

Continuous Renal Replacement Therapy using the Prisma® M 100
Bicarbonate Dialysis with Normocarb®

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| | |
|--|----|
| <u>1. ACCESS</u> | 4 |
| <u>2. Circuit Setup Guidelines</u> | 4 |
| <u>3. BLOOD FLOW RATE (BFR)</u> | 4 |
| <u>4. CVVH VS. CVVHD</u> | 4 |
| <u>5.0 SOLUTIONS</u> | 5 |
| <u>6.0 ANTICOAGULATION</u> | 7 |
| <u>6.1 Heparin Anticoagulation</u> | 7 |
| | 7 |
| <u>6.2 CrCU Normocarb Protocol For Use With CRRT Therapy (PRISMA)</u> | 8 |
| <u>7.0 REFERENCES</u> | 10 |
| <u>7.1 Prescription references</u> | 10 |
| <u>7.2 Access references</u> | 10 |
| <u>7.4 Anticoagulation references</u> | 10 |
| <u>7.5 Solution references</u> | 10 |
| <u>7.6 Nutrition references</u> | 11 |
| <u>7.7 Outcome references</u> | 11 |
| <u>7.8 Complication references</u> | 12 |
| <u>8.0 APPENDICES</u> | 13 |
| <u>8.1 Lactate vs. Bicarbonate for Dialysis or Replacement Solution</u> | 13 |

Substitution fluids and dialysate used in CRRT have been often primarily developed for intermittent hemofiltration or peritoneal dialysis. In CRRT techniques including dialysis also any ready-to-use dialysis solution may

be employed. In nearly all commercially available fluids lactate (30 - 45 mmol/L), which is converted to bicarbonate on an equimolar basis under physiological conditions, is used as the buffer to correct acidosis. The lactate buffer has the advantage of greater stability over a physiologic bicarbonate buffer. However, lactate is thought to have negative effects on hemodynamic parameters, and on metabolic parameters, e.g. enhanced protein catabolism and decreased regeneration rate of ATP due to the fact that conversion from lactate to bicarbonate needs energy. 13

Only a few studies until now compare different buffers used in substitution fluids. From these data it seems to be common sense that acetate-buffered substitution fluids should be avoided, as a significantly reduced control of acidosis compared to a lactate-buffered solution has been recently reported during CVVH..... 13

Solutions used in peritoneal dialysis have also been recommended as an alternative, but their high glucose concentration can lead to incomplete metabolism, requiring additional insulin with concomitant metabolic alterations in MODS patients. 13

Some studies are dealing with bicarbonate-buffered compared to lactate-buffered solutions. Major goals in these studies had been: control of uremia, control of acidosis and lactate concentration, metabolic changes, hemodynamic parameters and the concentration of the important serum electrolytes. 13

Under stable clinical conditions 2000 mmol of lactate per day are metabolized to bicarbonate on an equimolar basis. Critically ill patients with ARF, especially with concomitant sepsis or circulatory shock have been reported to display a reduced lactate tolerance. In these cases or with the use of the high-volume hemofiltration using an exchange volume of 4-6L/hour the physiological capacity of the liver in converting lactate to bicarbonate may be exceeded. 14

In our first experience, nitrogen excretion was significantly increased in patients receiving lactate-buffer on day 1-4 of CRRT, a result we could not reproduce in a later study. But lactate- associated protein catabolism may be relevant using high amounts of substitution fluids..... 14

Bicarbonate-solutions must be stable for a 24 hour period without precipitation of calcium carbonate or magnesium carbonate. Therefore, the magnesium and calcium concentration is reduced compared to the lactate-buffered solution. To adjust ionic strength the chloride concentration must be increased. Possible precipitation does not allow a higher phosphate concentration in one of the solutions, so phosphate must separately be substituted to avoid phosphate depletion, as MODS patients with ARF tend to develop hypophosphatemia leading to decreased respiratory and

cardiac function. The patients serum concentration of these electrolytes must therefore carefully be monitored and other electrolytes must be added if necessary. Especially the magnesium concentration in bicarbonate-solutions may be insufficient in patients with arrhythmias or depleted cardiac function..... 14

8.2 Sample CRRT Orders..... 16

? FOR CORRECTED CA⁺⁺ < 2.0 MMOL/L, GIVE CACL 1GM IN 100ML NS OVER 2HRS VIA CENTRAL LINE. CANCEL ANY PREVIOUS CA⁺⁺ BOLUS ORDERS. 17

8.3 Acute Renal Failure (ARF)..... 18

8.4 Description of Normocarb and Scientific Rationale for its use..... 25

8.5 Normocarb Product Information..... 29

1. Access

Vascular access will be placed by the ICU staff and should be preferably a dual lumen 12-14 Fr. access. Although flow and recirculation data is similar, it is preferable to have the access placed either IJ or subclavian as opposed to femoral but femoral access is acceptable if a catheter of sufficient length is used (20 cm). The preference that if the patient recovers and can switch to intermittent haemodialysis they can ambulate with out risk of bending a femorally placed catheter.

2. Circuit Setup Guidelines

Follow the manufacture guidelines. Priming of the circuit should be with normal saline. 5% albumin can be added if indicated. PRBC's should not be needed in adults for priming and may induce a "Bradykinin Release Syndrome" due to pH and membrane reaction.

