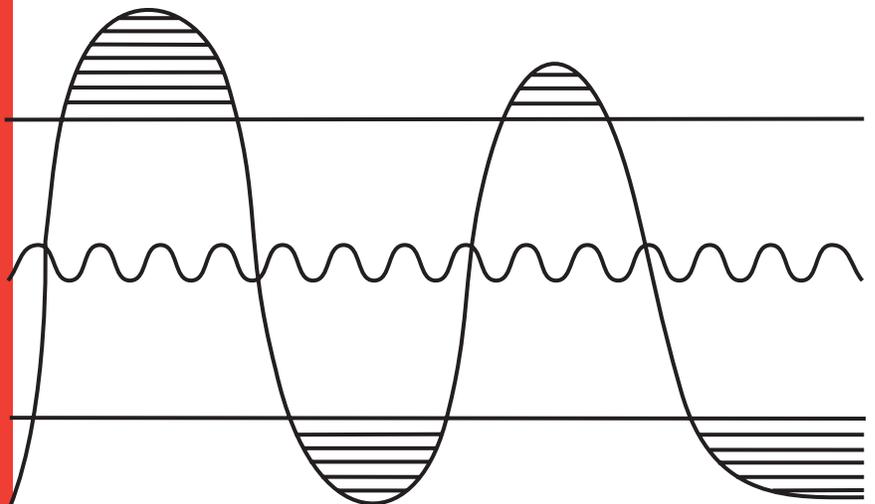


# **FACTOR REPLACEMENT BY CONTINUOUS INFUSION**

**Second Edition**



Information Paper on

# **FACTOR REPLACEMENT BY CONTINUOUS INFUSION**

**Second Edition**

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# PREFACE

This is the second edition of Factor Replacement by Continuous Infusion. The document was developed as a tool to assist health professionals who prescribe, prepare, administer or monitor factor replacement therapy. The purpose of this information paper is to remove some of the barriers to use of continuous infusion factor replacement.

Although the information in this document is current at the time of publication, drug doses, infusion methods and drug stability information may change. It remains the responsibility of all users of this document to judge its suitability for their practice. The authors and publishers assume no liability for injury resulting from use of this work.

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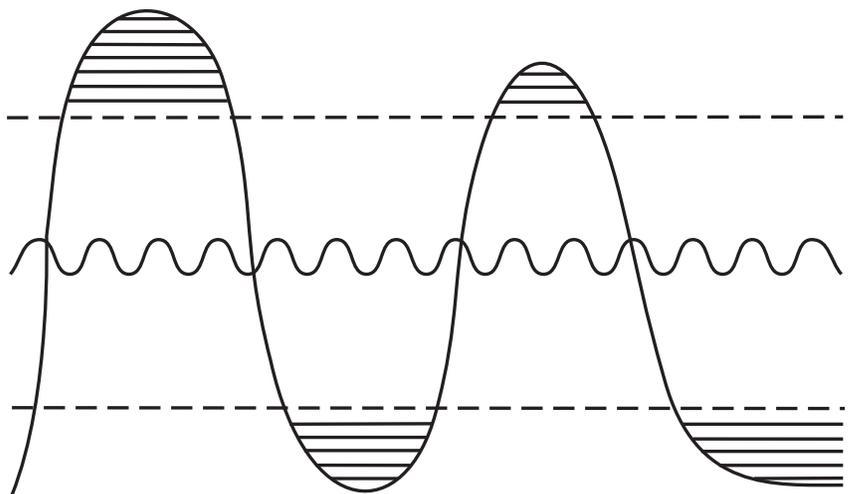
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# PART 1

# THEORY OF CONTINUOUS INFUSION FACTOR REPLACEMENT



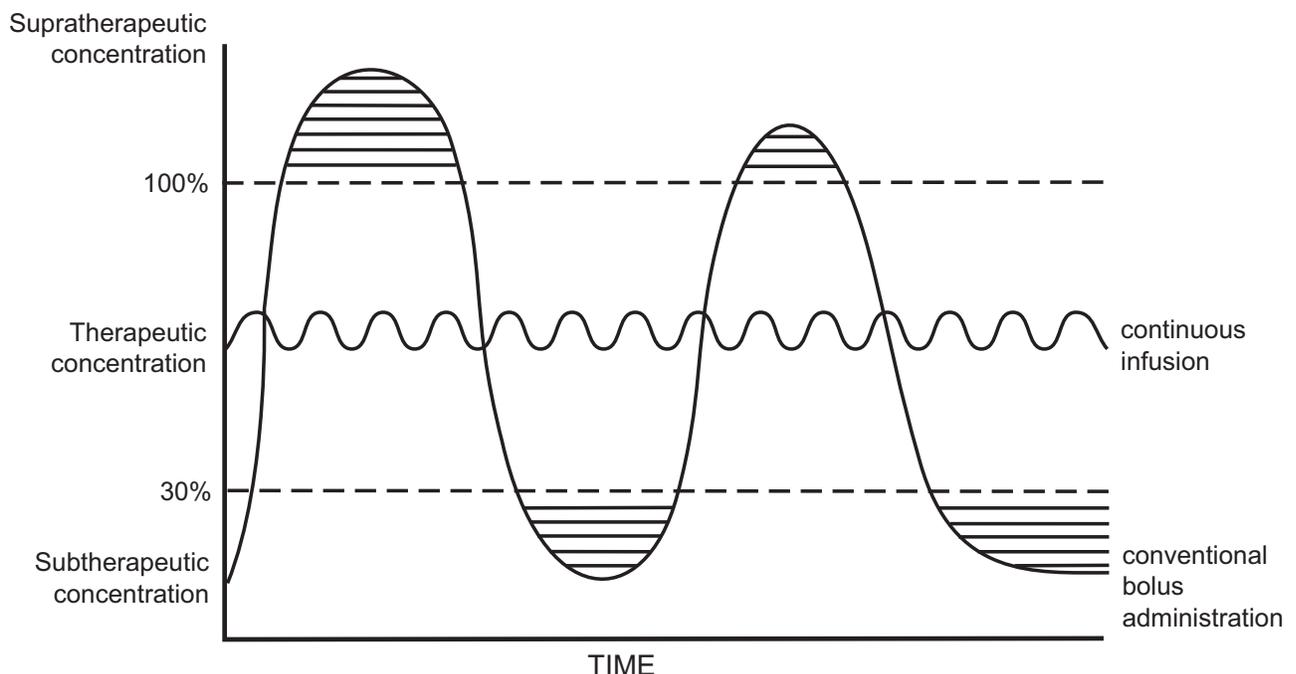
# 1.1 WHY USE CONTINUOUS INFUSION FACTOR REPLACEMENT

## Advantages of Continuous Infusion Factor Replacement

Continuous infusion factor replacement (CIFR) is not a new idea. The earliest report of CIFR dates back to 1970<sup>1</sup>. The safety and effectiveness of CIFR has been shown by several investigators<sup>1-14</sup>. Most information about CIFR comes from studies of Factor VIII replacement in patients with hemophilia A. Additional experience is being gained in patients with hemophilia B and patients with inhibitors. CIFR is the method of choice for factor replacement during surgery, trauma or serious hemorrhage. Patients may require CIFR for as little as 48 hours or as long as 3 weeks, depending upon the clinical case.

