Xanthine Derivatives for Kidney Protection in the Critically Ill Pediatric Population: A Systematic Review

Saul Flores1 Corissa N. Culichia2 Enrique G. Villarreal1,3 Fabio Savorgnan1 Paul A. Checchia1 Rohit S. Loomba2

1Division of Critical Care and Cardiology, Department of Pediatrics, Texas Children’s Hospital/Baylor College of Medicine, Houston, Texas, United States
2Division of Cardiology, Department of Pediatrics, Advocate Children’s Hospital, Oak Lawn, Illinois, United States
3Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo Leon, Mexico


Abstract

Different types of diuretics have been used to minimize fluid overload after resuscitation. This meta-analysis determined the effects of xanthine derivatives on creatinine, creatinine clearance, and urine output. Studies included data from pediatric patients, whoused theophylline or aminophylline, and included pre- and postxanthine data for at least one of the outcomes of interest. A total of 13 studies with 198 patients were included in the pooled analyses. The study recorded data prior, and a mean of 36 hours after xanthine administration. This meta-analysis demonstrates that xanthine derivatives in critically ill children, using a dose of approximately 5 mg/kg, lead to a statistically significant increase in creatinine clearance and urine output without significantly altering serum creatinine. Xanthine derivatives may be beneficial for fluid management in critically ill children. Further studies are warranted assessing the association with additional clinical outcomes.

Keywords

► pediatric patients
► critically ill children
► xanthines

Introduction

Fluid resuscitation is an important therapy in the initial management of critically ill children. It has been demonstrated that appropriate fluid resuscitation is associated with improved survival. Aggressive fluid resuscitation may lead to fluid overload that is associated with increased morbidity and mortality in this patient population.1,2 Although diuretics remain one of the mainstay therapies for fluid overload, these agents may be associated with decreased creatinine clearance, electrolyte disturbances, and effect failure due to diuretic resistance.

Xanthine derivatives, such as aminophylline and theophylline have emerged demonstrating prevention of oliguric acute kidney injury refractory to diuretic therapy, particularly in critically ill children due to acute heart failure, perinatal asphyxia, neonatal apnea, and respiratory distress.2–5 The precise mechanism by which xanthine derivatives have a diuretic effect has not been completely elucidated, but it appears to promote renal vascular vasodilation through adenosine receptor blockade and inhibition of cyclic nucleotide phosphodiesterase activity.1,2,6

The purpose of this meta-analysis was to assess the effects of xanthine derivatives (theophylline and aminophylline) on fluid balance and renal function in critically ill children.

Materials and Methods

End Points

A systematic review of the literature was performed to identify published retrospective, prospective, case series, and randomized clinical studies describing the use of xanthine derivatives
in pediatric patients. Meta-analyses were conducted to determine the effects of xanthine derivatives on the following endpoints: creatinine, creatinine clearance, and urine output. Creatinine is reported in mg/dL, creatinine clearance is reported in mL/min/1.73 m², and urine output is reported in mL/kg/h. The authors completed meta-analysis on outcomes that had ≥3 included studies.

Manuscript Search and Identification Strategy
Published manuscripts were identified by a systematic search of PubMed, Embase, and Cochrane databases from 1980 to 2018. The following search terms were used in isolation and various combinations: “xanthine derivative,” “aminophylline,” “theophylline,” “urine,” “creatinine,” “clearance,” “output,” “fluid,” “balance,” “acute kidney injury,” “cardiac surgery,” “children,” “pediatric” (►Supplementary Material 1, available in online version). No specific restriction on the year of publication was used. This was a newly conducted review with no previous review protocol having been established. Manuscripts published in a language other than English were excluded.

Evidence Acquisition
This systematic review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (►Supplementary Material 2, available in online version).

Manuscripts were initially screened by title and abstract with full text being retrieved for select manuscripts. These full text manuscripts were then reviewed by the authors for presence of bias and overall quality. Studies were discussed amongst the authors and differences in scoring of risk of bias and/or overall quality were resolved by consensus. The Cochrane Handbook for Systematic Reviews was used for quality evaluation.