3. Blood flow rate (BFR)

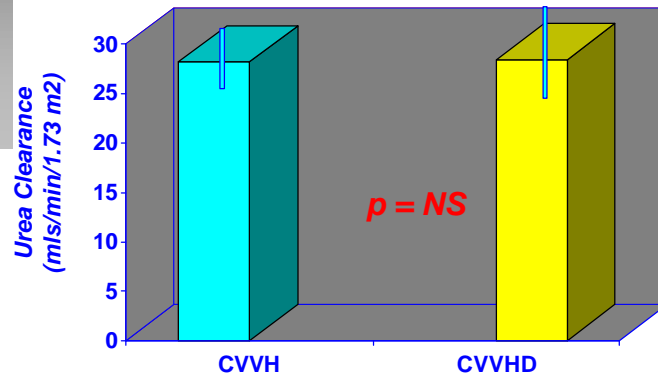
A blood flow rate of 100mls/min will allow for adequate flow. The maximum BFR of the PRISMA® is 180 mls/min. The higher the BFR, the less the potential for clotting but the trade off is more alarms. Patients with hepatic failure are often auto-anticoagulated and as anticoagulation may not be used, a higher blood flow may help to prevent clotting, ie. 125-150 ml/min. At 100 ml/min (6000 ml/hr) blood flow is much greater than dialysis and replacement flow rates (typically 1500-2000 ml/hr) so that clearance is NOT blood flow dependent and higher blood flow rates will not give higher clearances.

4. CVVH vs. CVVHD

Data has shown that if one keeps constant the amount of solution then urea clearance is similar in CVVH or in CVVHD.

Comparison of Urea Clearance: CVVH vs CVVHD

(Maxvold et al, Crit Care Med April 2000)



BFR = 4 mls/kg/min

Replacement Fluid/Dx FR = 2 l/1.73 m²/hr

SAM = 0.3 m²

In hemofiltration for sepsis, CVVH may have better cytokine clearance. We use a solution rate of 20 mls/kg/hr in either CVVH or CVVHD. The recent work of Ronco et al. suggests that there may be a survival benefit of higher flow rates but this was not confirmed by Bouman. Until this issue is resolved we recommend adjusting the patients clearance to at least prevent the urea and creatinine from rising further and preferably falling to a range of 1.5 - 2 x normal.

5.0 Solutions

Dialysis solutions choice can be bicarbonate based: Normocarb, Dialysis Sol'n Inc, Toronto, Canada (approved for dialysis in Canada and US); Hemosol BO, Hospal, Gottenberg, Sweden, (approved for dialysis in Canada), or lactate based: Hemofiltration sol'n by Baxter, Chicago, Illinois or peritoneal dialysis solution 0.5% (available in Canada only) or 1.5% PD solution, or pharmacy made solutions. Presently only pharmacy made solutions are "approved" for replacement solutions, but pharmacy made solutions run to the risk of ingredient error due to lack of standards that are adhered to by Industry. Although lactate based solutions are safe for peritoneal dialysis the amount of lactate the patient is exposed to is limited to 80 mmol every 4-6 hours. On high volume haemofiltration a patient may receive 4L/hour of 40 mmol/L lactate containing solution which can overwhelm a critically ill patients ability to metabolize the lactate load.

Commercially Available Solutions for dialysis * or for dialysis or infusion

| PREMADE SOLUTIONS ADDITIVES | RINGER'S LACTATE | 1.5% PD FLUID | Normocarb * | Baxter Hemofiltration Solution * |
|-----------------------------|------------------|---------------|-------------|----------------------------------|
| Na (mEq/L) | 130 | 132 | 140 | 140 |
| K (mEq/L) | 4 | 0 | 0 | 2 |
| Cl (mEq/L) | 109 | 96-102 | 106.5 | 117 |
| HCO ₃ (mEq/L) | 0 | 0 | 35 | 0 |
| Lactate (mEq/L) | 28 | 40 | 0 | 30 |
| Ca (mmol/L) | 1.5 | 1.5 | 0 | 1.5 |
| PO ₄ (mmol/L) | 0 | 0 | 0 | 0 |
| Mg (mmol/L) | 0 | 0.5-1.5 | 0.75 | 0.75 |
| Dextrose (mmol/L) | 0 | 83 | 0 | 55 |

*approved for dialysis only

Pharmacy Solutions for dialysis or infusion

| CUSTOM MADE SOLUTIONS | CALCIUM-BASED infusate/ DIALYSATE | PHOSPHATE BASED infusate/ DIALYSATE |
|--|-----------------------------------|-------------------------------------|
| NaCl (mmol/L) | 100 | 100 |
| NaHCO ₃ (mmol/L) | 40 | 40 |
| KCl (mEq/L) | 4 | 2 |
| K ₃ PO ₄ (mmol/L) | 0 | 1 |
| Lactate (mmol/L) | 0 | 0 |
| CaCl ₂ (mmol/L) | 1.75 | 0 |
| MgSO ₄ (mmol/L) | 0.75 | 0.75 |
| Dextrose (mmol/L) | 8 | 8 |
| Solutions are mixed with sterile technique in the pharmacy BUT THERE IS RISK OF ELECTROLYTE ERROR TO DUE LACK OF STANDARDS | | |

6.0 Anticoagulation

Many patients who require continuous renal replacement therapy (eg patients with hepatic failure, sepsis, haem/onc patients) will need no anticoagulation due to their underlying coagulopathy. Some patients must be on heparin due to their medical condition. In these patients if heparin is incorporated into the CRRT protocol, if the dialysis is interrupted for any reason, the heparin will also be interrupted for the same period of time. For this reason if the patient requires heparin for a reason other than circuit anticoagulation it should be given separately from dialysis and adjusted by the appropriate most responsible physician. In those patients who require anticoagulation either citrate or heparin can be used. The heparin protocol is below, for the citrate protocol please see the citrate protocol sheet.

6.1 Heparin Anticoagulation

Place a syringe of 100 units/ml of heparin in the heparin syringe holder. Load the patient with 20 units/Kg, then begin an infusion at 10 units/Kg/hr. Check PTT systemically. Aim for a PTT of 1.5 to 2.0 times normal. We do not use ACT's due to the variability in this technique and the cost of maintaining this system. Monitor platelets daily.

