Early, Frequent, and Efficient Hemodialysis: A New Trend or *Déjà Vu* From the 1970s?

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After more than a quarter century of dialysis, two factors are still present in dialysis treatment of chronic renal failure patients: inadequacy of technology (the artificial kidney acts as an artificial glomerulus) and inadequate use of technology in terms of dialysis initiation and frequency. This paper presents the results of two less unphysiological dialysis programs, introduced in Bologna at the beginning of the 1960s, which proved their clinical value and are now becoming trendy, at the end of this century. Features of these programs are twofold: (1) daily dialysis, which aims at making treatment more biologically suited to the patient; its validity relies on lower intra- and interdialytic osmotic fluctuations; (2) early dialysis, which aims at making the patient more biologically suited to the treatment. After more than 25 years it is evident that this treatment has fulfilled its original expectations versus late dialysis. There is a 40% improvement in survival, a 35% decrease in morbidity, and a 24% improvement in the cost/benefit ratio.

This report is based on a retrospective analysis of our overall experience and clinical results of chronic hemodialysis carried out in 224 patients on early dialysis and 1210 patients on late dialysis in Bologna from 1967 to 1997. Based on this experience, the following should be regarded as particularly important indications for early dialysis: adequate dialysis facilities; symptomatic patients despite renal creatinine clearances between 15 and 20 mL/min; patients unable to comply with dietary measures; children, to allow for adequate development; patients with diabetes mellitus; candidates for renal transplantation.

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Key words

Chronic renal failure, early dialysis, daily dialysis

Introduction

To understand the current status of dialysis and the role of daily and early dialysis programs, some reflections are necessary: we reflect on the course that dialysis has taken in order to be promoted as a science; the assonance between basic theory and applied knowledge; and the future of dialysis on the basis of its current status.

There is no doubt regarding the spectacular escalation of science that has occurred over recent years, the great leap from analytic to synthetic is no longer a utopia today. It is enough to reflect on the three new forms of technology now available (molecular biology, computer science, organ replacement). We also know that to rise to the status of a true science, any branch of knowledge should combine both theory and application.

If we look deeper into the nature of certain "scientific" programs, the so-called miracle, in many respects, seems actually a makeshift. This is of particular relevance to dialysis, the program that predominates in organ replacement therapy, in terms of the quality and quantity of results. In dialysis, in fact, the spectacular improvement in survival (Table I), thanks to spectacular improvements in technology, is associated with a disappointing lack of fulfillment of all the other original expectations: rehabilitation, quality of life, and cost/benefit ratio. In long-term results, therefore, there is an undoubted gap in clinical terms between appearances (a patient living on dialysis) and reality (a patient surviving on dialysis). If one reflects on the biology of the long-term dialysis patient, there is every reason for amazement at the survival afforded by this new form of "life," inexplicable, at least, by the canons of normal human physiology.

Regarding long-term dialysis results, the clinical gap between appearance and reality reflects the cultural gap behind those results, viz., the gap between the cognitive and the applicative evolution of dialysis science. This is all too little appreciated and far too little mentioned.

TABLE I Five-year patient survival on dialysis in St. Orsola hospital compared to an international European registry over four decades. Since the introduction of early dialysis in the St. Orsola program, the survival probability surpassed that reported by the international registry.

Decade	*Program*	*5-year survival*	*No. of patients*
1960	International Registry	20%	590
1960	St. Orsola, Bologna	5%	38
1970	International Registry	40%	4750
1970	St. Orsola, Bologna	50%	372
1980	International Registry	60%	9210
1980	St. Orsola, Bologna	75%	495
1990	International Registry	65%	21 712
1990	St. Orsola, Bologna	73%	1105

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The reasons for this reality are no doubt various, but, probably, *how* dialysis has been assessed is the primary one. By some, it was judged on purely technological grounds, on the principle "first technology then the patient," and the clinical effectiveness was even evaluated by mathematical formulas. For others (only a few) the guiding principle was "first the patient then technology," and the quality of life was the yardstick for evaluation.

In the history of dialysis these different attitudes should never be forgotten (Figure 1). They explain why only occasionally has the difference between myth and fact been clearly grasped. Chief among the myths are the misconceptions about a low protein diet, which is harmful when overprotracted, and about the so-called "artificial kidney," which, functioning simply as a glomerulus, can only counteract the effects of the lost renal excretory function and will never rehabilitate the patient from uremia.