Studies were included if they had data for pediatric patients (under 18 years of age), utilized either theophylline or aminophylline, and included pre- and postxanthine data for at least one of the outcomes of interest. Studies with nonpediatric patients, published only as an abstract, or published in a language other than English were excluded.

Data Extraction
Data were extracted using a data collection form created by the authors specifically for this study (►Supplementary Material 3, available in online version). Trial level data were extracted by two separate authors (S.F., R.L.) to confirm accuracy of the data. If no information was available for a particular outcome this was recorded. Authors of included studies were not contacted for additional data. Mean and standard deviations were collected for continuous variables. If median and range or median and interquartile range were presented then mean and standard deviation were calculated for use in the pooled analyses.

Bias Analyses
Bias analysis was performed for each specific study deemed eligible for inclusion. Specific attention was paid to patient selection, intervention selection, endpoint inclusion, and result reporting.

Data Analyses
Meta-analyses were conducted using Comprehensive Meta-Analyses Version 3.0 (Biostat; Englewood, New Jersey, United States). A fixed-effect model was run initially for each endpoint. Heterogeneity was assessed using two methods: (1) Q-statistics and its resulting p-value; and (2) I²-value. Heterogeneity was considered statistically significant if the p-value for the Q-statistic was less than 0.05 or the I²-value was greater than 50%. For endpoints with statistically significant heterogeneity a random-effects model was used for the pooled analyses. Results of pooled analyses for continuous variables are presented with mean difference and 95% confidence interval while results of binary variables are presented with odds ratio and 95% confidence interval.

Studies in which data were presented for more than two separate patient groups, each group of patients was treated as a separate study in the analysis. This is represented in the forest plots where appropriate. The true number of studies included for each endpoint is what is presented in the text.

For randomized trials, pre- and postxanthine data were collected for the xanthine arm only. Publication bias was assessed qualitatively by review of funnel plots and then quantitatively by means of an Egger analysis. These were conducted for each individual outcome. An Egger analysis with a p-value of less than 0.05 was considered to be statistically significant.

Results
Manuscript Identification and Characteristics
A total of 548 manuscripts were identified. Abstracts for these 548 manuscripts were reviewed and a total of 18 had their full text reviewed. A total of 13 studies with 198 patients were included in the final pooled analyses (►Tables 1 and 2). Study review and inclusion is outlined in ►Fig. 1. Of the 13 studies included in the final analyses, 3 were retrospective in nature while the remaining 10 were prospective in nature. Of these studies, 6 were done in a neonatal intensive care unit setting while the remaining 7 were done in a pediatric intensive care unit setting. Included studies ranged from 1995 to 2014 in regard to year of publication. Of the 13 included studies, 5 utilized aminophylline while the remainder utilized theophylline. All of the studies that included patients in the neonatal intensive care unit setting utilized theophylline. For studies utilizing aminophylline, an equivalent theophylline dose was calculated by multiplying the aminophylline dose by 0.8. This resulted in a mean xanthine dose of 5.7 mg/kg in theophylline equivalents. We calculated the mean and standard deviation (SD) of theophylline serum concentration, resulting in 10.64 ± 7.94 μg/mL.

The mean age of patients in the studies was 16 months with a range from 0 to 62.75 months. Studies recorded data immediately prior to xanthine administration and then a mean of 36 hours after xanthine administration.
Bias Analyses
Included studies were found to have low levels of bias. The greatest risk of bias appeared to stem from unpublished endpoints as several studies presented data for only a limited number of endpoints. We cited the studies included for each endpoint in the first sentence of their corresponding paragraph.

Serum Creatinine
A total of seven studies were pooled for the analysis of serum creatinine. This resulted in a total of 139 patients. The Q-statistic had a p-value of less than 0.05 and the I²-value was 71%, indicating significant heterogeneity. Thus, a random effects model was used. An Egger's regression was conducted and resulted in a p-value of 0.67, demonstrating no significant publication bias. There was no statistically significant difference noted in the serum creatinine after xanthine administration (p-value 0.055). The mean difference in serum creatinine was found to be −0.09 mg/dL with a 95% confidence interval of −0.20 to 0.01 (Fig. 2). Sensitivity analyses demonstrated no significant difference in the findings with respect to study design, xanthine used, xanthine dose, or time to repeat assessment.