A study by Van de Wetering, found that the coagulation of filters was clearly dependent on the PTT values but there was a similar close relation between the systemic PTT and the incidence of hemorrhage. When the PTT was twice the control between 45-55, the filter usage was 12.9 per 1000 hr. When the PTT was greater than 55, only 9 filters per 1000 hr were used. However, there was a threefold increase in the incidence of bleeding from 2.9/1000 hr in the normal ranges of PTT, to 7.4/1000 hr when the PTT was twofold prolonged between 45-55 and greater. Filter usage was not improved as PTT increased beyond 1.5 x normal, but bleeding consistently increased as PTT increased. He felt that a systemic PTT of 1.5 times (35-45 seconds), is associated with the best balance between filter life span and hemorrhagic complications.

Saline flushes can be used to help keep the filter open. The usual volume is 100 ml every hour. See protocol below for details

6.2 CrCU Normocarb Protocol For Use With CRRT Therapy (PRISMA)

- 1.0 Prime in CVVHD or CVVHDF Mode using ordered dialysate and replacement solutions if hemodiafiltration is planned.
Solutions will generally be as follows:
 - Dialysate – Normocarb 240mL in 3L Sterile Water for Irrigation
 - Replacement – 0.9%NS 1L, 0.45% NS, 0.45% NS with 50 mmol NaHCO₃, normocarb may be used off label on the order of a physician.Additives ordered by MD (eg. KCl 3 mmol/L for K⁺ < 3.5 mmol/L, Phosphate is best added into TPN or enteral nutrition supplement).
- 2.0 Attach infusion set with 100 cc buretrol to blue arm of Y-connector and prime with normal saline used for flushes (0.9% NS 1000ml).
- 3.0 Attach red arm of Y-connector to Red Access Line on the PRISMA set. When ready to start flushes clamp the red port from the patient and open the blue clamp on the Y-connector to allow the flush to run through. Monitor the flush carefully and reverse the clamps to open to the patient before the buretrol as completely emptied. Flushes are usually 100 ml and are performed every 60 minutes. Add the 100 ml to the fluid removal as below.
- 4.0 Connect the Prisma circuit to the dialysis catheter as per procedure and press start.
- 5.0 Set the flow rates in PRISMA as ordered. The blood flow rate should be set at 100ml/hr.
- 6.0 Patient Fluid Removal Rate is calculated by:
Net Ultrafiltration rate + flush rate = Pt. Fluid Removal Rate.
- 7.0 Connect the Prisma circuit to the dialysis catheter as per procedure and press start.
- 8.0 1 hour after initiation of therapy and every 12 hours thereafter, send the following blood work
 - ?? Chemistries (eg Lytes, Bun, Cr, Ca, Phos, Albumin)
- 9.0 Adjust the Replacement Rate if haemofiltration is requested
- 10.0 Temperature Regulation:
When blood is outside of the body a tremendous heat loss occurs. The use of the PRISMA THERM® on the infusion solution, the dialysis solution or the blood line

9-Bicarbonate Dialysis for Hepatic Failure and Lactic Acidosis: Tobe PRIMSA M100 Protocol

will aid in keeping eutermic. Additional overhead warmer or external warmer may be needed.

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8.0 Appendices

8.1 Lactate vs. Bicarbonate for Dialysis or Replacement Solution

From Dr. Horst Kierdorf, Syllabus: Workshop on Replacement and Dialysate Solutions for CRRT, Sixth International Conference on CRRT, San Diego, 2001.

Continuous renal replacement therapies (CRRT) are well accepted for critically ill patients with acute renal failure (ARF). To fulfill the three major aims of RRT in ARF: detoxification, fluid elimination and compensation of acidosis, today, daily fluid exchange in CRRT reaches 30-40 L and more. Therefore, the composition of the substitution-/ dialysate-fluid becomes more relevant.

Substitution fluids and dialysate used in CRRT have been often primarily developed for intermittent hemofiltration or peritoneal dialysis. In CRRT techniques including dialysis also any ready-to-use dialysis solution may be employed. In nearly all commercially available fluids lactate (30 - 45 mmol/L), which is converted to bicarbonate on an equimolar basis under physiological conditions, is used as the buffer to correct acidosis. The lactate buffer has the advantage of greater stability over a physiologic bicarbonate buffer. However, lactate is thought to have negative effects on hemodynamic parameters, and on metabolic parameters, e.g. enhanced protein catabolism and decreased regeneration rate of ATP due to the fact that conversion from lactate to bicarbonate needs energy.

Only a few studies until now compare different buffers used in substitution fluids. From these data it seems to be common sense that acetate-buffered substitution fluids should be avoided, as a significantly reduced control of acidosis compared to a lactate-buffered solution has been recently reported during CVVH.

Solutions used in peritoneal dialysis have also been recommended as an alternative, but their high glucose concentration can lead to incomplete metabolism, requiring additional insulin with concomitant metabolic alterations in MODS patients.

Some studies are dealing with bicarbonate-buffered compared to lactate-buffered solutions. Major goals in these studies had been: control of uremia, control of

acidosis and lactate concentration, metabolic changes, hemodynamic parameters and the concentration of the important serum electrolytes.

Uremia and acidosis (pH, base-excess) are sufficiently controlled during CRRT with an exchange volume of in average 30 L using either buffer. If patients with severe liver failure and lactic acidosis were excluded, no difference in hemodynamic and metabolic parameters between the solutions occurred. Plasma lactate concentration was elevated during lactate use in some cases, but lactate levels remained within normal limits in patients without liver impairment. Bicarbonate concentration in the solutions should exceed 35-40 mmol/L as in some cases the buffer capacity of the solutions were inadequate. In patients with severe liver failure or lactic acidosis solutions with lactate buffer were shown not to be indicated.

