Baxter Critical Care Institute

Managing Phosphate Levels During CRRT: Reactive vs Proactive Approach

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Baxter

Disclosure

This program is sponsored by and on behalf of Baxter Healthcare Corporation. I have been contracted by Baxter Healthcare Corporation to present this material on Baxter's behalf.

Managing Phosphate Levels During CRRT

Reactive Approach: Non-CRRT-circuit options

- IV as needed replacement
- Nutritional supplementation
  - Nasogastric tube or total parenteral nutrition (TPN)
  - If given through the GI tract, vitamin supplementation should be considered as vitamin D is required for intestinal absorption of phosphate

Proactive Approach: CRRT-circuit options

- CRRT Replacement Solution containing phosphate
- Electrolyte abnormalities may be corrected by changing the formulations and/or flow rates of dialysate and replacement solutions

Geerse DA, et al. Crit Care. 2010;14(4):R147.
Kellum JA. (2016). Oxford University Press.
Heung M, Mueller BA. Semin Dial. 2018 May;31(3):213-218.

Important Risk Information

IMPORTANT RISK INFORMATION

PRISMASOL renal replacement solution
PRISMASOL Initial U.S. Approval: 2006

PHOXILLUM renal replacement solution
PHOXILLUM Initial U.S. Approval: 2015

------ ---- --------- ---- **-INDICATIONS AND USAGE**---------- ----

PRISMASOL and PHOXILLUM solutions are indicated in pediatric and adult patients for use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolyte and acid-base imbalances. They may also be used in case of drug poisoning when CRRT is used to remove dialyable substances.

------ ---- --------- **-DOSAGE AND ADMINISTRATION**----------

- Therapy must be individualized based on the patient's clinical condition, fluid, electrolyte, acid-base and glucose balance.
- Solution must be mixed prior to use.
- Use only with extracorporeal dialysis equipment appropriate for CRRT.

------ ---- --------- ---- **--CONTRAINDICATIONS**---------- --------- ---- --- •

Known hypersensitivities to PRISMASOL and PHOXILLUM solutions.

------ ---- --------- -- **WARNINGS AND PRECAUTIONS**-----------

Electrolyte and Volume Abnormalities

PHOXILLUM and PRISMASOL solutions can affect electrolytes and volume and may result in hyperkalemia or hyperphosphatemia. Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorous, calcium, other electrolytes and acid-base balance throughout the procedure. Abnormalities may be corrected by changing the formulation of replacement solution and/or dialysate, supplementation, or adjusting flow rates appropriately.

PHOXILLUM replacement solutions contain hydrogen phosphate, a weak acid that may increase the risk of metabolic acidosis.

Blood Glucose Abnormalities

The use of PRISMASOL and PHOXILLUM replacement solutions can affect blood glucose levels resulting in hypo- or hyper- glycemia depending upon the dextrose content of the replacement solution. Monitor blood glucose levels regularly. Patients may require initiation of or modification of antidiabetic therapy or other corrective measures during treatment.

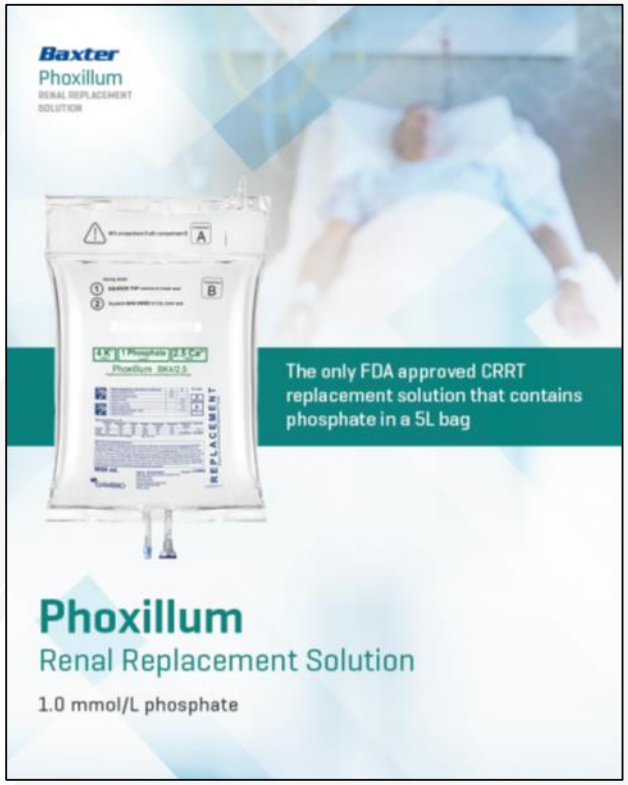
------- ---- --------- **---ADVERSE REACTIONS**---------- ----------

The following adverse reactions have been identified during postapproval use with these or other similar products and therefore may occur: Metabolic acidosis, Hypotension, Acid-based disorders, Electrolyte imbalance including calcium ionized increased, Hyperphosphatemia, Hypophosphatemia, Fluid imbalance.