What has been done to improve dialysis drawbacks? Very little by everyone involved. The *scientific world*, with its "waffle" on established clinical realities; its inability to listen to the patient and correct early mistakes; *society*, by continuing to demand the technological product regardless of the cognitive knowledge behind the product; and *industry*, which has continued to churn out technology differing in form but not in content.

In order to improve dialysis, a whole complex biotechnological revolution is required, and this must involve basic science as well as applicative knowledge. "Bioplant science" (see below) is the key to the future.

Can today's dialysis technology, if applied with different criteria, reduce the unphysiology of dialysis, the unphysiology of survival, and, hence, the pathobiology of the dialysis patient?

This report looks at the clinical facts of two programs put forward with this purpose in mind: daily dialysis, the aim of which is to make treatment more biologically suited to the patient, and early dialysis, the aim of which is to make the patient more biologically suitable for treatment.

Daily dialysis

This schedule, one hour of dialysis per day, was first proposed by us in 1972 (1) in the hope of reducing the osmotic disequilibria intra- and postdialysis. This was a very marked reduction of dialysis duration, considering the usual length of each session at that time (8–10 hours).

MYTH	Prolonged low protein diet before dialysis is not harmful.
FACT	Low protein diet invariably leads to malnutrition, which dialysis is unable to reverse.
MYTH	Dialysis fulfills its capacity for patient rehabilitation.
FACT	Effective rehabilitation from uremia never occurs on regular dialysis therapy, since the artificial kidney actually acts as an artificial glomerulus.

FIGURE 1 Misconceptions in dialysis.

Significant clinical improvements were observed, due to lower osmotic fluctuations. The program encountered problems of application in hospital dialysis, for logistic reasons. In home dialysis, however, it was recommended from the start and in my view still remains viable. A number of dialysis centers now use daily dialysis. We have no significant experience in long-term studies.

Early dialysis (ED)

Premises

Many variables may contribute to the clinical state of chronic uremic patients, for example, age, residual renal function, catabolic rate, and extrarenal complications. This variability may explain the perplexities that still exist regarding the optimal time to start substitution therapy in chronic uremia. The perplexities are made even greater by the controversy concerning the real potential of dialysis technology for patient rehabilitation. When to start dialysis in chronic uremia, therefore, is still an open question from both a clinical and a technological point of view.

Choosing the optimal time to start dialysis in chronic uremia implies a full understanding of the difference between *adequacy of dialysis* and *adequate use of dialysis*. These terms have frequently been used as synonyms, which is misleading. In clinical nephrology, technological efficiency does not necessarily coincide with clinical efficacy, so that some almost miraculous results of technology are, from a clinical point of view, unsatisfactory.

There are at least five important factors determining the commencement of dialysis in chronic uremia: (1) availability of dialysis facilities; (2) the patient's quality of life; (3) patient compliance with dietetic restrictions; (4) clinical signs and symptoms of uremia; and (5) the long-term plan of treatment, that is, dialysis itself or dialysis preceding renal transplantation.

Viewed as a whole, and considering the pathophysiology and pathobiochemistry of uremia on the one hand and the properties of dialysis technology on the other, the timing of dialysis initiation can be summed up under two main schedules: late obligatory dialysis and early optional dialysis. In late obligatory dialysis, therapy starts after a protracted low protein diet (LPD) regimen, with a residual glomerular filtration rate (GFR) of <5 mL/min and in the presence of potentially life-threatening clinical signs of uremia. In early optional dialysis, therapy starts sooner and after short-term or no previous LPD, with a residual GFR of 10–15 mL/min, and in the absence of major signs and symptoms of uremia.

We were the first to suggest early dialysis as a reliable method of artificial substitutive therapy in chronic uremia for preventing the appearance and progression of most uremic problems (2–4). There was criticism as well as appreciation of our first papers on ED (5,6). However, the criticism concerned the idea of ED, not our results, which unfortunately, in the long run, are still unique, so a useful exchange of information from different centers is at present impossible.