Conventional (bolus) factor replacement is associated with periods of subtherapeutic and suprathreshold factor levels (Figure 1). Suprathreshold factor levels usually occur in the early period after a bolus is administered. Subtherapeutic factor levels usually occur just prior to the next dose. Risk of bleeding is enhanced when factor levels are subtherapeutic. Suprathreshold levels contribute to increased cost of factor replacement therapy.

**Figure 1: Comparison of factor levels during conventional bolus replacement versus continuous infusion therapy**



When CIFR is administered correctly, subtherapeutic or suprathreshold factor levels rarely occur (Figure 1). CIFR is estimated to require 30% less concentrate when compared with conventional (bolus) factor replacement.<sup>15</sup> Martinowitz *et al* used CIFR and reduced the amount of factor concentrate by at least 50% while maintaining acceptable hemostasis following surgery.<sup>3</sup> **Major advantages of CIFR include decreased frequency of subtherapeutic levels, increased safety and decreased cost of factor replacement.**

For many patients, CIFR provides therapy with greater convenience. It eliminates the need for multiple, timed bolus injections. Ambulatory patients need not schedule their activities around factor dosing times. Scheduling of invasive procedures is made easier because subtherapeutic blood levels occur rarely. Hospitalized patients are less worried that their factor replacement therapy will be forgotten by busy staff. In hospitals, CIFR can reduce the risk of “late dose” medication errors. Blood level monitoring can be scheduled more conveniently because blood levels are influenced less by timing relative to dose administration. In addition, blood level monitoring can usually be reduced (compared with bolus replacement monitoring).

### **Disadvantages of Continuous Infusion Factor Replacement**

There are several reasons why the clinical, cost and convenience advantages of CIFR are not available to all patients who require factor replacement. For health care workers who are familiar with bolus factor replacement, switching to CIFR means learning a new set of parameters. Lack of familiarity with infusion devices may present the greatest stumbling block for some people. For others, it might be difficult to obtain an appropriate infusion device. Still other people might be uncomfortable learning or performing different dosage calculations. Information about extended stability (stability beyond times specified in the manufacturers’ inserts) may not be readily available. Depending upon current policies for conventional factor replacement in some centres, it may be necessary to increase the frequency of factor monitoring in the first 72 hours after surgery. For other centres, limited weekend or evening availability of factor level monitoring may be a barrier to CIFR. This can usually be worked around if surgical procedures are scheduled early in the week. Finally, there may be concerns regarding the sterility of concentrates that remain in an infusion device for longer than 24 hours.

### **Why does continuous infusion factor replacement require less product?**

Conventional (bolus) factor replacement is associated with periods of supra-therapeutic factor levels (Figure 1). Suprathreshold factor levels usually occur shortly after a bolus is administered. When CIFR is administered correctly, factor levels remain within a narrow therapeutic range (e.g., just enough to maintain hemostasis but not enough to cause high factor levels). Using CIFR to keep factor levels neither too high nor too low requires approximately 30% less factor compared with bolus replacement therapy.

**What is the desired factor level during continuous infusion factor replacement?**

It is important to remember that CIFR studies have maintained factor levels at lower levels than have been used historically in patients receiving conventional bolus therapy. In patients with severe hemorrhage, CIFR target levels have ranged from 30% to 50%.<sup>3,4,11</sup> In patients undergoing surgery, target ranges of 40% to 70% have been used.<sup>3,4,11</sup> If factor levels are maintained at levels greater than 70% during CIFR, cost savings through reduced factor use are unlikely to occur.

**When should continuous infusion factor replacement be used?**

Most of the CIFR experience has been in patients undergoing surgery (during the perioperative period) and for acute treatment of major bleeding episodes. Long-term ambulatory CIFR is being evaluated in some centres, but it is not yet considered to be standard therapy. CIFR should be used only in health facilities with the expertise needed to carry out CIFR in a safe, effective manner.

## **1.2 WHAT INFLUENCE DO VOLUME OF DISTRIBUTION, CLEARANCE, BIOAVAILABILITY AND DRUG STABILITY HAVE ON FACTOR DOSING?**

When a dose of factor concentrate is calculated for a patient, three major assumptions are made:

**Assumption 1: Factor distributes into body fluids in a reliable, reproducible way.**

**Volume of distribution** is the pharmacokinetic term used to describe factor distribution in the body. Most factor dose calculations are based upon the arbitrary assumption that factor distributes only into plasma. For example, 1 unit/kg of Kogenate is expected to raise the plasma factor activity level by 2% (Table 1). If the volume of distribution increases (e.g., factor distributes to sites other than plasma or plasma volume increases), the expected increase in factor activity will not occur.

**Assumption 2: 100% of the factor dose is available to the body.**

**Bioavailability** is the pharmacokinetic term for the portion of a dose that is available at the site of drug action.<sup>16</sup> How factor products are prepared influences bioavailability. For example, bioavailability is reduced if factor decomposes during preparation or infusion.

**Stability** is a term that describes how much drug decomposes following preparation and during infusion. In general, drugs are considered to be “unstable” (e.g., having inadequate potency) if the active amount of drug declines by 10% or more when compared with the labelled amount. In the case of factor

concentrates, manufacturers indicate stability times that maintain factor activity within 95% of the labelled amount. Current literature shows that many factor products retain activity within 80% or 90% of the labelled amount for periods longer than specified in the manufacturer's product insert (Appendix 1). Factor stability influences the amount of factor needed for replacement. If a patient receives factor prepared according to the manufacturer's instructions and using the manufacturer's stability times, no change in dose is necessary. If the same patient receives factor that has exceeded its stability time and the factor has only 80% of the labelled activity at the time it is administered, the dose would need to be increased by at least 20% to achieve the same effect.