Full prescribing information for PRISMASOL and PHOXILLUM can be found at www.baxterpi.com.

Phoxillum Renal Replacement Solution

Phoxillum Renal Replacement Solution is available in two formulas varying in calcium and bicarbonate



		Calcium Formula	Calcium-Free Formula
	Plasma*	PHOXILLUM BK 4/2.5	PHOXILLUM B22K 4/0
Potassium K^+ (mEq/L)	3.5–5.0	4.0	4.0
Calcium Ca^{2+} (mEq/L)	2.3–2.6†	2.5	0
Magnesium Mg^{2+} (mEq/L)	1.4–2.0	1.5	1.5
Sodium Na^+ (mEq/L)	135–145	140	140
Chloride Cl^- (mEq/L)	100–108	114.5	122.0
Phosphate HPO_4^{2-} (mmol/L)	0.8-1.5	1.0	1.0
Bicarbonate HCO_3^- (mEq/L)	22–26	32	22
Lactate (mEq/L)	0.5–2.2	0	0
Dextrose (mg/dL)	70–110	0	0
Osmolarity (mOsm/L)	280–296	294	290
NDC Number		24571-116-05	24571-117-05
Catalog Number		114905	114906

†Ionized Calcium

Compounded vs. Pre-Mixed CRRT Solutions

Pharmacy Compounding

- Made to order based on patient needs
- Vulnerable to ongoing shortages of injectable solutions, including phosphate
- Risk of contamination, even with proper mixing techniques
- Risk for human error in high-volume, high-acuity settings
- Increased pharmacy staff workload
- Waste due to limited shelf life after manipulation for electrolyte additives

Pre-Mixed Solutions

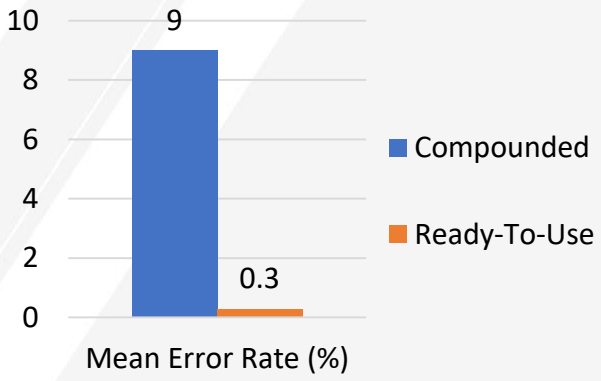
- Eliminates the need and stress of admixing with ready-to-administer bags
- Ready for clinicians to deliver an immediate and accurately prepared dose.
- Helps reduce potential errors related to compounding
- Premixed formulation that is free of human contact during the filling process.
- Manufacturing includes exclusive aseptic bag filling technology
- Routine utilization of pre-mixed solutions may confer significant cost savings

Phoxillum solution is the only FDA-approved pre-mixed replacement solution containing phosphate in a 5 L bag.

Heung M, Mueller BA. Semin Dial. 2018 May;31(3):213-218.
Shaw AR, et al. Am J Health Syst Pharm. 2018 Jun 1;75(11):808-815.
Godden et al. Am J Health Syst Pharm 2012 May 1;69(9):786-93.

Compounding CRRT Solutions is Associated with Medication Errors

- Study of errors in compounded vs. ready-to-use IV solutions in five hospitals
- The error rate for compounded IV mixtures was nine (9) times higher than for ready-to-use products



- The most common compounding error was deviation from labeled dose (69%), followed by incorrect base solution volume/content (16%)

Table 4.
Types of Errors Observed in I.V. Admixtures

Error Category	No. Errors					Total No. Errors (%)
	Mountain	Midwest	Pacific	Southeast	Northeast	
Unauthorized drug	9	0	1	0	0	10 (7)
Wrong dose (as % deviation from labeled dose)						
5.0–9.9	7	11	9	10	10	47 (32)
10.0–14.9[a]	0	6	4	9	2	21 (15)
≥15.0[b]	1	9	5	6	11	32 (22)
Wrong base solution						
Volume	1	1	1	5	0	8 (6)
Content	8	5	0	0	2	15 (10)
Omission	1	0	4	0	0	5 (3)
Wrong preparation technique	0	6	0	1	0	7 (5)

[a]For example, fluorouracil (11% deviation from labeled dose), potassium chloride (10%), and tobramycin (10%).
[b]For example, leucovorin (100% deviation from labeled dose), insulin (60%), dopamine (20%), and ciprofloxacin (33%).

"The clear difference in error rates between ready-to use products…and compounded admixtures…suggests that limiting the number of manipulations that must be performed to prepare a product reduces the likelihood of errors."

