CHAPTER 153

Indications for and Contraindications to Intermittent Hemodialysis in Critically Ill Patients

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OBJECTIVES

This chapter will:

1. Describe the major technical differences between intermittent hemodialysis and continuous renal replacement therapies to treat acute renal failure in acutely ill patients.
2. Discuss the advantages and limitations of intermittent hemodialysis in this setting.
3. Describe some technical aspects of both methods to help physicians in the choice of the best method for each clinical situation.

Until the early 1980s, intermittent hemodialysis (IHD) was the only available method to treat patients with acute renal failure (ARF) in intensive care units (ICUs). IHD first was developed for patients with chronic renal failure and was implemented by nephrologists. This explains why nephrologists became the specialists who administered IHD to patients in ICUs who had ARF. However, the implementation of IHD as derived from nephrology practices raised some concerns, especially about hemodynamic tolerance. The description of a new mode of renal replacement therapy (RRT), known as continuous arteriovenous hemofiltration, by Kramer et al.[1] in 1977 offered a new way to treat ARF. Given the arteriovenous access, the treatment was controlled directly by the arterial pressure, which led to better hemodynamic tolerance. In the absence of well-conducted comparative studies, venovenous hemofiltration or hemofiltration (corresponding to the evolution of continuous arteriovenous hemofiltration) gained wide acceptance in ICUs[2] for the treatment of ARF because of its supposedly better hemodynamic tolerance and its ease of use at the bedside.[3] Meanwhile, IHD improved, in particular for the treatment of ARF. Results of clinical studies led to IHD standards for patients in ICUs that were different from those for patients with chronic renal failure. Hemodynamic tolerance and therefore efficiency was improved by the use of synthetic membranes, bicarbonate-based buffers, and specific settings.[4] Regarding continuous methods, technical improvements permitted the development of several therapies such as hemofiltration, hemodialysis, or hemodiafiltration usually grouped under the term of continuous renal replacement therapy (CRRT).

An abundant literature has compared IHD with CRRT in terms of critically ill patient outcome. Despite conflicting results in retrospective studies, no significant differences in terms of mortality have ever been shown in prospective randomized studies including more than 1300 patients.[5,6] Regarding renal recovery, retrospective analysis suggests that IHD may have a negative impact,[7–9] but it remains controversial.[10,11] Therefore it appears that both methods can be used in critically ill patients and that almost all patients can be treated with IHD.[12] The two methods appear complementary and can be used for specific indications according to their advantages and limitations.

OPERATIONAL CHARACTERISTICS OF INTERMITTENT HEMODIALYSIS AND HEMOFILTRATION

In IHD, molecule removal is driven by a concentration gradient between the vascular compartment and the dialysate side. This method favors removal of small molecules because their high diffusibility across the membrane provides a high efficiency (clearance around 200 mL/min). This high clearance is responsible for a rapid decrease in the concentration gradient, which in turn leads to a drop in the removal rate, thus limiting the amount of solute removed (Fig. 153.1). These characteristics explain why IHD is used discontinuously, usually for 4 to 6 hours every day or every other day. Taking into account the high urea volume distribution and the high efficiency of the treatment, the refilling of urea from the interstitium to the vascular compartment is limited during the IHD session but occurs soon after the end of treatment. This explains the increase in serum urea after each session, called urea rebound. This phenomenon limits IHD efficiency.

Because of the rapid exchange of solute, high and fast osmolality variations may occur during treatment. These variations involve the vascular compartment and may induce or worsen cellular edema, leading to cerebral edema. In addition, along with the high ultrafiltration rate of IHD needed by the shortness of the session, these osmolality variations participate in hemodynamic impairment. However, the short duration of IHD sessions offers some advantages (Table 153.1). The nurse's workload is diminished, the patient's mobility is preserved, and bleeding risk is decreased because of low exposure to anticoagulants. Moreover, treatment can be performed without anticoagulation, with good efficiency

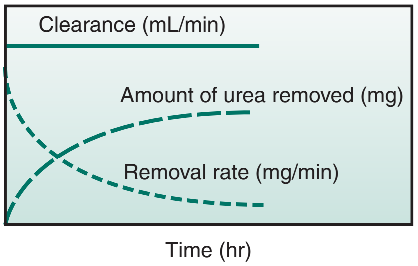

FIGURE 153.1 Representation of urea removal rate and amount of urea removed during intermittent hemodialysis.

