients with a history of CRBSI
  - Mean follow-up: 1 year
  - CRBSI: 0.19/1000CD (0.03–1.3) vs 2.02/1000CD (1.1–3.8) P: 0.008

- **Wouters Y, Clin Nut 2019**
  - Cohort study on 270 HPN for 10 years (338,531 CD) – 2% taurolodine
  - 203 CLABSI in 163 patients, CLABSI rate: 0.60/1000 CD
  - 9% of patients had side effects

- **Lambe C., JPEN 2018**
  - Citrate-1,35% taurolidine vs. saline - Retrospective cohort study
  - 40 children with histories of 2 CRBSI in previous 12 months
  - CRBSI rate: 4.16 /1000 CD without TL to 0.25 /1000 CD with TL (P < .001)
## Results: microorganisms

<table>
<thead>
<tr>
<th>Infection type – no. of CRBSI</th>
<th>Taurolidine (n=52)</th>
<th>Saline (n=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monobacterial bloodstream infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram positive – %</td>
<td>3 (100)</td>
<td>6 (43)</td>
<td>0.21</td>
</tr>
<tr>
<td>Gram negative – %</td>
<td>0 (0)</td>
<td>8 (57)</td>
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<tr>
<td>Polybacterial bloodstream infection</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Isolated fungemia</td>
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<td>1</td>
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<td>Unknown</td>
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<td>2</td>
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</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

### Gram-positive – no. of microorganisms

<table>
<thead>
<tr>
<th>Species</th>
<th>Taurolidine</th>
<th>Saline</th>
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<tbody>
<tr>
<td><em>Bacillus cereus</em></td>
<td>0</td>
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</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus salivarius</em></td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>Species not specified</td>
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<tr>
<td>Total</td>
<td>4</td>
<td>7</td>
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</table>

Wouters Y, AP&T 2018
## Results

### From 2008 to 2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Nb patients</th>
<th>Catheter days</th>
<th>Infections</th>
<th>rate/1000 catheter-days</th>
<th>p</th>
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<tbody>
<tr>
<td>2008</td>
<td>93</td>
<td>25527</td>
<td>61</td>
<td>2.39</td>
<td>Référence</td>
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<tr>
<td>2009</td>
<td>93</td>
<td>28171</td>
<td>62</td>
<td>2.20</td>
<td>0.72</td>
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<td>2010</td>
<td>94</td>
<td>29593</td>
<td>49</td>
<td>1.66</td>
<td>0.067</td>
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<td>27007</td>
<td>69</td>
<td>2.55</td>
<td>0.76</td>
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<td>29040</td>
<td>45</td>
<td>1.55</td>
<td>0.033</td>
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<td>96</td>
<td>30703</td>
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<td>1.11</td>
<td>0.0003</td>
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<tr>
<td>2014</td>
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<td>33427</td>
<td>36</td>
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<td>&lt;0.0001</td>
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