Flynn et al. Am J Health Syst Pharm 1997 May 1;54(9):1110.

Pre-mixed CRRT Solutions are Associated with Fewer Errors and less Patient Harm

Internet survey of CRRT medication errors

- 58% of 31 programs surveyed reported at least one error (2 anticoagulation, 16 compounding)
- 89% of reported CRRT solution errors were due to compounding
- All errors occurred in manually-prepared solutions; 0 errors were observed in pre-mixed commercial solutions
- 56% of compounding errors resulted in patient harm

Compounding Errors (N=16)

	Manually Compounded	Commercial Solution	P
Dialysate	9	0	0.005
Replacement	7	0	0.051
Total # Errors	16	0	<0.001

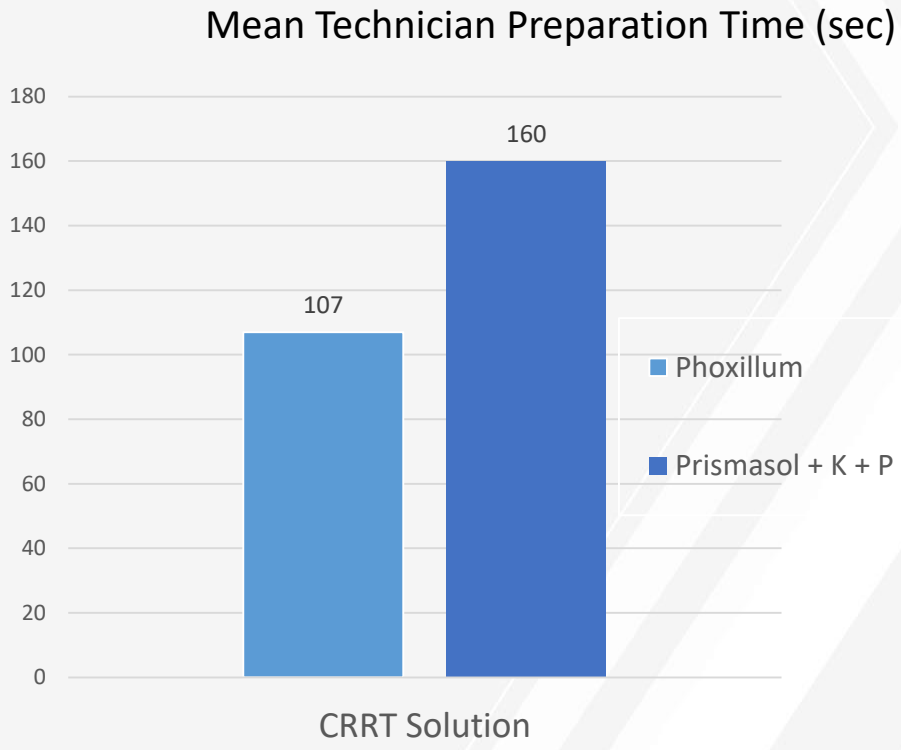
Level of Harm Resulting from Errors (N=16)

	Number (%) Errors	Harm Description
Error, No Harm	7 (44%)	N/A
Error, Harm	6 (38%)	Seizures related to hyper/hyponatremia
	1 (6%)	Cardiac arrest
Error Death	2 (12%)	Patient death

Barletta et al. Pediatr Nephrol 2006 Jun;21(6):842-5.

Pre-Mixed CRRT Solutions Reduce Preparation Time

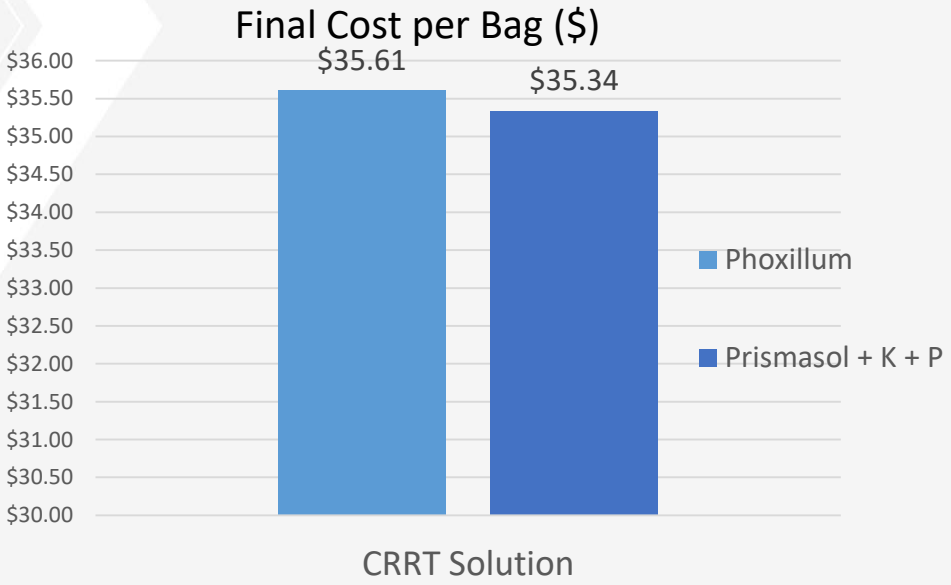
- Work times were recorded for manual addition of phosphate, potassium and/or bicarbonate to commercially-available products
- Pre-made CRRT solutions that contained physiological electrolyte concentrations required less technician and pharmacist time than solutions that needed addition of electrolytes in the pharmacy
- Choosing a solution that requires fewer entries into the CRRT solution bags can minimize the time associated with preparation and verification