**Assumption 3: Factor is eliminated from the body at a known rate.**

Clearance is the pharmacokinetic term that is used to describe the rate that factor is eliminated from the body. Clearance is a composite of elimination by many mechanisms: consumption of factor during clotting, reaction with inhibitors, renal elimination, biliary excretion, etc. Clearance changes during factor replacement therapy because the relative contribution of clotting and other mechanisms of factor elimination changes. For example, factor clearance is usually high during the early post-surgical period. Clearance usually declines within 4 to 5 days following surgery.<sup>3</sup> Patients who clear factor rapidly require more frequent bolus doses or higher CIFR infusion rates compared with patients that have normal factor clearance.

**What is the value of doing a factor survival study prior to starting continuous infusion factor replacement therapy?**

Factor survival (factor recovery, factor half-life) studies help to define factor clearance, including clearance caused by inhibitors. Although it is possible to initiate CIFR using published dosing recommendations, for some patients these doses yield factor levels that are lower than desired. Factor survival studies can help to identify patients that will require higher than usual bolus or continuous infusion factor doses. In general, a lower than expected factor recovery indicates that a higher bolus dose might be needed to initiate CIFR. A shorter than expected half-life indicates that a higher hourly continuous infusion dose might be needed. Not all clinicians agree that doing survival studies is valuable prior to surgery, since factor survivals change in the post-operative period.

Inhibitor antibodies to Factor VIII or Factor IX in treated hemophiliacs are generally detected and quantified by Bethesda assay. The assay is used as an *in vitro* surrogate test to predict abnormalities in the *in vivo* recovery and/or half-life of Factor VIII or Factor IX. The Bethesda assay remains the method of choice for routine use but it has certain limitations:

- Low titre inhibitors may be below the limit of detectability of the Bethesda assay and yet still have potential clinical significance. Low titre inhibitors could reduce the predicted recovery (half-life) of factor in a patient who requires intensive replacement therapy for major surgery.

- The Bethesda assay may not be easily accessible in all institutions where a hemophiliac is treated. The assay can be quite variable from one laboratory to another.
- In some patients, inhibitors exhibit “Type II pharmacokinetics”. This occurs if the apparent Bethesda titre increases with progressive dilution of the sample. The resulting uncertainty in titre can make it difficult to formulate a treatment plan for factor replacement therapy.
- It is possible that some inhibitors can preferentially accelerate clearance of Factor VIII or Factor IX from the body, rather than inhibit function. This type of inhibitor would not be detected by the Bethesda assay.

### How to do a factor survival study

Prior to major surgery it is often desirable to supplement Bethesda assay testing with a direct analysis of the recovery and circulating half-life of Factor VIII or Factor IX. This should be done within a few days of the procedure. Having a short time between the survival study and the procedure prevents a false result caused by development of a new inhibitor. Ideally, the patient’s factor level should be at or near the usual baseline value (e.g., the patient should not have been treated within the previous 3 to 4 days).

The patient should be weighed and the test dose of factor (25 -30units/kg, dose rounded to the nearest complete vial) should be administered. Blood should be drawn for factor assays immediately before and immediately following factor infusion. These values can be used to calculate recovery. For half-life determination, a limited sampling strategy can be used. A limited sampling survival study requires specimens to be taken just before and immediately after factor infusion plus at least two additional specimens (e.g., pre, post, 1-2hr, and 6hr). Where practical, a more extended sampling strategy can provide more precise information. If extended sampling is done, specimens should be taken just before and immediately after factor infusion plus at least three or four additional specimens (e.g., pre, post, 1hr, 3hr, 6hr, 12hr, and 24hr); the last specimen should be taken approximately 12 hours after factor infusion. If possible, a 24 hour specimen is also helpful. Specimens do not need to be taken at precisely scheduled intervals; however, it is critical to record the exact time that specimens are collected and the test dose is administered.

**Recovery** is calculated as the increment in Factor VIII or Factor IX (post-infusion value minus pre-infusion value) expressed as percent factor level (or units) per kilogram weight. For example, a patient whose factor level increases from 10% to 55% following 30units/kg Factor VIII would have an incremental factor recovery of  $(55\% - 10\%) = 45\%$ . For this patient, the factor recovery for every 1unit/kg administered is  $1.5\%$  ( $45\% \div 30\text{units/kg}$ ).

**Half-life** is estimated from the data points or can be calculated manually or by computer. If one of the samples has a factor level approximately midway between the pre-and post-

infusion levels, this time point can be taken as a rough estimate of the half-life. For example, if a patient's level immediately following factor infusion is 80%, at 6 hours is 40% and at 12 hours is 20%, the factor half-life is approximately 6 hours (the factor level declines by half every 6 hours). For greater precision, the data can be plotted on semi-log paper with the factor level plotted on the y-axis and time from infusion plotted on the x-axis. A best-fit curve performed either manually or by computer will allow estimation of the half-life. Further information about pharmacokinetic evaluation of factor levels can be found in the article by Messori and coworkers.<sup>17</sup>

**Why is a bolus dose needed to start a continuous infusion?**

CIFR **maintains** a therapeutic level of factor activity in the body. If CIFR were given **without** a bolus dose, the **time** to achieve a **therapeutic factor** level could be **as long as 5 days!** When a bolus dose is given to initiate therapy, therapeutic levels are achieved more quickly. Similarly, if a patient's factor level declines to subtherapeutic levels during CIFR, the quickest way to return to therapeutic levels is to administer a bolus.

**What happens if an infusion is interrupted?**

When an infusion is interrupted, the level of factor activity in the blood will begin to decline. The rate of decline is determined by the patient's clearance. Patients with rapid clearance will develop subtherapeutic factor levels more quickly than patients with normal clearance or slow clearance. During the early post surgical period when factor clearance is very high, subtherapeutic levels may develop within the first hour.

**Does the time to obtain blood levels change when continuous infusion is used?**

Bolus factor replacement is usually monitored by obtaining factor levels soon after the end of a bolus infusion (also known as **peak activity**). Peak levels are strongly influenced by the infusion duration and the timing of blood sampling relative to the dose time. Blood level monitoring of CIFR is convenient because sampling time is not dependent upon timing of the bolus dose. In addition, blood level monitoring is done less frequently when patients receive CIFR compared to conventional bolus replacement therapy.

## **1.3 WHAT ARE THE PRODUCTS THAT HAVE BEEN GIVEN BY CONTINUOUS INFUSION?**

Factor VIII, Factor VIII-vWAg and Factor IX can be given by continuous infusion. There are many factor products available for treatment of coagulation disorders (Table 1). Products for which literature describing CIFR is available are indicated in Table 2. Although other products might also be appropriate for delivery by CIFR, there are no published reports of experiences with these agents.