Under stable clinical conditions 2000 mmol of lactate per day are metabolized to bicarbonate on an equimolar basis. Critically ill patients with ARF, especially with concomitant sepsis or circulatory shock have been reported to display a reduced lactate tolerance. In these cases or with the use of the high-volume hemofiltration using an exchange volume of 4-6L/hour the physiological capacity of the liver in converting lactate to bicarbonate may be exceeded.

In our first experience, nitrogen excretion was significantly increased in patients receiving lactate-buffer on day 1-4 of CRRT, a result we could not reproduce in a later study. But lactate- associated protein catabolism may be relevant using high amounts of substitution fluids.

Bicarbonate-solutions must be stable for a 24 hour period without precipitation of calcium carbonate or magnesium carbonate. Therefore, the magnesium and calcium concentration is reduced compared to the lactate-buffered solution. To adjust ionic strength the chloride concentration must be increased. Possible precipitation does not allow a higher phosphate concentration in one of the solutions, so phosphate must separately be substituted to avoid phosphate depletion, as MODS patients with ARF tend to develop hypophosphatemia leading to decreased respiratory and cardiac function. The patients serum concentration of these electrolytes must therefore carefully be monitored and

other electrolytes must be added if necessary. Especially the magnesium concentration in bicarbonate-solutions may be insufficient in patients with arrhythmias or depleted cardiac function.

Two other major problems may occur in daily use of bicarbonate-solutions:

- a) The solution has to be mixed immediately before use from a buffer-free electrolyte solution and the bicarbonate-buffer. It must be realized that the administration of the buffer-free electrolyte solution may endanger the patients and it must be secured that the lone application of either the buffer or the buffer-free solution is impossible.
- b) The readily mixed bicarbonate-buffered solution has to be prepared in bags of special plastic sheeting to prevent evaporation of carbon dioxide. The solution must be stable for at least 24 hours without precipitation of calcium carbonate or magnesium carbonate.

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8.2 Sample CRRT Orders

| Yes | No | Doctor must check off appropriate orders |
|-----------------|----|---|
| Signature _____ | | |
| 1. | | Priming : ? M100 filter ? Other _____ ? CVVHDF Mode ? Other _____ |
| 2. | | Prime Solution : (please choose one) ?? Heparin 5,000U in 1L NS, total prime volume 2L ?? NO HEPARIN, N/S 2L for HIT patients |
| 3. | | Solutions : Dialysate : ? Normocarb 240mL/3L bag Sterile Water for Irrigation ?? Other : _____ Replacement : ? _____ |
| 4. | | Flow Rates : Blood Flow Rate : ? 100 mL/min ? Other : _____ mL/hr Dialysate Rate : _____ mL/hr (approx. 20mL/Kg) Replacement Rate : _____ mL/hr (for citrate protocol, start at 0mL/hr) Patient Fluid Removal Rate Calculation : (please fill in all spaces) Net Ultrafiltration rate _____ mL/hr + citrate rate _____ mL/hr + Ca++ rate _____ mL/hr + NS flush rate _____ mL/hr = _____ mL/hr Patient Fluid Removal Rate |
| 5. | | Anticoagulation (please choose one) ?? Citrate as per CrCU Citrate Protocol (as printed on reverse) ?? Heparin : (Not to be ordered if on systemic heparin) Initial Heparin Bolus _____ Units IV Heparin 1000U/mL via 20mL syringe to run at _____ U/hr Maintain PTT in range _____ secs.(recommend 35-45s) Monitor PTT q6h. Notify physician if out of range ?? NS flush _____ mL, q _____ hour ?? None |
| 6. | | Lab Work : ? Electrolytes, BUN, Cr q6h ? Ca++ profile, BS, CBC q12h |
| 7. | | Other : ? CaCl infusion 4gms in 1L D5W at 50mL/hr via central line |

17-Bicarbonate Dialysis for Hepatic Failure and Lactic Acidosis: Tobe PRIMSA M100 Protocol

? If $K^+ < 3.5$ mmol/L, add KCl 3 mmol/L to dialysate (ie.

9mmol in 3L bag)

? For Corrected $Ca^{++} < 2.0$ mmol/L, give CaCl 1gm in 100mL NS
over 2hrs via central

line. Cancel any previous Ca^{++} bolus orders.

8. For temporary disconnection, maintain dialysis catheter with :
(choose one)

?? Heparin 1,000U in 500 mL NS

?? NO HEPARIN, NS 500 mL (for HIT patients)

8.3 Acute Renal Failure (ARF)

An abrupt decrease in renal function accompanied by an increase of the plasma creatinine by 50 to 100 $\mu\text{mol/L}$ daily (1 mg/dl). ARF complicates approximately 5% of hospital admissions and up to 30% of admissions to intensive care units^{1,2}. Most ARF is reversible. The causes of ARF can be divided into three main groups: Hypoperfusion of the kidneys where the parenchymal tissue is preserved (prerenal ARF, 55% of cases); Disease of the renal parenchyma itself (renal ARF, 40%); and Diseases causing obstruction to urine flow from the kidney (postrenal ARF, 5%). Most cases of renal ARF are caused by acute tubular necrosis usually caused by ischemia of the most oxygen dependant part of the kidney the actively absorbing tubules.

The mortality rate for acute renal ARF approximates 50% and has changed little in the last thirty years². Mortality rates are much higher when accompanied by other system failure, particularly respiratory failure following trauma or major surgery. Oliguria (urine output < 400 ml/d) at the time of presentation is associated with a poorer prognosis and likely reflects a more severe renal injury and or underlying disease^{3,4}. Mortality rates are higher in older debilitated patients and those with multi-organ system failure⁵⁻⁷.