Shaw AR, et al. Am J Health Syst Pharm. 2018 Jun 1;75(11):808-815.

PRACTICE RESEARCH REPORTS RENAL REPLACEMENT THERAPY

Preparation times and costs for various solutions used for continuous renal replacement therapy



Only Approved/On-Label Drug Additives:

Phosphate 1.2 mmol/L, as potassium phosphate or sodium phosphate, is the only approved drug addition for **Prismasol** solution. Total potassium concentration should not exceed 4 mEq/L.

Phosphate 0.2 mmol/L, in the form of sodium phosphate, may be added to **Phoxillum** solution up to a total final concentration of 1.2 mmol/L.

Pre-mixed solutions are not more expensive

Shaw AR, et al. Am J Health Syst Pharm. 2018 Jun 1;75(11):808-815.

Overview of Clinical Evidence

Six published studies evaluated commercially-available phosphate-containing CRRT solutions

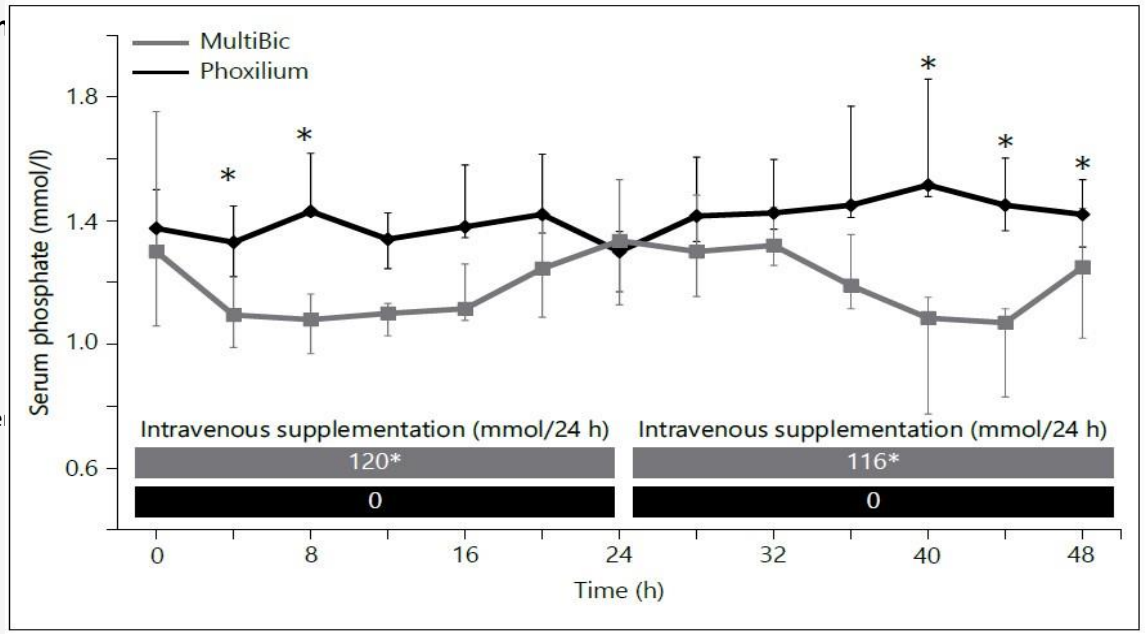
First Author	Solution	Country	# Patients	Study Design	Results
Besnard	**Phoxilium***	France	10	Crossover	Serum phosphate maintained in normal range without supplementation
Broman	**Phoxilium***	Sweden	42	Prospective comparison	Hypophosphatemia reduced significantly vs. control group
Pistolesi	**Phoxilium***	Italy	75	Single-arm	Normal phosphate levels in 88% of patients after 72 hours
Godaly	**Phoxilium***	Sweden	112	Retrospective comparison	Hypophosphatemia reduced significantly vs. control group
Thompson Bastin	**Phoxillum**	United States	1,396	Retrospective comparison	Significant reductions in hypophosphatemia, prolonged ICU stay and mechanical ventilation
Crowley	**Phoxillum**	United States	60	Retrospective comparison	Significantly less hypophosphatemia with no differences in hypoglycemia