Table 1: Summary of factor products

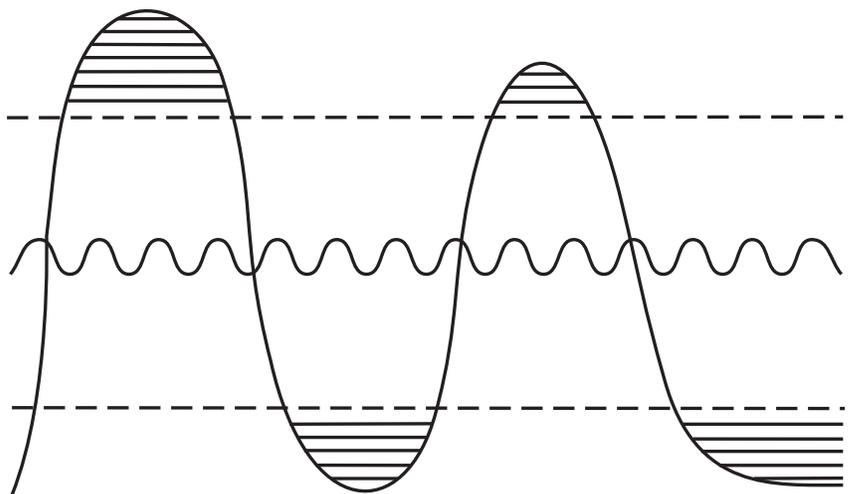
<b>Product</b>	<b>Manufacturer</b>	<b>Derivation</b>	<b>Factor</b>	<b>Dose-Response Relationship</b>	<b>Reference</b>
Alphanine SD	Alpha Therapeutic	human plasma	IX	1 units/kg increases FIX activity by 1%	18
BeneFix	Wyeth	human recombinant	IX	1 units/kg increases FIX activity by 0.4 - 1.2%	33
Bioclote	Centeon	human recombinant	VIII	1 units/kg increases FVIII activity by 2%	36
Haemate P	Centeon	human plasma	VIII-	1 units/kg increases FVIII activity by 2%	19
	(Behringwerke)		vWF	1 units/kg increases vWF:RCoF activity by 1.5%	
Helixate FS	Aventis	human recombinant	VIII	1 units/kg increases FVIII activity by 2%	47
Hemofil M	Baxter	human plasma	VIII	1 units/kg increases FVIII activity by 2%	20
Humate P	Aventis-Behring	human plasma	VIII-	1 units/kg increases FVIII activity by 2%	34
			vWF	1 units/kg increases vWF:RCoF activity by 1.5%	
Hyate:C	Speywood	porcine plasma	VIII	1 units/kg increases FVIII activity by 1.5%	21
Immunine VH	Immuno	human plasma	IX	1 units/kg increases FIX activity by 0.8%	22
Koate HP	Bayer	human plasma	VIII	1 units/kg increases FVIII activity by 2.5%	23
Kogenate	Bayer	human recombinant	VIII	1 units/kg increases FVIII activity by 2%	24
Kogenate FS	Bayer	human recombinant	VIII	1 units/kg increases FVIII activity by 2%	35
Monoclote P	Aventis	human plasma	VIII	1 units/kg increases FVIII activity by 2%	25
Mononine	Aventis	human plasma	FIX	1 units/kg increases FIX activity by 1%	26
Recombinate	Baxter	human recombinant	FVIII	1 units/kg increases FVIII activity by 2%	27
Refacto	Wyeth	human recombinant	FVIII	1 units/kg increases FVIII activity by 2%	48

Table 2: Reports of experience using continuous infusion factor replacement

Product	Reference
BeneFix	37, 38
CSL Antihæmophilic factor (AHF)	39
Factorate II	15
Haemate P	12, 40
Haemosolvate Factor VIII	41
Hemophil M	6
Hyate:C	9
Kogenate	6, 31
Konyne-80	2, 13
Monoclate M or Monoclate P	4,6,7,8,10,14
Mononine	5, 42
Octavi	3

# PART 2

# PRESCRIBING AND MONITORING CONTINUOUS INFUSION FACTOR REPLACEMENT



## 2.1 HOW TO START A PATIENT ON CONTINUOUS INFUSION FACTOR REPLACEMENT

### How to calculate the dose and infusion rate

CIFR is always started with a bolus dose of factor. This raises the factor level to the desired level. The continuous infusion is started immediately after the bolus dose is given. The continuous infusion maintains the factor level at the desired level.

Factor concentrates are supplied in vials ranging from 250units to 1500units per vial. The pharmacy or blood bank issues the number of units closest to that prescribed by the physician. Drug wastage is eliminated because only complete vials are used (e.g., for a calculated 800unit dose, 360units vial plus 510units vial could be provided). Product should not be discarded in order to arrive at the exact dose which has been calculated for the patient. Doing so increases the potential for medication errors (calculation) and increases wastage costs.

### Calculate the bolus dose of factor to achieve a desired pre-determined factor level

To calculate the bolus dose you will need to know:

- patient's weight (kg)
- desired factor level (e.g., 100%)
- the percentage increase in factor level that is produced by a given amount (units/kg) of factor (refer to Table 1 or the manufacturer's package insert).

**First**, determine how many units of factor (units/kg) will be needed to achieve the desired factor level (e.g., 100%). This is done by dividing the desired factor level by the percentage increase in factor level that is produced by a given amount of factor. For example, to achieve a desired factor level of 100% with Kogenate in patient with a native FVIII level of 0%, 50units/kg would be needed as a bolus (100% divided by 2% for every 1unit/kg administered).

**Second**, calculate the amount of factor needed for the patient you are treating. To do this, multiply the patient's weight by the number of units per kilogram calculated above. For example, a 70kg patient who needs to achieve a factor level of 100% with Kogenate would need 3500units (50units/kg multiplied by 70kg).

**Finally**, reconstitute and administer the bolus dose. The rate of administration should be adapted to the response of the individual patient. Manufacturer recommended maximum infusion rates range from 2 to 10ml/min. Most patients will tolerate infusion rates of 5ml/min. Vasomotor adverse effects (e.g., hypotension) can occur if factor concentrates are infused too quickly. Patients should be encouraged to self-administer the bolus if they are knowledgeable. The continuous infusion should be started immediately following the bolus.

**Calculate the continuous infusion dose of factor replacement to maintain the desired pre-determined factor level**

To calculate the continuous infusion dose you will need to know:

- patient's weight (kg)
- desired continuous infusion rate  
*The usual continuous infusion rate for adults is 2-4units/kg/hr. The usual continuous infusion rate for children is 4-5units/kg/hr.<sup>30</sup>*

Appendix 2 and Appendix 3 provide quick references for CIFR dose calculations.