TABLE 153.1

Advantages and Limitations of Intermittent Hemodialysis and Hemofiltration

	ADVANTAGES	LIMITATIONS
Intermittent hemodialysis	High clearance for small molecules	Hemodynamic tolerance
	Patient's mobility	Abrupt osmolality variations
	Several patients treated per day with one machine	Fluid management over short period
	Low or no anticoagulation	Dialysis dose not predictable
	Low bleeding risk	Microbiologic dialysate safety
	Lower cost	Nurse training
Hemofiltration	Good hemodynamic tolerance	Anticoagulation and bleeding risk
	Continuously adaptable metabolic control	Low patient mobility
	Low osmolality variations	Frequent unplanned interruptions (coagulation + + +)
	Better fluid management	One monitor needed per day for each patient
	Removal of medium-molecular-weight substances	Fluid storage
	Sterile fluid bags	Nurse workload
		Higher cost

given the short duration and the high blood flow.[13,14] In addition, from a practical point of view, one machine can treat several patients a day, whereas continuous therapies require one monitor for each patient-day. Yet IHD presents some technical limitations (see Table 153.1): it demands a specific water production, more complex training of care providers and, in many countries, the intervention of a nephrology team.

Hemofiltration refers to all extrarenal therapies that use convection as the mechanism of solute or water removal. Therefore solute and water removal is driven by a pressure gradient between the blood and ultrafiltrate sides of the membrane. The solute concentration in the ultrafiltrate side is then similar to the blood concentration, and small molecule clearance rate exactly correlates with the ultrafiltration rate (around 25 mL/min). This low clearance rate explains the necessity to use hemofiltration continuously. Two other RRT methods use continuous patterns, either based on diffusion (continuous venovenous hemodialysis [CVVHD]) or combining diffusion and convection (continuous venovenous hemodiafiltration). All of these continuous therapies are collectively called CRRT. The specific characteristics of hemofiltration account for many advantages: no abrupt variation of osmolality, the management of net ultrafiltration over 24 hours, and an increase in the amount of urea removed, considering the interstitium's potential to refill the plasma compartment. This explains the better hemodynamic tolerance and efficiency usually reported with the use of hemofiltration. In addition, the convection mechanism allows a higher efficiency of removal of middle-molecular-weight substances, with a potential effect on inflammatory mediators. In contrast, the continuous aspect of this method entails some limitations (see Table 153.1): high dose of anticoagulation, lack of patient mobility, higher nurse's workload, and frequent unplanned interruptions of treatment.

INTERMITTENT HEMODIALYSIS AND CONTINUOUS RENAL REPLACEMENT THERAPY: IS ONE BETTER THAN THE OTHER?

The debate between the proponents of IHD and CRRT is ongoing, with valuable arguments on both sides. Several studies have compared the two methods, but most of them were nonrandomized, retrospective trials. Many methodologic biases preclude conclusions to be drawn from the results of these studies; the membranes were not standardized (biocompatible in CRRT, cuprophane in IHD), different therapies were pooled in CRRT (arteriovenous and venovenous methods) or in IHD (peritoneal dialysis and IHD), and some studies compared two groups enrolled at different times (historical IHD group). Probably the most important limitation is the lack of standardization for efficiency (i.e., dialysis dose) and hemodynamic tolerance in IHD. Indeed, we know that hemodynamic tolerance can be improved significantly with the use of specific settings in IHD for critically ill patients[4] and that dialysis dose needs specific attention.[15] Nevertheless, these studies reported conflicting results, either in favor of CRRT or not.