* **Phoxilium** Bicarbonate-buffered solution for hemodialysis and hemofiltration 1.2 mmol/L Phosphate is not available in the United States

Phosphate-Enriched CRRT Solution Reduces Incidence of Hypophosphatemia

- Crossover study comparing CVVHDF of (**Phoxilium*** 1.2 mmol/L phosphate) vs. standard (MultiBic)
- 10 patients in septic shock 48h on each solution
- Serum potassium and phosphate levels were maintained in the normal range without any supplementation with **Phoxilium** solution
  - **Phoxilium** solution was associated with slight hypocalce and metabolic acidosis
- Phosphate supplementation significantly reduced **Phoxilium** group
  - (0 vs. 234 mmol per 48h), p<0.05
- Glucose levels similar in both groups

Crossover study design



Serum phosphate levels during the 48-hour CVVHDF treatment according to the replacement and dialysate fluids used. **Phoxilium** solution is shown as a black line and MultiBic as a grey line. Supplementation of intravenous phosphate is represented as a black line for **Phoxilium** solution and as a grey line for conventional treatment. * p < 0.05.

* **Phoxilium** Bicarbonate-buffered solution for hemodialysis and hemofiltration 1.2 mmol/L Phosphate is not available in the United States

Besnard N, et al. Blood Purif. 2016;42(1):18-26.

Phosphate-Containing Solution Reduces Incidence of CRRT Hypophosphatemia

Acta Anaesthesiol Scand 2011; 55: 39–45
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
doi: 10.1111/j.1399-6576.2010.02338.x

Phosphate-containing dialysis solution prevents hypophosphatemia during continuous renal replacement therapy

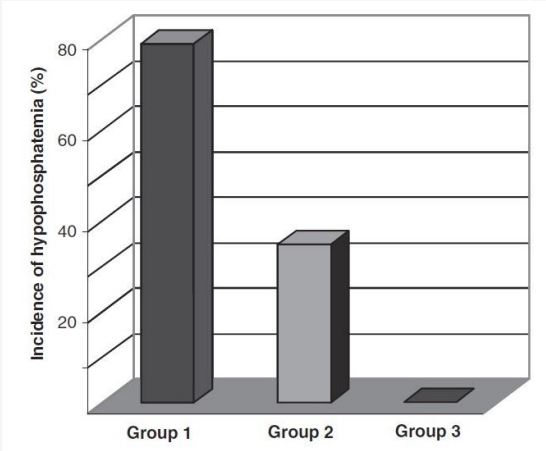
M. Broman[1], O. Carlsson[2], H. Friberg[1], A. Wieslander[2] and G. Godaly[2]
[1]Department of Anaesthesiology and Intensive Care, Lund University Hospital, Lund, Sweden and [2]Gambro Lundia AB, Lund, Sweden

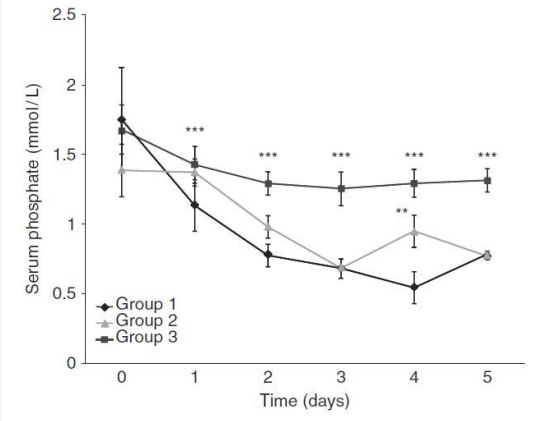
42 consecutive CVVHDF patients

- Phosphate-containing solution (**Phoxilium***) vs. routine non-phosphate-containing solution (**Hemosol** B0**)

	Dialysis Solution	Replacement Solution
Group 1 n = 14	**Hemosol**	**Hemosol**
Group 2 n = 14	**Phoxilium**	**Hemosol**
Group 3 n = 14	**Phoxilium**	**Phoxilium**