- To use the table, look at the top of the table.
- Identify the column with the desired continuous infusion rate.
- Now identify the row that is closest to the patient's weight.
- Move across the row until you intersect with the column that corresponds to the desired continuous infusion rate.
- The number in that box is the amount of factor replacement that must be infused per hour to maintain the therapeutic factor levels following a bolus dose.

**Example:** A 70kg adult patient receiving continuous infusion Kogenate at 2units/kg/hr would need to receive 140units/hr of Kogenate to maintain therapeutic factor levels following a bolus dose.

It is a particular challenge to provide continuous infusion therapy to patients with low body weight (e.g., less than 20kg). If factor concentrate is used without further dilution (e.g., Kogenate 100units/ml), the calculated infusion rate will be below the acceptable infusion rate limits of most equipment. In these patients, factor concentrate must usually be further diluted to achieve an acceptable infusion rate. Research has shown that factor concentrate stability decreases when concentrate is further diluted.<sup>29,31,43,48</sup> Clinicians should be aware that factor dose requirements may be higher than those described above if diluted factor concentrate is used.

**What kind of equipment is needed to administer a continuous infusion?**

The equipment used to administer CIFR may differ from one Hemophilia Centre to another depending upon available equipment and prescriber preference. Selection of the optimal pump system should be based upon the degree of interaction between the concentrate and the pump material (e.g., plastic tubing), the precision, convenience, cost, size and simplicity of operation of the pump.

The equipment of choice is a low flow-rate ambulatory infusion pump or syringe pump. These systems permit concentrate to be administered without further dilution. Factor concentrates are most stable when administered without further dilution.<sup>31-32,48</sup> If a conventional volumetric pump is used, dilution of concentrate might be required to remain within the flow rate capabilities of the pump. Diluted concentrate results when reconstituted factor concentrate is mixed with normal saline in an infusion container (e.g., Buretrol<sup>®</sup>, plasma pac). Although use of either a low flow-

rate ambulatory pump or conventional volumetric pump is appropriate for CIFR therapy, ambulatory pumps offer advantages of greater concentrate stability and patient/caregiver convenience. For example, some patients may require refills of the device only once a day or even less frequently.

Sample criteria for selection of an infusion device are listed in Table 3. Additional criteria for ambulatory devices include weight of the device, portability, cost of the device, cost and availability of consumable equipment (infusion cassettes), and type and cost of service warranties.

**Table 3: Criteria for selection of an infusion device**

<b>Issue</b>	<b>Sample criterion</b>
<i>safety</i>	no risk of electric shock no source of air leak
<i>reliability</i>	minimal risk of technical problems
<i>simplicity</i>	easy to handle by professional and non-professional
<i>alarms</i>	occlusion air in line low battery general malfunction
<i>accuracy</i>	≤ 5% deviation from the declared rate
<i>precision</i>	0.1ml/hr (low-flow ambulatory pump) 5ml/hr (conventional volumetric)

**Factor Replacement via Low Flow Rate Ambulatory Infusion Pump or Syringe Pump**

- Reconstitute the factor concentrate as directed by the manufacturer. To ensure stability and sterility, concentrates should be prepared using **aseptic technique and a horizontal (Class I) laminar airflow hood, if available.**
- Determine the factor concentration (units/ml) that results.
- Calculate the hourly infusion rate by dividing the desired hourly dose by the factor concentration (e.g., hourly rate of 140units/hr using concentrate at 100units/ml = 1.4ml/hr).
- Fill the infusion device with a convenient volume of reconstituted concentrate. Ensure that the attached tubing is primed with concentrate. If the concentrate was not reconstituted and prepared in a laminar airflow hood, **the volume should be adequate to provide therapy for no more than 24 hours.** This should reduce the chance of infection if the product were contaminated during preparation.
- Administer the bolus dose IV direct (1- 5ml/min) at a rate adjusted for patient tolerance, then start the continuous infusion. To prevent thrombophlebitis and if the hourly infusion rate is too low to maintain vessel patency, the concentrate may be Y-connected to an infusion of 0.9% Sodium Chloride Injection. The reconstituted concentrate should be positioned so that there is minimal dilution with the normal saline (e.g., select the Y-site closest to the accessed blood vessel). **Central venous access should be used if it is available.**

## Factor Replacement via Conventional Volumetric Pump

- Reconstitute the factor concentrate as directed by the manufacturer. To ensure stability and sterility, concentrates should be prepared using **aseptic technique and a horizontal (Class I) laminar airflow hood, if available.**
- Dilute the factor concentrate in a reasonable volume of 0.9% Sodium Chloride injection. The dilution should be the minimum amount to make an infusion rate that can be run safely on the pump and also keep the vein patent. If concentrate reconstitution and dilution were not done using a laminar airflow hood, not more than a 24 hour supply should be prepared. This should reduce the chance of infection if the product were contaminated during preparation.
- Determine the factor concentration (units/ml) that results.
- Calculate the hourly infusion rate by dividing the desired hourly dose by the factor concentration (e.g., hourly rate of 240units/hr using concentrate at 25units/ml = 9.6ml/hr).
- Administer the bolus dose IV direct (1- 5ml/min) at a rate adjusted for patient tolerance, then start the continuous infusion.

# DOSAGE AND INFUSION CALCULATION EXAMPLES

## Patient Case #1

RS is an 8 year old male (24kg) with severe hemophilia A. He presents to the emergency department with a soft tissue bleed to his left calf. The plan is to give him a bolus dose of recombinant Factor VIII, to be followed by continuous infusion for treatment of this potentially limb-threatening bleed. The Pharmacy (Blood Bank) has “Product Y” vials of 250units/4ml, 500units/4ml and 1000units/10ml.

### 1. What initial bolus dose would be needed to achieve a level of 80%?

Table 1 indicates that 1unit/kg “Product Y” increases factor activity by 2%, therefore the bolus dose needed to increase his Factor VIII level to 80% is  $(80\% \text{ divided by } 2\%) = 40\text{units/kg}$ . His body weight is 24kg, therefore his bolus dose should be 960units (40units/kg multiplied by 24kg).

Bolus dose = 1000units (available vial size; this is 4% more than the ordered dose)

The total volume of the dose is 10ml. At 2ml/minute, the time required to give this bolus IV direct would be approximately 5 minutes.