Most patients who survive ARF recover enough renal function to live normal lives. Renal recovery often occurs prior to transfer from the ICU but may take 4-6 weeks to resolve. Patients treated with a form of dialysis known as continuous renal replacement therapy (CRRT) are switched to standard hemodialysis or even peritoneal dialysis after transfer out of the intensive care setting. The average duration of therapy with continuous renal replacement therapy is 6.75 days⁸. There is a trend toward more therapy with CRRT vs. Intermittent hemodialysis for patients with ARF in the ICU.

Why CRRT and not intermittent Hemodialysis

Acute renal failure in the intensive care unit is accompanied by metabolic derangements and high overall mortality. Acute intermittent hemodialysis (HD) has been the standard therapy in the past but problems with the rapid correction of fluid and electrolytes have led to the development of continuous renal replacement therapies. The standard dialysate for intermittent HD is now bicarbonate buffered. Bicarbonate dialysate has definite advantages, in critically ill patients, over acetate dialysis which is associated with vascular instability and hypoxia⁹ and lactate based dialysate in the acute setting has also been associated with lower blood pressures¹⁰. Bicarbonate dialysate has only been possible in the intensive care unit with intermittent HD, however, CRRT is felt to offer advantages over intermittent hemodialysis for critically ill patients in the intensive care setting^{11,12}. During CRRT, dialysis occurs 24 hours-a-day. Solute and volume removal are continuous, eliminating the large shifts occurring between body compartments during intermittent HD which may lead to

hypotension and interfere with renal recovery. For intermittent HD to achieve the same solute clearance as CRRT may require 5 or more sessions weekly¹³, with resulting resource implications. Thus there are theoretical advantages to bicarbonate CRRT over intermittent HD. CRRT has not yet been shown to be superior to intermittent HD in terms of renal recovery and patient survival¹⁴. This may be due to insufficient patient numbers in studies or possibly due to other factors such as sub-optimal dialysate solutions used for CRRT.

Intermittent HD in the ICU uses regular hemodialysis machines which do not use sterile dialysate, although the dialysate is clean and largely pyrogen free. There is a theoretical and practical advantage for using sterile dialysate. In chronic HD, a limited but significant number of pyrogenic reactions occur, and these can be reduced by filtering the dialysate¹⁵. Up until now, no commercially available sterile bicarbonate was available for CRRT and those units wishing to use this dialysate had to rely on their hospital pharmacy to prepare it. Because of the expense of preparing sterile dialysate in quantity, most pharmacies are unwilling to produce such solution for any length of time.

Modalities of CRRT in the ICU

The simplest form of CRRT which uses the most physiologic semipermeable membrane is peritoneal dialysis. However, the peritoneum or diaphragm has often been violated surgically or through trauma, there is often respiratory compromise and the risks of hyperglycemia and peritonitis, as well as the need for surgical implantation of the catheter make this an important but infrequently used modality. There is some early evidence that extracorporeal forms of CRRT may offer advantages in survival over peritoneal dialysis^{11,12}.

Extracorporeal circuits for conducting renal replacement therapy may be driven by the patient's own blood pressure using arterial and venous access or may be pump driven using only venous access. Those with arterial and venous access are denoted with (CAV) for continuous arterial venous, and those using a pump and only venous access are denoted as (CVV) for continuous veno-venous, indicating that blood is pumped from a vein and back into a vein. Therapy that results only in slow ultrafiltration is referred to as CAVUF or SCUF for short (slow continuous ultrafiltration) or CVVUF for the pump driven venous circuit. High volume ultrafiltration with replacement solution to prevent volume depletion, where the filtered volume is large enough (ie. 12 - 18 litres per day) to give some solute clearance (100% by convection) is designated as CAVH or CVVH. When dialysis solution is passed across the membrane to increase clearance (diffusion), hemodialysis results, CAVHD and CVVHD. When both hemodialysis and hemofiltration are used, it is called hemodiafiltration, CAVHDF or CVVHDF. Whether hemodiafiltration has an advantage over hemodialysis has not yet been shown, and the high cost of replacing liters of crystalloid daily, has resulted in the use of CAVHD and CVVHD as the standard modalities in many critical care units.

Veno-venous dialysis eliminates the need for prolonged arterial access, reducing potential morbidity, but requires a blood pump, with attendant air, blood leak and pressure detectors and alarms. Many devices are available which can carry out veno-venous dialysis safely, without requiring an additional nurse for patient management.

Why bicarbonate dialysate is preferable

During the development of chronic dialysis, bicarbonate buffered dialysate was made at the bedside, but had a risk of bacterial growth and endotoxin contamination. Machines to make dialysate online were developed but because calcium and bicarbonate could not be stored in the same concentrate because of precipitation, acetate dialysis was developed. When the technology for dual proportioning machines became available, most units switched back to bicarbonate dialysate. It is possible to use the less expensive single proportioning machines, with calcium free bicarbonate buffered concentrates, and deliver calcium directly to the blood stream¹⁶.