- Hypophosphatemia: 78.5% Group 1, 35.7% Group 2, 0% Group 3





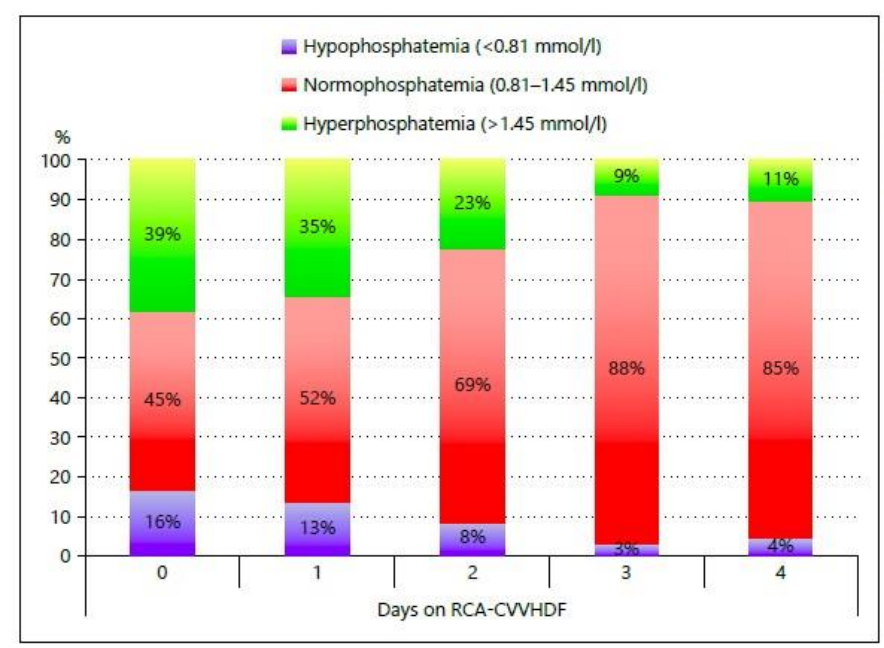
* **Phoxilium** Bicarbonate-buffered solution for hemodialysis and hemofiltration 1.2 mmol/L Phosphate is not available in the United States
****Hemosol** is not available in the United States.

Broman M, et al. Acta Anaesthesiol Scand. 2011 Jan;55(1):39-45.

Reducing CRRT-Induced Hypophosphatemia: Extended Experience

Retrospective analysis of 75 patients with cardiac surgery associated AKI treated with CRRT

- RCA-CVVHDF, median duration 9 days
- **Phoxilium*** dialysate and post-dilution replacement fluid
- After 72 hours of treatment serum phosphorus levels were normal in 88% of patients
- During entire treatment period, only 3.8% of patients met criteria for mild hypophosphatemia and <1% met criteria for moderate hypophosphatemia



Distribution of patients in relation to phosphatemia throughout RCA-CVVHDF days.

* **Phoxilium** Bicarbonate-buffered solution for hemodialysis and hemofiltration 1.2 mmol/L Phosphate is not available in the United States

Pistolesi V, et al. Blood Purif. 2017;44(1):8-15.

Phosphate-Containing CRRT Solution Reduces Hypophosphatemia

Retrospective analysis of 112 patients treated with CRRT

- Control group was treated with **Hemosol** B0 (**) (no phosphate; n = 36) as dialysis and replacement fluid, study group received **Phoxilium*** (phosphate; n = 76) as dialysis fluid and **Hemosol** B0 as replacement fluid
- Hypophosphatemia occurred in **15%** of the treatment days in the control group compared with **7%** in the study group (P = 0.027)
- A total of 41.9% of the patients in the control group and 38.6% (P = 0.262) of the patients in the study group showed hyperphosphatemia prior to CRRT due to AKI; once CRRT was initiated, incidences of hyperphosphatemia were low in both groups