Eight prospective randomized studies have been published.[12,16–22] The study by Mehta et al.[16] found a significantly higher mortality in the CRRT group, whereas the seven other studies found no significant difference between the methods in terms of mortality.[12,17–22] In the Mehta study,[16] however, despite randomization, the IHD and CRRT patient groups were not comparable for several covariates (number of organ failures and severity score), but the multivariate analysis showed no relation between the mode of RRT and mortality. Most of those studies present major weaknesses, such as randomization failure,[16] modifications of therapeutic protocol during the study period,[18] combination of different types of CRRT,[16] and small number of heterogeneous groups of patients enrolled.[17–20] However, the multicenter Hemodiafe study, conducted by Vinsonneau et al.,[12] enrolled 360 patients and found no significant difference in survival between the two groups (60-day survival, 32% for IHD vs. 33% for CRRT). In that study, both techniques were standardized for membrane polymers and dialysis buffers, factors known to affect the ability of patients to tolerate renal replacement therapies. In addition, guidelines based on results of the study by Schortgen et al.[4] were provided to improve hemodynamic tolerance of IHD.

Regarding renal recovery, the literature provides conflicting results. Retrospective or observational studies report a higher rate of dialysis dependency at ICU or hospital discharge when IHD was used as first line compared with CRRT.[7,8] These studies have some important limitations. Allocation of treatment (IHD or CRRT) depended on patient's baseline characteristics. CRRT was applied in more severe patients, leading to a higher mortality and probably a lower number of patients at risk to become dialysis dependent. Thus the evaluation of dependency in survivors induced an evident bias in favor of CRRT. Two recent observational studies used propensity score[10] or marginal structural Cox model[11] to decrease the impact of allocation bias and differences in baseline or time-dependant confounding factors. In the study from Liang et al.[10] of 4738 patients included with Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 AKI, 28.2% received RRT. In multivariable analysis no difference was found in the odds ratio of recovery at day 90 (OR:1.19, 95% CI: 0.91–1.55, $p = .20$) or day 365 (OR:0.93, 95% CI: 0.72–1.2, $p = .55$) for patients initially treated with IHD or CRRT. The study from Truche et al.[11] found similar results including 1360 patients receiving RRT with a composite primary end point (mortality and dialysis dependency at day 30). In this study, subgroup analysis showed that CRRT was favored in patients with higher weight gain at RRT initiation (HR for mortality and dialysis dependency at 30-day: 0.54, 95% CI: 0.29–0.99, $p = .05$) but deleterious in patients without shock (HR for mortality and dialysis dependency at 30-day: 2.24, 95% CI: 1.24–4.04, $p =.01$). These results are in agreement with those found in prospective randomized studies.[9]

Therefore the two methods seem to provide similar outcomes in critically ill patients as long as they are performed by experienced teams with strict adherence to guidelines to improve hemodynamic tolerance. Therefore the operational characteristics of each method with its advantages and limitations (see Table 153.1) permit one to propose some good indications for IHD and some debatable ones. In fact, there is no a priori contraindication to IHD, given that prospective studies report similar survival rates for patients with ARF, even with multiple-organ dysfunction syndrome, who undergo the treatment.[12]

Nevertheless, in some cases, hemofiltration may appear more suitable, as for example, in patients with severe hemodynamic instability, especially when high ultrafiltration rates are needed. Finally, the advantages of one method compensate for the limitations of the other—situations in which one probably should not be used are ideal for use of the other. This is in agreement with the recent Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury that recommend to "use continuous and intermittent RRT as complementary therapies in AKI."[15] Therefore it is possible to propose more specific indications for IHD, even though either method can provide adequate treatment for ARF in the ICU. This is all the more true when new developments are implemented such as high efficiency hemofiltration to enhance delivered dose or sustained low-efficiency dialysis to enhance the tolerance of IHD.

The choice should be determined in light of the two main objectives of RRT, adequate delivered dialysis dose and good hemodynamic tolerance to avoid ischemic events. Therefore the better method is the one that permits these objectives to be achieved for each patient.