Creatinine Clearance
A total of 6 studies were pooled for the analyses of creatinine clearance. This resulted in a total of 67 patients. Not all studies described how creatinine clearance was calculated. Mazkereth's and McLaughlin's studies used the following formula: [(urine creatinine × volume of urine/plasma creatinine) × (1.73/m²)]. The Q-statistic had a p-value of less than 0.05 and the I²-value was 88%, indicating significant heterogeneity. Thus, a random effects model was used. An Egger's regression was conducted and resulted in a p-value of 0.05, demonstrating no significant publication bias. A statistically significant

Table 1 Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Aminophylline or theophylline</th>
<th>NICU or PICU</th>
<th>Mean loading dose (mg/kg)a</th>
<th>Age in months (mean ± SD)c</th>
<th>Gestational age in weeks (mean ± SD)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axelrod et al</td>
<td>2014</td>
<td>Retrospective cohort study</td>
<td>31</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>–</td>
<td>45.6 ± 63.6</td>
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</tr>
<tr>
<td>McLaughlin et al</td>
<td>2000</td>
<td>Retrospective cohort study</td>
<td>10</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>6 (4.8)</td>
<td>33.9 ± 44.76</td>
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<tr>
<td>Tamburro et al</td>
<td>2014</td>
<td>Prospective interventional</td>
<td>34</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>3 (2.4)</td>
<td>51.5 ± 11.5</td>
<td></td>
</tr>
<tr>
<td>Bell et al</td>
<td>1998</td>
<td>Prospective interventional</td>
<td>10</td>
<td>Theophylline</td>
<td>PICU</td>
<td>2.93</td>
<td>51.2 ± 64.62</td>
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<td>1999</td>
<td>Prospective interventional</td>
<td>8</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>6 (4.8)</td>
<td>13.88 ± 14.3</td>
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<tr>
<td>Da Silva et al</td>
<td>2011</td>
<td>Retrospective cohort study</td>
<td>4</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>3 (2.4)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>McLaughlin and Abitbol</td>
<td>2005</td>
<td>Randomized clinical trial</td>
<td>10</td>
<td>Aminophylline</td>
<td>PICU</td>
<td>5 (4)</td>
<td>62.75 ± 66.58</td>
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<td>Lochan et al</td>
<td>1998</td>
<td>Randomized clinical trial</td>
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<td>2</td>
<td>39 ± 2</td>
<td></td>
</tr>
<tr>
<td>Bakr</td>
<td>2005</td>
<td>Randomized clinical trial</td>
<td>20</td>
<td>Theophylline</td>
<td>NICU</td>
<td>5</td>
<td>39.2 ± 1.4</td>
<td></td>
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<tr>
<td>Bhat et al</td>
<td>2006</td>
<td>Randomized clinical trial</td>
<td>40</td>
<td>Theophylline</td>
<td>NICU</td>
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<td>38.2 ± 0.79</td>
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<tr>
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<td>2006</td>
<td>Randomized clinical trial</td>
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<td>Theophylline</td>
<td>NICU</td>
<td>1</td>
<td>28.7 ± 1.6</td>
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<tr>
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<td>Retrospective cohort study</td>
<td>5</td>
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<td>NICU</td>
<td>1</td>
<td>33.4 ± 3.85</td>
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<td>Theophylline</td>
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<td>39.3 ± 1.6</td>
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<td>Theophylline</td>
<td>NICU</td>
<td>6</td>
<td>31.1 ± 2.8</td>
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</tbody>
</table>

Abbreviations: NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; SD, standard deviation.
aNeonatal intensive care unit or pediatric intensive care unit.
bIn parenthesis, theophylline equivalents. These are calculated by multiplying aminophylline by 0.8.
cFor patients in the PICU, age in months is provided.
dFor patients in the NICU, gestational age is provided.
difference was noted in the creatinine clearance after xanthine administration (p-value 0.01). The mean difference in creatinine clearance was 9.39 mL/min/1.73 m² with a 95% confidence interval of 2.26 to 16.51 (►Fig. 3). Sensitivity analyses demonstrated no significant difference in the findings with respect to study design, xanthine used, xanthine dose, or time to repeat assessment.