The criticism raised by our first paper on ED was partly justified and partly not, as we subsequently made clear. The unquestionably violent reaction (the paper was called "iconoclastic") (7) had the great merit of highlighting our contribution with its first-ever exposé of certain hard facts: standard late dialysis (LD) fails to rehabilitate from uremia, and ED can prevent many uremic problems. Most problems that ED involves (ethical, logistic, clinical) have already been dealt with in previous papers.

The present report is a detailed résumé of more than 25 years of experience with ED. The results concern the clinical effects of earlier "removal" of uremic toxins (8) and the effects of earlier blood-material interaction.

Clinical effects of earlier removal of uremic toxins

This program was suggested in an attempt to ameliorate the results of dialysis in real clinical terms. Traditional dialysis had proved virtually unable to reverse uremia; early dialysis was proposed as an attempt to prevent it.

Early dialysis is a question of choice. When residual creatinine clearance (Ccr) drops below 20 mL/min, the physician and the patient can opt for either early dialysis and a liberalized diet or late dialysis and a restricted diet. Patient compliance is a major problem in the dietary therapy of chronic renal failure. If this proves to be insurmountable or the patient remains symptomatic, dialysis should start straight away. Table II shows the number of patients who commenced early or late dialysis at the St. Orsola Hospital. The greatest experience on early optional dialysis refers to patients who showed clinical signs of uremia (refractory anemia, unresponsive hypertension, nausea or vomiting), patients who still had a relatively high residual Ccr (10–20 mL/min), and patients who had little or no preliminary dietary intervention, since they would not comply with severe dietetic restrictions.

The patients had an almost normal diet associated with dialysis, the frequency of which (one, two, or three times weekly) varied according to contemporary variations of residual Ccr. Diet, residual Ccr, and dialysis were tailored to satisfy the patient's metabolic needs, to enhance the clinical performance of the technology, and to optimize long-term clinical results. Differences in working rehabilitation, mean potential income, and cost/benefit between the two available programs of dialysis, early optional and late obligatory, are significant (Table III). During the years of dialysis, many uremic problems, whether metabolic (alterations in carbohydrates, lipids, and calcium and phosphorus) or clinical (atherosclerosis, osteodystrophy, or peripheral neuropathy), were much better controlled in early optional dialysis, resulting in improved candidacy for renal transplantation. In fact, post-transplant survival is better in patients coming from early than in those coming from late dialysis (Figure 2). The improved clinical and metabolic rehabilitation afforded by early dialysis very likely enhances the patient's "resources" to face both the surgery-related and the immunosuppression-related post-transplant demand.

At present, early optional dialysis is an acknowledged therapy program in chronic uremia aimed at offsetting the drawbacks of both LPD and dialysis by readjusting the patient-machine combination. The improved clinical results that early dialysis affords are probably due to better general condition of the patient at the beginning of treatment (harmful effects of LPD are avoided), the maintenance of renal endocrine function at more than 10%–20 % of residual renal function, and earlier removal of toxins, water, etc., by the machine.

TABLE II Number of patients treated with early and late renal replacement therapy at the Institute of Nephrology, University of Bologna, 1967–1997

	All patients	*Nondiabetics*	*Diabetics*
Early dialysis	224	208	16
Late dialysis	1210	1138	72
Total	1434	1346	88

TABLE III Quality of life in early and late dialysis. Implicit social value.

	Early dialysis	*Late dialysis*
Working rehabilitation index (WRI)	0.75	0.59
Mean potential income (MPI)	8.77	6.9
Cost/Benefit (C/B)	2.25	3.23

$$\text{WRI} = \frac{A + \tfrac{1}{2} B}{100},$$

where A = percent of patients aged 25–60, fit for full-time employment; B = percent of patients aged 25–60, fit for part-time employment; MPI = WRI × mean net annual income from salaried work in U.S. dollars; MRI calculates the earning potential, regardless of actual employment status.

$$\text{C/B} = \frac{\text{Total cost of patient treatment}}{\text{MPI}}.$$

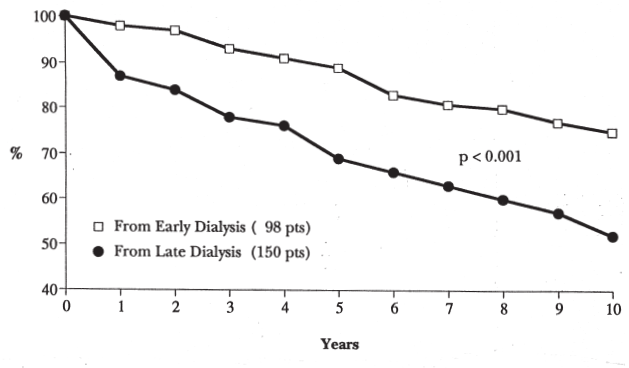

FIGURE 2 Ten-year graft survival in renal transplanted patients coming from early and late dialysis.