SITUATIONS IN WHICH INTERMITTENT HEMODIALYSIS SHOULD BE PREFERRED

IHD is indicated to treat the metabolic syndrome of acute ARF and to manage fluid balance.[23] The best indications are acute metabolic or toxic situations in acutely ill patients without uncontrolled hemodynamic instability. The need to treat a patient without using anticoagulation and the preference to permit patient mobility are other good indications. Inefficient hemofiltration for repeated filter clotting despite adequate anticoagulation and insufficient metabolic control can be good indications as well. Given the low efficiency of diffusion in removing middle-molecular-weight substances, IHD cannot be considered for modulation of inflammatory processes, but to date, no evidence does support the use of RRT to modulate inflammation.[24]

Complications of Acute Renal Failure

IHD is certainly the most powerful method to easily and quickly control life-threatening situations associated with ARF. This is the case for severe hyperkalemia, severe metabolic acidosis, and also pulmonary edema with fluid overload in oliguric patients without severe hemodynamic impairment. These situations require rapid control of the disorder and usually are associated with an uncompromised hemodynamic situation.

Hyperkalemia

The advantage of IHD for removal of small molecules is more evident in transient disorders (hyperkalemia complicating the acute phase of ARF) but could be questionable in case of persistent abnormalities such as tumor lysis syndrome and severe hyperphosphatemia.[25] These situations can justify a combination of IHD early in the course of treatment followed by the use of a continuous modality once sufficient initial control is achieved.[26] This strategy enables good metabolic control without iterative peaks of concentration.

Metabolic Acidosis

Severe uncontrolled metabolic acidosis in shock remains a classic indication for RRT despite the lack of consensus.[23] Lactic acidosis related to tissue hypoperfusion accounts for the major cause, and bicarbonate infusion is usually insufficient. Using hemofiltration in a standard way may achieve insufficient control, especially when liver dysfunction is present. Indeed, Levraut et al.[27] demonstrated that standard hemofiltration clearance accounted only for 3% of blood clearance in patients with normal lactate levels and stable hemodynamic status.[28] IHD offers a higher clearance of lactate and a greater bicarbonate exchange. IHD must be used repeatedly during the acute phase, and hemofiltration can be used thereafter but without a lactate buffer.

Other situations of life-threatening lactic acidosis in which IHD is useful are metformin intoxication and complications of nucleoside analogue treatment in patients with human immunodeficiency virus.[29] Hemofiltration and IHD have been used successfully in such situations, according to various case reports. It appears, however, that low-volume hemofiltration (25 mL/min) is unable to control the situation,[30] so high-volume (34 ± 6 mL/min) hemofiltration is mandatory.[31] In contrast, hemodialysis providing high clearance can lead to significantly better lactate removal during the emergency phase.[32] According to the consensus from the EXTRIP Workgroup (EXtra corporeal TReatment In Poisoning Workgroup), the experts recommend IHD use with bicarbonate buffer as initial treatment in case of severe lactic acidosis related to metformin intoxication and repeated subsequent sessions with either IHD or CRRT.[28]

Azotemia

For azotemia control, IHD is a good method, although its efficiency can be limited by urea rebound. In addition, time-averaged urea concentration is reported to be higher with IHD than that obtained with hemofiltration.[16] However, IHD can be improved to obtain similar time-averaged urea values.[12,20] As reported by Clark et al.,[33] who used a computer-based model designed to permit individualized RRT prescription, IHD and CRRT can achieve similar efficiency in azotemia if IHD is performed every day. In the study from Schiffl et al.,[34] daily IHD improved the tolerance and the prognosis of RRT. Even if more recent high-quality atn study[15] has challenged the results from Schiffl et al., in some hypercatabolic patients, high-efficiency daily IHD is probably the best method to control azotemia, given the inability of hemofiltration to deliver target dialysis doses in these patients. Indeed, the mean duration of CRRT reported in clinical studies is between 16 and 20 hours,[35,36] and the delivered dose systematically lower than prescribed, leading to a decrease in efficiency with no steady-state situation.[37] This approach can be supported by the high crossover rate from hemofiltration to IHD in the Hemodiafe or Convint study, for uncontrolled azotemia.[12,22]