### 2. What continuous infusion dose would be needed to maintain the level at 80%?

- To maintain the level at 80%, children require initial infusion rates in the range of 4 -5units/kg/hr.
- At a dose of 4units/kg/hr, RS would need  $(4\text{units/kg/hr} \times 24\text{kg}) = 96\text{units/hr}$ .
- Each 1000units/10ml vial would last approximately 10 hours  $(1000\text{units} \div 96\text{units/hr} = 10.4\text{hr})$ .
- If administered as a concentrate (without additional dilution), the hourly infusion rate would be 1ml/hr  $(1000\text{units} = 10\text{ml}/10\text{hr})$ .

Options for continuous administration should be identified for this patient (e.g., central versus peripheral venous access and infusion rates appropriate for each type of venous access; low flow infusion pump versus conventional volumetric pump) before proceeding with the prescription and administration of Factor VIII concentrate.

### 3. How could the infusion be administered?

Although an infusion rate of 1ml/hr is compatible with most low flow infusion devices, this infusion rate is not compatible with most conventional volumetric infusion devices.

**Assumptions:** A low flow ambulatory infusion device is available. Central venous access is not available. The minimum infusion rate for the peripheral IV to maintain patency is 10ml/hr. Review of **Appendix A** reveals that “Product Y” is most stable when prepared at a concentration not less than 83units/ml.

Although the low flow ambulatory infusion device is compatible with infusing “Product Y” at 1ml/hr, this rate is insufficient to maintain vessel patency (10ml/hr desired). One potential solution is for RS to receive his CIFR by peripheral IV by Y-connecting the Factor VIII concentrate (prepared at a concentration of 100units/ml, infusing at 100units/hr = 1ml/hr via the ambulatory infusion device) to a normal saline IV running at  $\geq 10\text{ml/hr}$  (the rate needed to maintain vessel patency) via the conventional volumetric pump.

Some infusion pumps may require special equipment for the Y-connector set-up. When infusing factor concentrates at low flow rates, remember to:

- use tubing with minimal dead space
- **prime the low flow ambulatory infusion device’s IV tubing with Factor VIII concentrate before connecting it to another line**
- **make the Y-connection at the point closest to the patient**

Failure to take these measures may result in the patient receiving no Factor VIII product for several hours. For example, if the Factor VIII hourly flow rate is 1ml/hr and the tubing dead space between the low flow ambulatory pump and the Y-site is 5ml, it may take up to 5hours for the product to reach the main IV line.

## Patient Case #2

TL is a 80kg man with severe hemophilia B who is scheduled for a total knee replacement. The plan is to administer a bolus dose of Factor IX concentrate followed by CIFR to ensure hemostasis for this procedure. The Pharmacy/ Blood Bank has BeneFix vials of 520units, 960units and 1130units per vial.

### 1. What initial bolus dose would be needed to achieve a level of 100%

Factor survival studies on TL revealed that he receives a yield of 0.8% per unit per kilogram when treated with BeneFix. The bolus dose needed to achieve a Factor IX level of 100% for this patient is (100% divided by 0.8%) = 125units/kg. His body weight is 80kg, therefore his bolus dose should be 10,000units.

$$\begin{aligned} \text{Bolus dose} &= 7 \times 960 = 6720 \\ \text{(using available vial sizes)} &+ 3 \times 1130 = \underline{3390} \\ &10110 \text{ units} \end{aligned}$$

### 2. What continuous infusion dose would be needed initially after surgery to maintain a level of 80-100%?

The physician has ordered Benefix 3units/kg/hr to be started immediately after the bolus has been given. This infusion is to be continued post-operatively.

- At a dose rate of 3units/kg/hr, TL will require (80kg)(3units/kg/hr) = 240units/hr.
- Each 960-unit vial provides (960units divided by 240units/hr) = 4 hours of therapy.
- If administered without further dilution the hourly infusion rate would be 2.4ml/hr (240units/hr ÷ 100units/ml).

Options for continuous infusion should be identified for this patient before proceeding with the administration of BeneFix. For example, what is the appropriate infusion rate for the venous access that is available (e.g., peripheral or central venous access)? What type of equipment is available (e.g., low flow rate versus conventional volumetric pump)? What is the minimum concentration of BeneFix that is stable in the equipment that is available?

### 3. How could the infusion be administered?

Although an infusion rate of 2.4ml/hr is compatible with most low flow infusion devices, this infusion rate may not be compatible with all volumetric infusion devices. BeneFix is stable for up to 7 days when prepared at a concentration of 100units/ml (Appendix A).

**Assumptions:** A syringe pump with an infusion range capacity of 1ml/hr to 100ml/hr (maximum syringe size = 50ml), and a conventional volumetric pump (minimum rate = 10ml/hr) are available. Central venous access is not available. The minimal infusion rate for the peripheral IV to maintain patency is 10ml/hr. The treating facility's policies require that not more than 24 hours of an intravenous solution be prepared at one time (e.g., for product not prepared under a laminar airflow hood).

Although the syringe pump is compatible with infusing BeneFix at 2.4ml/hr, this rate is insufficient to maintain vessel patency (desire 10ml/hr). TL could receive his CIFR by peripheral IV by Y-connecting the Factor IX concentrate (prepared at a concentration of 100units/ml, infusing at 240units/hr = 2.4ml/hr via the syringe pump) to another normal saline IV running at  $\geq 10$ ml/hr (the rate needed to maintain vessel patency).

Some infusion pumps may require special equipment for the Y-connector set-up. When infusing factor concentrates at low flow rates, remember to:

- use tubing with minimal dead space
- **prime the low flow ambulatory infusion device's IV tubing with Factor IX concentrate before connecting it to another line**
- **make the Y-connection at the point closest to the patient**

Failure to take these measures may result in the patient receiving no Factor IX product for several hours. For example, if the tubing isn't primed with Factor IX concentrate, the hourly flow rate is set at 2.4ml/hr, and if the tubing dead space between the pump and the patient is 20ml, it may take up to 8hours for the product to reach the patient's circulation.

## 2.2 HOW TO MONITOR CONTINUOUS INFUSION FACTOR REPLACEMENT

### General monitoring considerations

The IV site should be monitored for signs of phlebitis. Instruct the patient to report any discomfort at the IV site. If signs or symptoms of phlebitis occur (even in the presence of a patent vein), a new IV site should be established for CIFR. Factor concentrates are known to cause chemical phlebitis. If it is available, central venous access is the preferred route for CIFR.

**Many factor concentrates are plasma-derived blood products.** Until such time as all products are recombinant and free of serum albumin, patient-monitoring parameters used for blood products should apply during CIFR. **Other drugs should not be infused through the same line (same central venous catheter lumen) or mixed in the solution that contains factor concentrate.**

### When to do blood levels

The minimum monitoring that is required during CIFR is:

- 30 to 60 minutes after the bolus is administered
- upon arrival in the recovery room
- 8 - 24hours after the continuous infusion is started
- daily, preferably with morning bloodwork, on every day that CIFR is administered.