Effects of blood/material interaction

A problem originally unforeseen, and still under study, deals with the earlier effect of blood/material interaction. As we know now, hemodialysis causes a complex series of intradialytic biological reactions, which involve various systems (immune, coagulative, etc.) and which are alleged to be mostly related to the bioincompatibility of materials.

Since in ED treatment starts earlier, the key question is whether the earlier biology activation differs in ED versus LD and so influences the long-term results.

A complete review of the matter is under study in our Department and will be published elsewhere. Here, we will consider only some aspects of such a complex problem, concerning the immunological and the platelet/coagulation systems in an intra- and postdialysis period. Various parameters studied so far show that the intradialysis and immediate postdialysis changes (activation spikes during dialysis and a possible further increase one hour after) occur in early and late dialysis without any significant differences, and concern both the immunological (Figure 3) and the platelet-coagulative parameters (Figure 4).

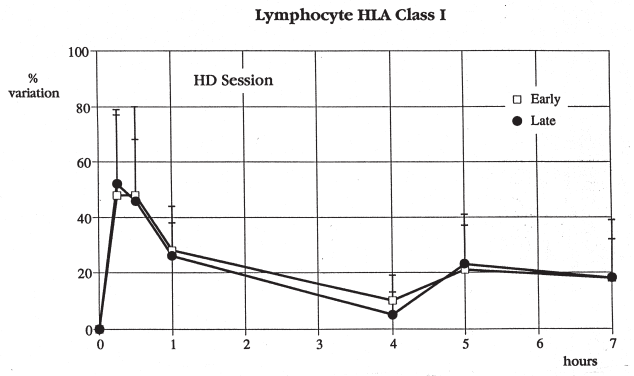

FIGURE 3 Lymphocyte HLA class I antigen behavior during the dialysis session and 3 hours after the end to the session. Comparison between early and late patients.

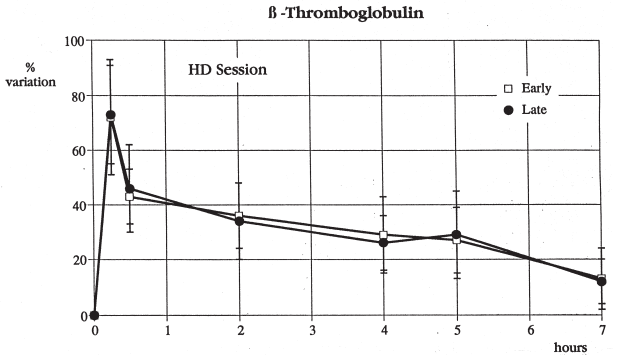

FIGURE 4 β-Thromboglobulin evaluation in early and late patients, during the dialysis session and 3 hours afterward.

The problem is more complex and still partly unresolved in long-term studies. It is known that with long-term dialysis, the protracted blood/material interaction may result in the appearance of a new population of lymphocytes or lymphocytes with new functional properties. We categorized these findings as a sort of "biological rejection"of dialysis, very likely related to the bioincompatibility of materials.

Whatever the cause, do the long-term results differ in ED from LD?

In vivo lymphocyte DNA synthesis shows a higher activity in the ED than in the LD, but only in the first years. Then the difference tends to disappear with time (Table IV). The same behavior applies to HLA class I antigens and to the phagocytic activity of monocytes and neutrophils (Table V). In the short term it is higher in ED than in LD; then the differences disappear with time. In summary, the effects of blood/material interactions do not differ significantly in ED compared to LD. Therefore, the alleged lesser risk of infection in ED due to neutrophil, monocyte, and lymphocyte activation and, by contrast, the possible role of platelet/coagulation system activation in development of atherosclerosis *are both purely matters for speculation*.