Poisoning

Many toxic substances can be removed from the blood by extrarenal therapies. Some poisonings require rapid removal because they are life threatening. How efficient the extrarenal therapy is in removing the toxic substance is determined by the latter's characteristics. The toxin must be of low molecular weight (<500 Da), with high water solubility, low protein-bound fraction, and low volume of distribution (<1.5 L/kg). In addition, the clearance offered by the extrarenal technique is paramount, because one of the main prognostic factors is the rapidity of toxic elimination. IHD is the best method in these situations because it can remove toxic substances from the blood more rapidly than hemofiltration.[38] The expert panel from the EXTRIP Workgroup recommends the use of IHD as the first line of extracorporeal treatment in severe poisoning with salicylate,[39] theophylline,[40] and lithium.[41] CRRT can be considered if IHD is unavailable.[32,30–41]

Risk of Hemorrhage and Contraindication to Anticoagulants

Filter patency and line patency are major determinants of filter life span and therefore of delivered dialysis dose. IHD can be performed with the use of a low dose of or no anticoagulant, representing a major advantage in patients who are at high risk for bleeding or have any contraindication to anticoagulation. In addition, it seems easier to use IHD to treat patients with heparin-induced thrombocytopenia and as an alternative treatment to heparin (danaparoid), given the pharmacologic properties of these molecules and the difficult management of these treatments in continuous methods.[42] IHD's advantages are related mainly to the short duration of each session (4–6 hours) and to a higher blood flow than that of hemofiltration. With shorter hemodialysis, the coagulation activation induced by extracorporeal circuit should be less.[40] Heparin-free hemodialysis has been reported in ICU patients to be safe and efficient, delivering dialysis doses equivalent to those of hemodialysis using heparin.[13] Continuous therapies using saline flush and predilution hemofiltration without anticoagulant have been reported.[43] However, this method may be time consuming for nurses, and predilution clearly reduces the delivered dialysis dose. With automated machines in CRRT, regional citrate anticoagulation (RCA) becomes more and more successful especially among patients with high bleeding risk. Monchi et al.[44] reported a longer lifespan of the hemofilters and less transfusion when using citrate versus heparin. A recent systematic review analyzed 14 randomized controlled trials in CRRT and confirmed a significant longer circuit lifespan and reduced bleeding events in citrate-use group compared with heparin, but there was no difference in mortality.[45] Recently, the KDIGO Clinical Practice Guidelines for Acute Kidney Injury and the French Intensive Care Society recommended the use of RCA as the preferred anticoagulation modality for CRRT in patients without contraindications for citrate.[15,24] Intermittent RRT is being developed with RCA on slow-efficiency extended hemodialysis (SLED) modality with good safety and efficacy data.[46] Despite promising strategy to improve the safety of CRRT in bleeding risk patients, RCA presents important limitation. Its use is not recommended in cases of severe hepatic failure, which is very frequent in sepsis condition, and its implementation requires close monitoring and experience to avoid severe complications (i.e., hypo- or hypercalcemia, hypomagnesemia, metabolic acidosis or alkalosis, citrate accumulation). These limitations prevent the widespread use of RCA and still may offer some advantages of IHD over CRRT in case of bleeding risk.

Other Indications

After primary care in patients treated with hemofiltration, when the hemodynamic situation improves, switching to IHD improves ICU care and patient comfort. Moreover, the patient's greater mobility makes transport of the patient outside the ICU for diagnostic evaluations such as computed tomography and magnetic resonance imaging easier, aids in the prevention of bedrest-related complications (decubitus ulcer, venous thrombosis, atelectasis), and helps start rehabilitation. Indeed, IHD can be an alternative for some patients for whom hemofiltration is not suitable because of iterative surgical procedures and frequent treatment interruptions that would lead to low delivered dialysis doses.

SITUATIONS IN WHICH INTERMITTENT HEMODIALYSIS SHOULD BE AVOIDED

Given the operational characteristics of IHD, this method is probably not the best one in severely hemodynamically unstable patients or in patients at risk of cerebral edema. Furthermore, fluid balance management in patients with fluid overload seems to be easier with continuous methods of dialysis.