**NOTE:** Ready access to a Hemostasis Laboratory is desirable. Some laboratories prefer daytime and weekday hours for testing. When possible, arrange for factor monitoring to be done in the morning on a weekday.

Blood levels should also be done:

- during surgery, if there is excessive blood loss
- if the patient needs to return to surgery
- if there is evidence of bleeding
- if the continuous infusion is interrupted for 60 minutes or more
- if a supplemental bolus is given

### How to interpret blood levels taken during continuous infusion factor replacement

If the level taken 8 -12 hours after the bolus is below the acceptable range defined by the treating physician, then the continuous infusion rate is inadequate. A supplemental bolus of factor concentrate should be given to increase the blood level to the desired level and the infusion rate should be increased. The usual increase for continuous infusion is 1unit/kg/hr. **A change in infusion rate alone rarely produces the desired target level within an acceptable time frame. Giving a supplemental bolus is the fastest, most reliable way to return the factor level to the target range.**

If the level taken 8 -12 hours after the bolus is higher than the desired target level, then the continuous infusion rate is too high. If the level is extremely high (e.g., greater than 120%), levels can be lowered by temporarily stopping the infusion (usually for **no more than 60 minutes**). **In most cases, a decrease in infusion rate will be adequate to correct the high level.**

**What should be done if the factor infusion is interrupted?**

- If the infusion is interrupted more than 60 minutes, restart the infusion immediately.
- Notify the Hematologist immediately. A supplemental bolus or factor level monitoring may be required.
- Administer the bolus or obtain a factor level if prescribed by the Hematologist.

**When are supplemental bolus doses needed during continuous infusion factor replacement therapy?**

- If the initial bolus dose is not sufficient to achieve the desired target range.
- If a supplemental bolus dose does not achieve the desired target range.
- If the continuous infusion is not adequate to maintain the desired target range.
- If the continuous infusion is interrupted and factor level declines to less than the desired target range.

**Summary of Parts 1 and 2**

Continuous infusion is a safe and effective way to administer factor replacement. When CIFR is administered correctly, bleeding occurs infrequently and factor concentrate use can be reduced by at least 30% (compared with conventional bolus factor replacement). CIFR provides therapy with greater convenience because it eliminates the need for multiple, timed bolus injections. In addition, blood level monitoring can be performed less often. CIFR is always started immediately following a bolus dose of factor. The equipment of choice for CIFR is a low flow rate ambulatory infusion pump or syringe pump. Although use of either a low flow-rate ambulatory pump or conventional volumetric pump is appropriate for CIFR therapy, ambulatory pumps offer advantages of greater concentrate stability and patient convenience. The clinical, cost and convenience advantages of CIFR can be made available to all patients who require factor replacement if health care workers become more familiar with dosage calculations and infusion methods for CIFR.

# SUMMARY OF KEY POINTS

- Reconstitute factor concentrate according to the manufacturer's instructions in a horizontal (Class 1) laminar airflow hood if possible. Rotate or agitate vials *gently* until concentrate is completely dissolved. Concentrate dissolves most easily when at room temperature (temperature should not exceed 30°C).
- Choose intravenous equipment (ambulatory pump, volumetric pump) most appropriate to your clinical setting.

**If using a syringe pump or ambulatory infusion device**, fill the syringe or cassette with reconstituted concentrate. To prevent thrombophlebitis and if the hourly infusion rate is too low to maintain vessel patency, the concentrate may be Y-connected to an infusion of 0.9% Sodium Chloride Injection. The reconstituted concentrate should be positioned so that there is minimal dilution with the normal saline (e.g., select the Y-site closest to the accessed blood vessel).

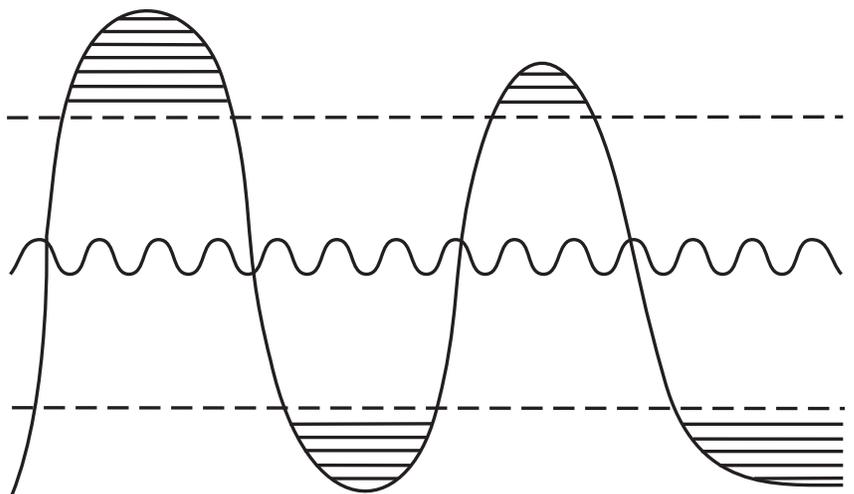
**If using a volumetric infusion device**, dilute the reconstituted concentrate with normal saline as directed in the physician order or according to policies of your institution (using extended stability data from Appendix A). The dilution should be the minimum amount to make an infusion rate that can be run safely on the pump and also keep the vein patent.

- Use central venous access if it is available.
- Administer the bolus dose at a rate adapted to the response of the patient (usually not more than 5ml/minute). Patients should be encouraged to self-administer the bolus if they are knowledgeable and able to do so.
- **Start the continuous infusion immediately following the bolus.**
- **DO NOT** interrupt the continuous infusion.
- If the infusion is stopped inadvertently for 60 minutes or more, notify the Hematologist immediately. Obtain a factor level or give a supplemental factor bolus if prescribed.
- **DO NOT** infuse other drugs through the same line (same central venous catheter lumen) or mixed in the solution that contains factor concentrate.
- Obtain blood levels as prescribed (usually 30 to 60 minutes after the bolus is administered; upon arrival in the recovery room; 8 -24hours after the continuous infusion is started; daily, preferably with morning bloodwork on every day that continuous infusion is administered).
- Monitor the IV site for signs of phlebitis. Instruct the patient to report any discomfort at the IV site. Establish a new IV site if signs or symptoms of phlebitis occur, even in the presence of a patent vein.