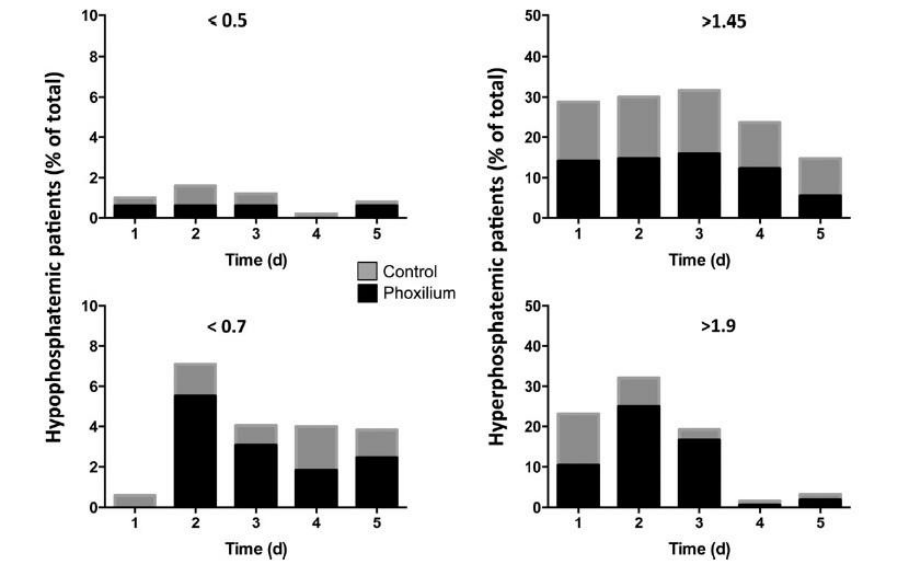


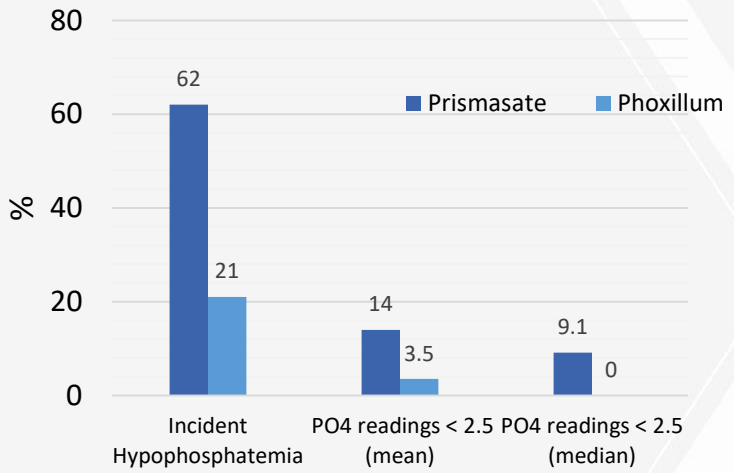
Fig. 3. Phosphate variations in patients treated for >72 h with CRRT.

* **Phoxilium** Bicarbonate-buffered solution for hemodialysis and hemofiltration 1.2 mmol/L Phosphate is not available in the United States
Hemosol is not available in the United States.

Godaly G, et al. Clin Kidney J. 2016 Apr;9(2):205-10.

Phoxillum Solution Reduces Hypophosphatemia, ICU Stay and Ventilator Time

- Single-center, retrospective, cohort study of 1,396 adult patients who received CRRT during their ICU stay
  - **Prismasate** non-phosphate CRRT solution: 511 pts
  - **Phoxillum** phosphate-containing CRRT solution: 885 pts
- Incidence Hypophosphatemia (serum phosphorous < 2.5 mg/dL) was higher in non-phosphorus CRRT solution group than in the **Phoxillum** solution group (62% vs. 21%, p < 0.0001)
- The non-phosphate solution group had significantly higher proportions of PO4 readings < 2.5 mg/dL than the **Phoxillum** solution group (p < 0.0001)
- Use of non-phosphate solution was associated with an 8.5 fold increase in hypophosphatemia (OR 8.53, 95% CI 6.29-11.57,p = 0.0001)
- Non-phosphate solution independently predicted durations of ICU stay and mechanical ventilation (p < 0.001)



Variable	Odds Ratio	Std. Error	P>|z|	95% Confidence Interval
Prismasate	8.53	1.32	<0.0001	6.29, 11.57
Age	1.00	0.005	0.767	0.99, 1.01
AA race	0.76	0.21	0.339	0.43, 1.34
Other race	0.59	0.66	0.638	0.07, 5.33
Male gender	0.55	0.08	<0.0001	0.41, 0.75
Service Line				
Surgery/Tra	1.06	.284	0.827	0.63, 1.79
CT Surg	1.33	.319	0.230	0.83, 2.13
Cardiology	1.14	.289	0.599	0.69, 1.87
Transplant	1.48	.538	0.284	0.72, 3.02
Surgery other	1.42	.620	0.423	0.60, 3.3
Neuro	5.77	4.33	0.020	1.32, 25.1
Sofa Score	0.95	0.19	0.025	0.92, 0.99
Weight (kg)	0.99	0.003	0.001	0.98, 0.99

Ventilator days	Beta Coef.	Robust Std. Error	P>|t|	[95% Conf. Interval]
Prismasate	5.634	0.95	<0.000	3.78, 7.49

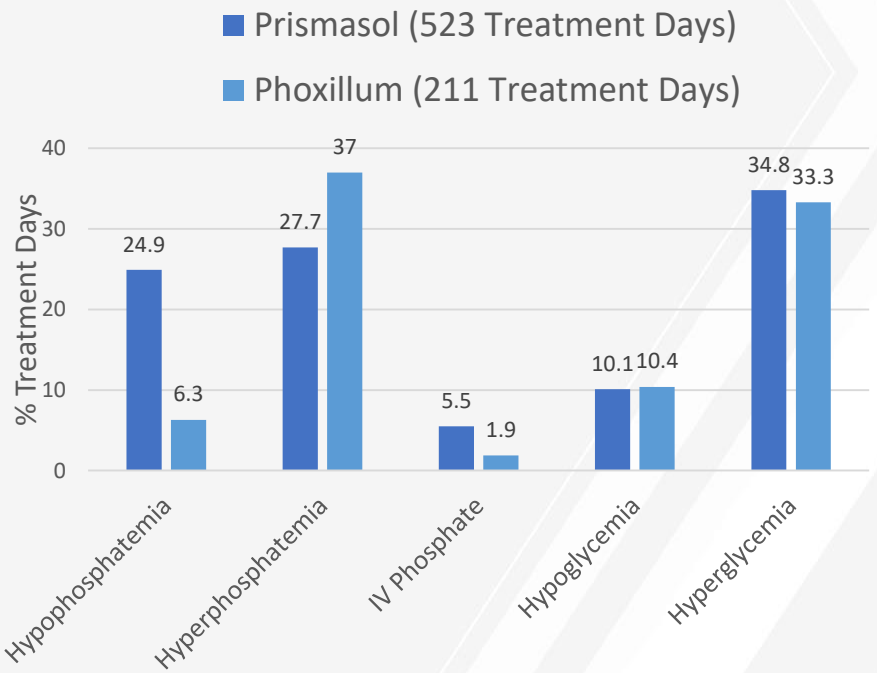
ICU days	Beta Coef.	Robust Std. Error	P>|t|	[95% Conf. Interval]
Prismasate	5.98	1.45	<0.0001	3.13, 8.83