Urine Output
A total of seven studies were pooled for the analyses of urine output.1,3,5,6,8,13,14 This resulted in a total of 54 patients. Urine collection varies from one study to another, but the majority of the studies collected urine hourly for a total of 6 to 12 hours. The Q-statistic had a p-value of less than 0.05 and the I²-value was 92%, indicating significant heterogeneity. Thus, a random effects model was used. An Egger’s regression was conducted and resulted in a p-value of 0.14, demonstrating no significant publication bias. A statistically significant difference was noted in the urine output after xanthine administration (p-value <0.0001). The mean difference was 3.36 mL/kg/h with a 95% confidence interval of 2.37 to 4.36 (►Fig. 4). Sensitivity analyses demonstrated no significant difference in the findings with respect to study design, xanthine used, xanthine dose, or time to repeat assessment.

Discussion
The results from this meta-analysis demonstrated that administration of xanthine derivatives to critically ill pediatric patients can lead to statistically significant increase in creatinine clearance and urine output. These analyses utilized data from studies using a mean dose of 5.7 mg/kg (in theophylline equivalents) of xanthine and had a mean time interval of 36 hours until postadministration values were collected.

Data from this meta-analysis are also suggestive that administration of xanthine derivatives was associated with significant improvement in renal excretory function in critically ill children with acute kidney injury and fluid overload refractory to diuretics. This may be of even more impact in particular subsets of pediatric critically ill patients, such as those with congenital heart disease, where the prevalence of acute kidney injury in children with congenital and acquired heart disease following cardiac surgery ranged from 28 to 52%.2 In addition, children with congenital heart disease can be more sensitive to fluid changes and more susceptible to complications such as pulmonary edema, cardiac dysfunction, and hypoproteinemia.6,16,17 Thus, effective management of fluid overload and subsequent acute kidney injury may be able to decrease associated morbidity and mortality.2,6,16,17 It is important to note that most of the patients included in this meta-analysis were receiving concomitant diuretic regimens during the administration of xanthines. Diuretics may have contributed to urine output in the results, but this diuretic interaction should be studied further.

Xanthine derivatives act in a dose-dependent manner at the level of kidney vasculature by two primary mechanisms: at low doses (theophylline equivalent of 2–3 μg/mL) there is adenosine receptor antagonism, inhibiting adenosine’s vasoconstriction of afferent arterioles. Adenosine-mediated vasoconstriction decreases blood flow through the glomerulus, promoting increased solute concentration.1 Xanthine derivative inhibition of adenosine-mediated renal vasoconstriction causes increase in renal blood flow, thus, increasing

Table 2 Outcomes by study

<table>
<thead>
<tr>
<th>Studya</th>
<th>Year</th>
<th>Theophylline serum concentration</th>
<th>Serum creatinine</th>
<th>Creatinine clearance</th>
<th>Urinary output</th>
<th>eGFRb</th>
<th>Inotrope score</th>
<th>Na and K excretionc</th>
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<td>Axelrod et al</td>
<td>2014</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<td></td>
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<tr>
<td>McLaughlin et al</td>
<td>2000</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td></td>
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<tr>
<td>Tamburro et al</td>
<td>2014</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Bell et al</td>
<td>1998</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<td>Pretzlaff et al</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Da Silva et al</td>
<td>2012</td>
<td>x</td>
<td>x</td>
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<tr>
<td>McLaughlin and Abitbol</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Bakr</td>
<td>2005</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Bhat et al</td>
<td>2006</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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<td>Jenik et al</td>
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Abbreviation: eGFR, estimated glomerular filtration rate.
aMeta-analysis and forest plots were performed in outcomes with three or more studies.
bEstimated glomerular filtration rate.
cSodium and potassium excretion.
glomerular filtration rate. This also leads to an increase in creatinine clearance and urine output as identified in this meta-analysis. At high doses (theophylline equivalent dose greater than 10 μg/mL) there is inhibition of type IV phosphodiesterase. This mechanism increases cyclic adenosine monophosphate levels which indirectly may impact proximal tubular reabsorption and increase urinary excretion of sodium.