Severe Hemodynamic Instability

Several studies performed with small sample sizes have reported better hemodynamic tolerance with CRRT than with IHD.[17–19] However, the latest prospective studies comparing IHD and CRRT did not find significant differences, in terms of mean arterial pressure, in the two treatment groups.[12,20,22] IHD tolerance can be improved significantly in acutely ill patients, as reported by Schortgen et al.,[4] although in the Hemodiafe study, three patients were switched from IHD to continuous venovenous hemodiafiltration because of hemodynamic instability.[12] Thus, even with strict guidelines, IHD may not be well tolerated. Use of IHD in patients with severe hemodynamic instability can be a real problem for a clinician with little experience with the method. Schiffl et al.[34] reported that alternate-day IHD for 3.5 hours with a mean net ultrafiltration around 1 L/hr leads to a hypotension rate of 25 ± 5% and worsening of organ dysfunction. Thus, given the deleterious effects of hypotension and ischemic events in kidney function, continuous methods appear better suited to patients with severe hemodynamic instability, especially in teams with low experience in IHD use.

Fluid Overload

Basically, it seems obvious that managing net fluid loss for 24 hours is easier and better tolerated than doing so over 4 or 6 hours. To demonstrate this beneficial effect of continuous treatment, Augustine et al.[19] performed a study comparing continuous venovenous hemodialysis with IHD in critically ill patients with optimized setting for hemodynamic tolerance. These investigators found better hemodynamic stability with continuous therapy despite a significant increase in net fluid loss during 3 days (cumulative median value), –4 L versus +1.5 L ($p < .001$). Mehta et al.[16] reported in their prospective randomized study that target net fluid loss was not achieved in 28% of the IHD group compared with 9% in the continuous therapy group.[16] A particular situation is the patient with congestive heart failure and major fluid overload that is refractory to diuretics. Slow continuous ultrafiltration is probably the best method for such a patient and can be given along with hemofiltration in patients with ARF. Two other studies report a decrease in fluid overload and neurohormonal activation and no safety problems with the use of continuous hemofiltration or slow continuous ultrafiltration.[47,48]

Risk of Cerebral Edema

Rapid osmolality variations with IHD may induce cerebral edema in patients at risk—for instance, those with brain injury or trauma or who have undergone neurosurgery. Very few studies have addressed these issues, but in small or case report studies, continuous methods of hemodialysis seem to be superior to IHD as far as keeping the risk of intracranial hypertension or cerebral edema low.[49]

Davenport et al.[50,51], performed two studies to compare IHD and hemofiltration in patients with severe hepatic failure associated with acute renal failure. Both studies report better results for hemofiltration in terms of mean arterial pressure, cardiac index, intracranial pressure, and cerebral edema. However, the beneficial effect of continuous methods must be evaluated against the bleeding risk induced by anticoagulation. In fact, IHD using increased sodium concentration in the dialysate can be performed with caution by trained physicians in patients at risk for cerebral edema.

CONCLUSION

IHD is still helpful in the management of life-threatening situations if performed by physicians and nurses well trained and experienced in its use. However, the advantages and limitations of IHD and continuous methods appear complementary. Technologic advances to improve the efficiency and the tolerance of either method allow their routine use for any clinical situation. Prolonged intermittent dialysis (SLED) allows better fluid removal and hemodynamic stability, and the use of citrate in continuous therapy will enable easier management. Consequently, the choice of method rests primarily on availability and the best experience of the ICU team.

Key Points

1. Intermittent hemodialysis (IHD) is suitable for patients with transient life-threatening conditions and without hemodynamic instability.
2. In some specific settings, use of IHD leads to better hemodynamic tolerance than continuous methods of dialysis.
3. IHD and hemofiltration are two complementary methods for the treatment of acute renal failure and can be used at different times in the same patient according to the evolution of the disease.
4. IHD still has a place in the range of renal replacement methods used in the intensive care unit.

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A complete reference list can be found online at ExpertConsult.com.

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