# PART 3

# REFERENCES AND APPENDICES



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## Appendix A: Stability of Factor Concentrates when Stored in Plastic Syringes at Room Temperature\*

## APPENDICES

Product	Potency (U/ml)	Additives	Stability <sup>a</sup>	Reference
Alphanine	100	nil	≥ 80% at 8 hrs	32
Benefix	100	nil	≥ 100% at 8 hrs	32
	10	nil	≥ 100% at 8 hrs	
	5	nil	≥ 100% at 8 hrs	
Benefix	100	nil	> 90% at 7 days	37
		heparin 4U/ml	> 90% at 4 days	
Bioclote	50	nil	> 75% at 3 days	45
		heparin 5U/ml	> 75% at 28 days	
		vancomycin 0.25mg/ml	> 75% at 7 days	
Bioclote	100	nil	> 75% at 3 days	45
		heparin 5U/ml	> 75% at 7 days	
		vancomycin 0.25mg/ml	> 75% at 3 days	
Bioclote	250	nil	> 75% at 7 days	45
		heparin 5U/ml	> 75% at 14 days	
		vancomycin 0.25mg/ml	> 75% at 14 days	
Beriate HS	25	nil	> 80% at 7 days	30
		nil	> 80% at 7 days	
Factonord	50	nil	> 80% at 7 days	30
Haemate-P	25	nil	> 80% at 7 days	30
Hemofil M	24	nil	> 80% at 7 days	30
Hyate:C	5	normal saline	> 90% at 1 day	29
Hyate:C	15	normal saline	> 90% at 3 days	29
Hyate:C	30	normal saline	> 90% at 3 days	29
Immunate	50	nil	> 95% at 2 days <sup>b</sup>	44
Immunate	100	nil	> 95% at 2 days <sup>b</sup>	44
Immunine	40	nil	> 90% at 2 days <sup>b</sup>	44
Immunine	120	nil	> 90% at 2 days <sup>b</sup>	44
Kogenate	100	nil	> 90% at 7 days	31
		heparin 4U/ml	> 90% at 7 days	
Kogenate	83-121U/ml	nil (PVC tubing)	80%-90% for first 4ml thru tubing, then >90% at 7 days <sup>b</sup>	45
		heparin 4U/ml (PVC tubing)	70%-80% for first 4ml thru tubing, then ≥100% at 7 days <sup>b,c</sup>	
		nil (PVC tubing)	80%-90% for first 4ml thru tubing, then >90% at 7 days <sup>b</sup>	

**Appendix A: Stability of Factor Concentrates when Stored in Plastic Syringes at Room Temperature\* (continued)**

<b>Product</b>	<b>Potency (U/ml)</b>	<b>Additives</b>	<b>Stability<sup>a</sup></b>	<b>Reference</b>
Kogenate	83-121U/ml	nil (PE tubing)	35%-90% for first 5ml thru tubing then >90% at 7 days <sup>b</sup>	31
		heparin 4U/ml (PE tubing)	25%-70% for first 5ml thru tubing then ≥ 100% at 7 days <sup>b,c</sup>	
Kogenate	2	normal saline	< 20% at 3 hours <sup>b</sup>	43
Kogenate	10	normal saline	< 70% at 3 hours <sup>b</sup>	43
Kogenate	146	nil	> 90% at 2 days	43
			> 70% at 12 hours <sup>b</sup>	
Kogenate FS	25	dextrose 5% or normal saline	< 40% at 4 hours	46
Kogenate FS	140	nil	> 80% at 3 days	46
Kryobulin TIM	25	nil	> 80% at 20 days	30
Monoclate P	100	heparin 1U/ml (Abbott)	> 80% at 15 days	
		heparin 1U/ml (Abbott)	> 80% at 7 days <sup>b</sup>	4
Monoclate P	100	enoxaparin 1 anti-Xa U/ml	> 80% at 15 days	
		enoxaparin 1 anti-Xa U/ml	> 80% at 3 days <sup>b</sup>	4
Mononine	102.5	nil	> 80% at 28 days	5
Octaliquid	50	nil	> 80% a 28 days	30
Octanativ-M	101	nil	> 80% at 7 days	30
Octavi	25	nil	> 80% at 28 days	30
Profilate HS	48	nil	> 80% at 1 day	30
Profilate OSD	24	nil	> 80% at 1 day	30
Recombinate	110	nil	> 80% at 28 days	30

\* 20-24° Celsius

<sup>a</sup> all solutions prepared using aseptic technique in laminar airflow hood; values reflect percent factor activity retained compared with baseline values

<sup>b</sup> stored in bag/cassette of ambulatory infusion reservoir

<sup>c</sup> 30°C

PVC polyvinyl chloride plastic

PE polyethylene plastic

**Appendix B: Continuous Infusion Factor Replacement Dose Chart  
(Body Weight Less than or Equal to 50kg)**

<b>Body Weight (kg)</b>	<b>Units / Hour 2units/kg/hr</b>	<b>Units / Hour 3units/kg/hr</b>	<b>Units / Hour 4units/kg/hr</b>	<b>Units / Hour 5units/kg/hr</b>
6	12	18	24	30
8	16	24	32	40
10	20	30	40	50
12	24	36	48	60
14	28	42	56	70
16	32	48	64	80
18	36	54	72	90
20	40	60	80	100
22	44	66	88	110
24	48	72	96	120
26	52	78	104	130
28	56	84	112	140
30	60	90	120	150
32	64	96	128	160
34	68	102	136	170
36	72	108	144	180
38	76	114	152	190
40	80	120	160	200
42	84	126	168	210
44	88	132	176	220
46	92	138	184	230
48	96	144	192	240
50	100	150	200	250

**Appendix C: Continuous Infusion Factor Replacement Dose Chart  
(Body Weight Greater than 50kg)**

<b>Body Weight (kg)</b>	<b>Units / Hour 2units/kg/hr</b>	<b>Units / Hour 3units/kg/hr</b>	<b>Units / Hour 4units/kg/hr</b>	<b>Units / Hour 5units/kg/hr</b>
52	104	156	208	260
54	108	162	216	270
56	112	168	224	280
58	116	174	232	290
60	120	180	240	300
62	124	186	248	310
64	128	192	256	320
66	132	198	264	330
68	136	204	272	340
70	140	210	280	350
72	144	216	288	360
74	148	222	296	370
76	152	228	304	380
78	156	234	312	390
80	160	240	320	400
82	164	246	328	410
84	168	252	336	420
86	172	258	344	430
88	176	264	352	440
90	180	270	360	450
92	184	276	368	460
94	188	282	376	470
96	192	288	384	480
98	196	294	392	490
100	200	300	400	500

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