Bicarbonate dialysate has definite advantages, in critically ill patients, over acetate dialysis which is associated with vascular instability and hypoxia^{9,17}. Lactate may not be benign in high doses. Davenport et al.¹⁰ studied the effect of lactate dialysate during machine hemofiltration in 22 patients with acute renal failure, felt to be too unstable to tolerate standard acetate hemodialysis, and also in 12 patients with chronic renal failure, as controls. During the lactate load hyperlactatemia occurred in all patients, but was significantly greater at all times in the patients with acute renal failure. The serum bicarbonate concentration increased in the CRF group (24.9 mmol/L post treatment vs. 22.0 mmol/L pre treatment), but dropped slightly in the ARF group (21.3 mmol/L post treatment vs. 21.4 mmol/L pre treatment). Of interest 55% of the patients in the ARF group had a decline in serum bicarbonate levels vs. only 10% in the CRF group. Changes in hydrogen ion concentration correlated significantly with increases in blood lactate levels. Mean arterial pressure fell during CVVH in the ARF group (85 pretreatment to 67 post treatment $p > 0.05$), while it remained stable in the CRF group suggesting an increased sensitivity in the more critically ill patients. They concluded that lactate administration greater than the utilization threshold, particularly in the most critically ill patients, resulted in accumulation, worsening the acid-base status¹⁰.

Jenkins et al.¹⁸, studied six pediatric CAVHD patients during seven episodes of metabolic acidosis which were not corrected with lactate or acetate dialysate. After switching to bicarbonate dialysate improvements in pH and serum HCO₃ were seen in all seven cases, particularly those with the most marked elevations of the anion gap. They concluded that bicarbonate dialysate may be preferable to lactate or acetate dialysate in CAVHD patients with persistent metabolic acidosis¹⁸.

Concerns have been raised that the infusion of large quantities of D,L-lactate from Ringer's solution or peritoneal dialysis solution could lead to increased catabolism and cerebral dysfunction^{19,20}. Also hyperglycemia may be induced by peritoneal dialysis solution which has a high glucose concentration. Lactate based solutions are kept at low pH, usually 5.4 to prevent caramelization of the glucose solution. The effect of continuously exposing blood to such a low pH solution is unknown.

Why bicarbonate dialysate is not easy to use in the ICU

Although bicarbonate buffered dialysate is the preferred dialysate for CRRT its use is limited by the nature of bicarbonate solutions. If left for periods of time bicarbonate solutions are at high risk for bacterial growth and endotoxin contamination and CO₂ loss leads to loss of bicarbonate. Calcium cannot be exposed to the solution, particularly bicarbonate concentrates or else precipitation will occur. In intermittent HD, clean bicarbonate dialysate with calcium is proportioned by an expensive machine. Bicarbonate buffered solution for peritoneal dialysis is not yet available, although attempts at stabilizing solutions with glycylglycine are ongoing²¹. Bicarbonate buffered dialysate can be prepared by the pharmacy, but it must be used quickly, before precipitation or loss of CO₂ and the effort to sterilize such fluid in the quantities needed may overstretch the pharmacies resources. Dialysate produced from hemodialysis machines can be carried to the ICU in jugs or bags but is not sterile and must be used quickly. Leblanc et al. describe such a method with backfiltering to reduce the risk of bacterial contamination²², and use this solution up to 72 hours. However, it requires technical support and storage facilities.

Present experience with bicarbonate dialysate in the ICU

On-line bicarbonate production requires a hemodialysis machine, care to prevent precipitation of bicarbonate with calcium or magnesium and the risk of bacterial overgrowth and endotoxin production. Tam et al. working with the late Dr. P.R. Uldall, developed a method of CVVHD which used dialysate produced from bicarbonate proportioning machines and a brilliantly simple method to adjust the ultrafiltration rate^{23,24}. However, the dialysate had to be prepared by a technical team, transported to the ICU and could only be stored for hours. Leblanc et al. have reported successful use of bicarbonate dialysate for CRRT produced from an Althin-1000 dialysis machine (Althin CD Medical Inc, Miami, FL)²². Dialysate was backfiltered through a hollow-fiber polysulphone dialyser drained into sterile 12-15-L plastic bags and stored a maximum of 72 hours prior to use for CRRT. In 13 patients treated with both lactate and bicarbonate buffered solutions bicarbonate levels were significantly higher during bicarbonate dialysis (21.8 ± 3.4 vs. 17.8 ± 3.1 mEq/L, $p=0.002$). Glucose levels were also significantly lower in the bicarbonate treated group²². One other study has looked at bicarbonate dialysis during CRRT in pediatric patients and found an improvement of metabolic control using bicarbonate over lactate or acetate dialysate¹⁸.

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24-Bicarbonate Dialysis for Hepatic Failure and Lactic Acidosis: Tobe PRIMSA M100 Protocol

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8.4 Description of Normocarb and Scientific Rationale for its use.

Normocarb is a bicarbonate buffered dialysate concentrate designed to produce 1080 ml of sterile bicarbonate dialysate when added to 1000 ml of sterile water under aseptic conditions. The final electrolyte composition of the dialysate when diluted appropriately is as follows (in mmol/L).

| | |
|------------------|-------|
| Na | 140 |
| K | 0 |
| HCO ₃ | 35 |
| Mg | 0.75 |
| Cl | 106.5 |
| Glucose | 0 |
| Calcium | 0 |

The following is the rationale for the choice of the above electrolyte composition.

Glucose

Historically glucose was added to peritoneal dialysis solutions to facilitate ultrafiltration by maintaining an osmotic gradient between the blood and dialysate¹. Presently dialysates for chronic hemodialysis may be glucose free or normoglycemic (0.2-0.25% dextrose). Hemodialysis against a glucose free dialysate results in a net glucose loss of approximately 1 gm per litre fully equilibrated dialysate, or 24 to 36 gm per day during CRRT. This may induce ketogenesis or gluconeogenesis in chronic dialysis patients who may be malnourished or who are receiving beta-blockers². Patients on CRRT with a glucose free dialysate could be at risk if no additional glucose support such as dextrose in water by intravenous or total parenteral nutrition (TPN) or oral feeds was provided. Dextrose free dialysate enhances potassium clearance³. Therefore dextrose was left out for practical reasons. To prevent caramelization of dextrose the pH must be kept low. This is the reason that peritoneal dialysis fluid is kept at pH 5.4. Patients often complain about pain on filling, and this has been linked to the low pH. Patients with ARF are usually quite acidemic and it is counter-intuitive to dialyze against a low pH solution. Additionally, terminal sterilization of peritoneal dialysis solution can produce glucose degradation products which are thought to be harmful to the vascular endothelium. A dextrose free solution avoids these problems, however, care must be taken in the ICU setting to ensure that a patient is at least receiving a dextrose in water drip (ie. D5W at 20 cc/hour provides 1 gm glucose per hour). In a recently completed trial, Zimmerman et al. there was no statistically difference in glucose levels between the Normocarb (glucose free) and lactate (glucose 0.5%) groups.