The improved relative risk (RR) of infection in ED (Table VI) is mainly related to the improved nutritional status that early treatment implies, and the lower risk of atherosclerosis should be traced to the earlier control of hyper-

TABLE IV Lymphocyte *in vivo* DNA synthesis (percent DNA synthesizing cells) and HLA class I lymphocyte surface antigens (fluorescence intensity)

Year of dialysis	*1*	*5*	*10*
Early dialysis			
DNA	5.7 ±2.6[a] (*n*=25)	1.0±3.5 (*n*=14)	8.0±3.1 (*n*=8)
HLA class I	190±52 (*n*=25)	183±66 (*n*=14)	201±56 (*n*=8)
Late dialysis			
DNA	2.0±2.3[a] (*n*=22)	3.0±1.9 (*n*=12)	4.0±2.9 (*n*=7)
HLA class I	165±73 (*n*=22)	188±48 (*n*=12)	194±71 (*n*=7)

[a] $p < 0.05$.

TABLE V Phagocytic activity of polymorphonuclear neutrophils (PMN) and monocytes (M) (positive reaction increase percent)

	Year of dialysis	*1*	*5*
Early dialysis	PMN	72±6[a] (*n* = 10)	84±12 (*n* = 8)
	M	61±8[b] (*n* = 10)	68±13[b] (*n* = 8)
Late dialysis	PMN	56±9[a] (*n* = 11)	79±14 (*n* = 7)
	M	42±16[b] (*n* = 11)	51±9[b] (*n* = 7)

[a] $p < 0.01$.
[b] $p < 0.05$.

TABLE VI Overall results in 1434 patients treated with early dialysis (ED, n = 224) and late dialysis (LD, n =1210) at St. Orsola Hospital over the period 1967 to 1997

	5 years		*10 years*		*20 years*	
	ED	*LD*	*ED*	*LD*	*ED*	*LD*
Survival (%)	82[a]	68[a]	64[b]	39[b]	24	12
Malnutrition (%)	9[b]	31[b]	16[b]	35[b]	36	44
Infection (RR)	0.7[b]	1.2[b]	0.9	1.1	0.9	1.1
Cardiovascular (RR)	0.6[b]	1.1[b]	0.7	1.1	1.1	0.9

[a] ED vs LD: $p < 0.001$.
[b] ED vs LD: $p < 0.005$.
RR = relative risk of death due to infections or cardiovascular complications.

tension and fluid balance. *The lack of significant negative effects due to earlier blood/material contact and the clinical benefits due to earlier uremic toxin removal confirm the clinical role of ED in the long run, in terms of survival and quality of life.*

So, considering all the pros and cons, we maintain that the following should be regarded as reliable indications for early dialysis: adequate dialysis facilities; symptomatic patients despite Ccr around 15%–20%; patients reluctant to comply with dietary measures; children, to allow for adequate development; patients with diabetes mellitus; and patients who are candidates for renal transplantation.

Conclusions

Renal replacement therapy (and, in general, organ replacement therapy) is a multidisciplinary reality, which has required and still requires the integration of various branches of science. Historically, classical medicine developed according to the dominant *cosmological* (in ancient Greece) or *anthropological* (since the Renaissance) conceptions. By contrast, the study of dialytic medicine has followed a mainly *technological* course, which is important when it comes to grasping the technical potential of the device, but is inappropriate for subsequently judging the clinical reality of the patient. Culturally, too, techno-dialysis has all too often drawn on the modern cult of the image, which is certainly improper, since it is based too much on the outside appearance of the event and not enough on an overall judgment regarding its validity.

To improve clinical dialysis, therefore, new programs should aim at making treatment biologically closer to the whole person and physiologically closer to the organ. The "bioplant trend," the aim of which is to make the device more biological and thereby "humanizing" or to make the so-called artificial kidney less unphysiological, is the science of the future. It represents the cultural platform for the *intelligent* artificial kidney, where the underlying aims are to replace all the functions of the human organ by an integrated feedback of *electronics*, *biology*, *computers*, and *biointeractive materials*.

Future trends, *ergo*, must be devoted to making treatment more humanized. But a similar increase in humanizing also needs to be extended to the whole of today's techno-medicine. This is an ethical "must" for science, since it reappraises the doctor/patient equation. It is in the doctor, not the hardware, that the patient trusts and hopes, and for the doctor him/herself, helping the sick is the highest expression of his/her knowledge.

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