* Both models p<0.0001
* Beta coef adjusted for age, race, service, SOFA score, weight

Thompson Bastin et al. American Journal of Respiratory and Critical Care Medicine 2019;199:A5994

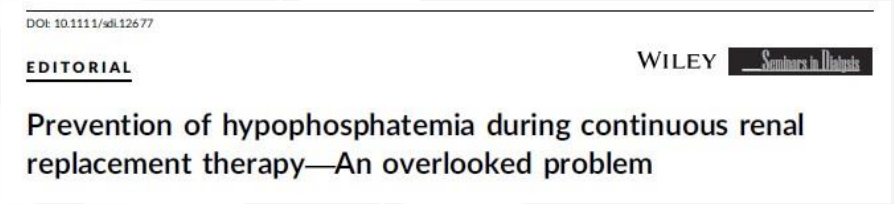
Impact of Phoxillum Solution on Phosphate and Glucose During RRT

- Single-center, retrospective analysis of 60 patients
  - **Prismasol solution**: 523 days of CVVH
  - **Phoxillum** solution: 211 days of CVVH
- The **Prismasol** solution group had more treatment days with hypophosphatemia (phosphate < 2.5 mg/dL) vs. the **Phoxillum** solution group **(24.9% vs. 6.3%, p < 0.0001)**
- The **Phoxillum** solution group had more treatment days with hyperphosphatemia (phosphate > 4.3 mg/dL) vs. the **Prismasol** solution group **(37.0% vs. 27.7%, p < 0.0001)**
- **Prismasol** solution patients received more days of intravenous phosphate repletion vs. **Phoxillum** solution patients **(5.5% vs. 1.9, p = 0.013)**
- Prevalence of dysglycemia (BG <70 or >180) did not differ between groups



Crowley C, DeGrado J, Charytan D. Crit Care Med. 2019 Jan;47(1):702.

2018 Editorial Highlights Benefits of Phosphate-Containing Solutions


DOI: 10.1111/sdi.12677

EDITORIAL

WILEY Seminars in Dialysis

Prevention of hypophosphatemia during continuous renal replacement therapy—An overlooked problem

"The recent availability of a commercial phosphate-containing CRRT solution may provide a balance between hypophosphatemia risk, workload and patient safety."

	Phosphate Supplementation Approach	Advantages	Disadvantages
Reactive	Physician-guided intravenous, oral/enteral supplementation	• Use of clinical judgment • Ease of titration • Oral/enteral or IV options can be used synergistically	• Relies on high level of vigilance and regular laboratory data • Vulnerable to solution shortages
Reactive	Protocol-guided intravenous, oral/enteral supplementation	• Automated • Easily titratable	• May promote less vigilance • May be reactive vs. proactive • Vulnerable to solution shortages
Proactive	CRRT solution supplementation (pharmacy compounding)	• Provides steady-state base phosphate level • Titratable	• Potential for errors and/or contamination • Increased pharmacy workload • Vulnerable to solution shortages
Proactive	Commercial phosphate-containing CRRT solution	• Provides steady-state base phosphate level • No pharmacy manipulation required	• Fixed level and non-titratable

Summary

- Hypophosphatemia is an important electrolyte abnormality in critically ill patients
  - Associates with impaired oxygen delivery, and physiologic consequences
- Patients receiving CRRT are at increased risk of hypophosphatemia, muscle weakness, prolonged MV
- CRRT solutions are available to help reduce risk and time of admixing
- Phosphate containing CRRT solutions are associated with improved phosphate balance
  - Despite electrolyte protocols to replace outside the circuit
- Phosphate containing CRRT solutions, and avoidance of hypophosphatemia may improve muscle function resulting in fewer MV days and shorter ICU LOS

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Thank you!

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