Sodium

Dialysate sodium was maintained at hypo-osmolal levels in chronic dialysis to reduce interdialytic weight gain and thirst. However, this induced fluid shifts and predisposed patients to hypotension during dialysis. Dialysate sodium levels are now typically 138-143 mmol/L during chronic dialysis⁴. As 140 is the normal serum sodium concentration this was chosen for Normocarb.

Potassium

Most patients dialysed for acute renal failure have hyperkalemia. The dialysate was therefore formulated with no potassium. However, as dialysis for more than a few days will result in potassium losses, potassium often must be added later. This is easily accomplished by adding 3 or 4 mmol/L to the dilute solution.

Bicarbonate

In chronic haemodialysis bicarbonate was the initial buffer of choice. However, because of its instability in aqueous solutions at neutral pH in the presence of divalent cations, acetate was substituted in the early 1960's. Acetate is no longer used in chronic dialysis because with newer large surface area, high flux membranes, acetate flux of 300 mmol/hour or more can occur, resulting in acetate accumulation as the amount translocated exceeds the patients capacity to metabolize the base⁵. Patients exposed to large amounts of acetate developed nausea, peripheral vasodilation, decreased myocardial contractility, metabolic acidosis and hypoxemia⁶. Hypoxemia during acetate dialysis was thought to be caused by loss of CO₂ into the dialysate. The respiratory rate decreased maintaining an unchanged arterial carbon dioxide level, resulting in lower oxygen saturations from a reduced minute ventilation by approximately 25%⁷.

Hemodialysis with a bicarbonate buffered dialysate prevents these complications. Bicarbonate in the dialysate prevents loss of bicarb from the blood into the dialysate as happens when acetate or another buffer is used and does not lead to hypoxemia. Bicarbonate concentrates support the growth of gram-negative bacteria such as *Pseudomonas*, *Acinetobacter*, fungi and yeast⁸. Strict guidelines have been developed for the acceptable limit of bacterial growth and for the presence of pyrogen(lipopolysaccharide) in the dialysate for chronic dialysis which is not sterile. Bicarbonate buffered dialysate in the range of 30-35 mmol/L has been recommended. Most chronic hemodialysis units set their machines to provide bicarbonate levels of 35 mmol/L to adequately deal with patients acidemia. Bicarb levels higher than 40 mmol/L have an increased risk for development of metabolic alkalosis⁵.

Calcium

Patients on chronic dialysis are susceptible to hypocalcemia and an attempt is made to provide a positive calcium balance to prevent renal osteodystrophy. In the setting of renal failure requiring dialysis, 61% of calcium is not bound to plasma proteins and is in a diffusible equilibrium during hemodialysis⁹. As a result calcium may be lost in a calcium free dialysate up to 40 mg/L (1.0 mmol/L). This can be prevented by adding calcium into the dilute dialysate at 1.75 mmol/L or 7.0 mg/dl or giving calcium intravenously at the same rate it is being lost. Reductions in ionized calcium have been linked to increased vascular instability during hemodialysis⁴.

Chloride

This is the main anion in the dialysate. Because its concentration is defined by the constraints of maintaining electrical neutrality in the dialysate, the concentration is dependent on the concentration of the cations and bicarbonate.

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8.5 Normocarb Product Information

THERAPEUTIC CLASSIFICATION

Dialysate Concentrate for Hemodialysis.

DEVICE DESCRIPTION

A clear, sterile, nonpyrogenic, calcium-free bicarbonate renal dialysis concentrate.

Composition:

NORMOCARB (Undiluted): NORMOCARB contains 82.84 g/L sodium chloride (NaCl), 2.06 g/L magnesium chloride (MgCl₂) and 39.7 g/L sodium bicarbonate (NaHCO₃) in water for injection.

Dialysate Solution [NORMOCARB (Diluted)]: The dialysate solution (diluted NORMOCARB), when prepared as directed, contains the following:

| Component | Concentration | |
|---------------------------------|---------------|---------|
| | (mMol/L) | (mEq/L) |
| Sodium (Na) | 140.0 | 140.0 |
| Magnesium (Mg) | 0.75 | 1.5 |
| Chloride (Cl) | 106.5 | 106.5 |
| Bicarbonate (HCO ₃) | 35.0 | 35.0 |
| Total Anions | 141.5 mEq/L | |
| Total Cations | 141.5 mEq/L | |

The nominal measured final conductivity of the dialysate solution is 140 mmhos/cm at 25°C.

If required in patients on insulin or with hypoglycemia, 12 mL of D50W may be added to the sterile water when preparing the dialysate to provide a concentration of 10.2 mEq/L of dextrose in the diluted solution.

Potassium chloride may be added by physician's orders, usually up to 4 mEq/L. Calcium chloride [up to 1.25 mMol/L (2.5 mEq/L)] may be added to the diluted solution by physician's orders.

INTENDED USE/INDICATIONS

NORMOCARB, after dilution, is indicated for use in Continuous Renal Replacement Therapy (CRRT).