An important finding only included in two studies was that electrolytes do not appear to be impacted by the use of xanthine derivatives. Da Silva et al and Pretzlauff et al reported that even though sodium and potassium urinary excretion doubled as early as within 2 hours from initiation of aminophylline, serum sodium and potassium showed no change from baseline. These finding need further evaluation as they can minimize blood extraction and laboratory assessment.

Aminophylline and theophylline have similar side effect profiles. They are associated with stimulating the central nervous system, increasing smooth muscle relaxation, and increasing inotropy and chronotropy. Theophylline toxicity may lead to nausea, vomiting, headaches, and seizures. The concentration at which the current pooled-analyses showed beneficial effects in critically ill pediatric patients is lower than levels at which toxicities have been demonstrated.

While these pooled analyses are able to summarize the current data and also increase the total number of patients when compared with the source studies, there are some limitations associated with this study. All the data utilized represent study level data and not patient level data, thus limiting the degree to which subgroup analyses can be performed. Some of the outcomes were found to be heterogeneous. To minimize the impact of heterogeneity on the pooled outcomes, random effects models and sensitivity analyses were used where appropriate. Despite the large number of studies identified, all of the source studies were limited by the number of patients enrolled.

Despite the aforementioned limitations, the current study does offer insight into impact of xanthine derivatives in assisting with fluid removal in critically ill children. Additional studies are still warranted, however. A large multicenter study of children admitted to either a neonatal or pediatric intensive care unit should be conducted. Such a study would enroll...
Fig. 2  Forest plot displaying the change on serum creatinine after 36 hours of administration of xanthine derivatives. Mean difference with 95% CI from individual studies. A nonsignificant effect (mean difference of $-0.099, p=0.055$) at decreasing serum creatinine was observed after the administration of xanthine derivatives. Square: represents the individual studies effects. Horizontal line: represents the CI of a study. Diamond: represents the overall summary effect. CI, confidence interval; Total, number of patients.

Fig. 3  Forest plot displaying the change on creatinine clearance after 36 hours of administration of xanthine derivatives. Mean difference with 95% CI from individual studies. A significant effect (mean difference of 9.391, $p=0.001$) at increasing creatinine clearance was observed after the administration of xanthine derivatives. Square: represents the individual studies effects. Horizontal line: represents the confidence interval of a study. Diamond represents the overall summary effects; however, it is missing in the figure because it appears out of the upper range (difference of >8.00). Arrowhead: represents data out of the upper range in the figure (difference of >8.00). CI, confidence interval.

Fig. 4  Forest plot displaying the change in urine output after 36 hours of administration of xanthine derivatives. Mean difference with 95% CI from individual studies. A significant effect (mean difference of 3.369, $p<0.0001$) at increasing urine output was observed after the administration of xanthine derivatives. Square: represents the individual studies effects. Horizontal line: represents the confidence interval of a study. Diamond: represents the overall summary effects. Arrowhead: represents data out of the upper range in the figure (difference of >8.00). CI, confidence interval.
patients with a predefined degree of fluid overload and randomize patients to placebo versus xanthine derivative. A single dose of either aminophylline or theophylline at a predefined dose would then be administered. Data regarding the following would be collected immediately prior to xanthine administration and after: degree of fluid overload, urine output per kilogram per hour, serum creatinine, creatinine clearance, blood urea nitrogen level, electrolyte levels, presence of acute kidney injury, need for hemodialysis. Data would be collected at intervals of 8 to 12 hours depending on the specific outcome. As the pooled analyses were not able to demonstrate a statistically significant difference in serum creatinine this can be used to perform a sample size calculation for such a study. Utilizing a mean difference of 0.09 in serum creatinine as was noted in the current study, it would take approximately 104 patients in each arm (208 total) to detect a difference in serum creatinine after 36 hours of xanthine administration in critically ill children with 90% power. It would take a smaller sample size to detect a mean increase in urine output of similar extent to what was noted in the current pooled analyses.

**Conclusion**

This meta-analysis demonstrated that xanthine derivatives therapy in critically ill children using a dose of approximately 5 mg/kg leads to a statistically significant increase in creatinine clearance and urine output through 36 hours of administration without significantly altering serum creatinine. Larger randomized studies characterizing aminophylline for fluid removal in pediatric patients are warranted.

**Conflict of Interest**

None declared.

**References**