Continuous renal replacement therapy is a dialysis continued 24 hours a day to treat critically ill patients with renal failure. NORMOCARB is not approved for infusion.

CRRT is usually administered to patients in intensive care who require dialysis and are hemodynamically unstable, or whose liver function is either impaired or at risk of impairment. Patients with liver impairment typically are more challenging to manage and may have high requirements for bicarbonate due to ongoing lactic acidosis. Use of lactate- based solutions for dialysis may not correct metabolic acidosis if the liver cannot metabolize more lactate into bicarbonate. The bicarbonate-free lactate-containing dialysis solution will actually remove some bicarbonate from the patient. In addition to a bicarbonate-based dialysis solution, patients with liver impairment and/or severe metabolic acidosis may require additional intravenous infusions of bicarbonate to maintain their pH within acceptable parameters.

The aims of CRRT are control of fluid balance, control of plasma electrolytes, control of acid-base balance and removal of products of metabolism.

CONTRAINDICATIONS

There are no known contraindications to the use of NORMOCARB.

WARNINGS AND PRECAUTIONS

NORMOCARB IS NOT FOR INFUSION.

After prolonged dialysis there is a risk of hypocalcemia and even the possibility of hypoglycemia. This can be prevented with ongoing nutrition, monitoring and replacement, if necessary.

NORMOCARB must be diluted with sterile water before use. DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY OTHER DILUENT EXCEPT STERILE WATER.

The patient's hemodynamic, fluid, electrolyte and acid-base balance should be monitored throughout the procedure.

Since NORMOCARB is potassium- and calcium-free, close monitoring of the patient's potassium and calcium levels must be carried out during CRRT. It is recommended that these levels are followed twice daily or according to local CRRT protocols.

NORMOCARB must not be used if a precipitate has been formed or if container seals have been damaged.

NORMOCARB should not be used in dialysate proportioning intermittent hemodialysis machines.

Use in Pregnancy:

No information is available on the use of NORMOCARB during pregnancy.

Administer to pregnant women only if clearly needed and the potential benefit outweighs the potential risk.

ADVERSE EVENTS

The most common complications during hemodialysis are, in descending order of frequency, hypotension (20 - 30%), cramps (5 - 20%), nausea and vomiting (5 - 15%), headache (5%), itching (5%), chest pain (2 - 5%), back pain (2 - 5%), and fever and chills (<1%).

Less common but serious complications observed during hemodialysis include disequilibrium syndrome, hypersensitivity reactions, arrhythmia, cardiac tamponade, intracranial bleeding, seizures, hemolysis and air embolism. Healthcare practitioners should also be aware that dialyzer reactions may occur in patients.

DOSAGE AND ADMINISTRATION

NORMOCARB MUST BE DILUTED BEFORE USE. For dilution, one 240 mL vial of NORMOCARB should be added to 3 L of sterile water to make 3.24 L of dialysate solution. See RECONSTITUTION below for detailed instructions.

Individualization of Treatment:

The volume of dialysate solution (diluted NORMOCARB) administered will depend upon the fluid balance of the individual patient, the target fluid balance to be achieved, the body weight and the amount of fluid removed from the patient's circulation during the process of dialysis. **DOSAGE MUST THEREFORE BE AT THE DISCRETION OF THE PHYSICIAN.**

The usual dosage range commonly used is as follows:

Adults: Usual dialysate flow rate is 1000 to 2000 mL/hr or 20 mL/Kg/hr.

Children: Usual dialysate flow rate is 2 L/1.73 m²/hr.

Elderly: Usual dialysate flow rate as per adults but will depend on the hemodynamic condition of the elderly patient.

For patients requiring dextrose, D50W may be added to the dialysate according to physician's orders (see RECONSTITUTION below for detailed instructions).

RECONSTITUTION (Preparation of Dialysate Solution Using NORMOCARB and Sterile Water)

Requirements:

? NORMOCARB, 1 vented IV transfer set, 1 20 G needle

? 3 L of sterile water

? Alcohol swabs

Important Considerations Before Reconstitution:

NORMOCARB must be diluted before use with sterile water only -- do not use normal saline, Ringers Lactate or any other diluent. D50W may be added to sterile water, if required by physician's orders, as described in the method below. Do not manufacture more dialysate than can be used in a 24-hour period.

Method:

- 1) Remove bag of sterile water from outer protective bag and wipe injection port on bag with alcohol swab.
- 2) Using aseptic technique:
 - a) Assemble IV line, needle, and close clamp
 - b) Spike vial
 - c) Connect needle to bag
- 3) Using vial hanger, hang vial from IV pole.
- 4) Open clamp and empty contents of one 240 mL vial into a 3 L bag of sterile water to make 3.24 L of dialysate.

- 5) **Special Consideration:** For patients requiring dextrose, 12 mL of D50W may also be added to the bag of sterile water, to make 3.25 L of dialysate with a concentration of dextrose of 10.2 mEq/L according to physician's orders.
- 6) Clamp IV line.
- 7) Remove "Medication Added" sticker from vial, fill out required information and apply to bag.
- 8) Disconnect needle and IV set.
- 9) Shake to mix by rocking or rolling the bag and contents thoroughly. When diluted, solution contains approximately (mEq/L): Na 140, Mg 1.5, Cl 106.5, HCO₃ 35.0.
- 10) Connect bag to CRRT dialysis circuit and institute dialysis.

COMPATIBILITY

NORMOCARB is physically and chemically compatible with a wide variety of diluents. **HOWEVER, FOR USE IN DIALYSIS, NORMOCARB MUST BE DILUTED WITH STERILE WATER. DO NOT USE NORMAL SALINE, RINGERS LACTATE OR ANY DILUENT OTHER THAN STERILE WATER.** NORMOCARB is compatible with all systems used for CRRT.