Kidney International, Vol. 67 (2005), pp. 2448–2453

Access to, and outcome of, renal transplantation according to treatment modality of end-stage renal disease in France

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Access to, and outcome of, renal transplantation according to treatment modality of end-stage renal disease in France.

Background. Although peritoneal dialysis (PD) is recognized as one of the methods of treatment of end-stage renal disease (ESRD), there have been recurrent concerns about the access of patients treated by this modality to kidney transplantation (KTx), as well as reports showing increased complications of KTx in such patients, such as graft thrombosis and infections.

Methods. The aim of this study was to provide a comprehensive view of the impact on transplantation of pretransplant modality of treatment of ESRD using a multivariate analysis of the French database. From 1997 to 2000, after exclusion of pediatric patients, multiple transplantations, and living donors, 6420 were patients registered on the waiting list, and 3464 were transplanted.

Results. Using a Cox proportional hazard analysis, we found a shorter waiting time for PD patients (RR 0.71, $P < 0.0001$), which became equivalent to hemodialysis (HD) patients when taking into account the transplant center as a variable (RR 1.0, $P = 0.95$). Concerning graft survival, only preemptive transplantation had a significant impact, being associated to a decreased risk of graft failure (RR 0.46, $P = 0.005$).

Conclusion. Our study supports the concept that the choice of any pretransplant dialysis modality does not influence waiting time for transplant or the results of transplantation.

Several renal replacement therapies are available for patients with end-stage renal disease (ESRD), namely hemodialysis (HD), peritoneal dialysis (PD), or preemptive transplantation (Pre-T) [1], but the selection for any given individual depends on many variables, including his acceptance of therapy modalities and pretransplantation strategy. HD is by far the most frequent modality used for renal replacement therapy in many countries. The frequency of patients with ESRD treated by PD reached 15% in many industrialized countries, but is only around 10% in France [2].

For a long time, many physicians have been reluctant to propose PD to candidates for kidney transplantation. There have been reports that transplanted patients previously on PD had more frequent graft thrombosis [3, 4] or infections [5] compared to patients treated with HD. When looking at transplantation outcomes, equivalent [6] or inferior results [7] have been reported for PD patients. However, recent studies have shown that PD is associated with a lower incidence of post-transplant delayed graft function (DGF) compared to HD [8, 9].

Although these concerns might have a detrimental impact on the waiting time of PD patients, recent studies have shown, on the contrary, a faster access to transplantation of PD patients [6, 10].

The relationship between the choice of ESRD treatment (HD, DP, or Pre-T) modality, waiting time, and graft survival depends on many variables.

The aim of this study was, thus, to evaluate at a national scale by multivariate analysis the role of ESRD treatment on the likelihood to receive a transplant (waiting time), and on patient and graft survivals after kidney transplantation.

METHODS

Patient population

In France, it is mandatory to register donors, candidates, as well as graft and recipient follow-up, in the national information system of the French Transplantation Agency (Etablissement Français des Greffes).

We reviewed the data of all the patients that were registered on the national French waiting list between January 1997 and December 2000, as well as all recipients of a kidney graft during the same time frame. A total of 6420 registrations and 3464 grafts performed by 37 centers were finally included in the analysis after exclusion of living donors, pediatric recipients (<16 years), multiple organ transplants, nonresident, and retransplant registrations.

Key words: peritoneal dialysis, kidney transplant, graft survival, waiting time.

Received for publication July 12, 2004
and in revised form October 27, 2004, and December 22, 2004
Accepted for publication January 7, 2005

Recipient and graft criteria considered for adjustment were: recipient age at registration and at transplantation, gender, blood group, diabetes mellitus, peak panel reactive antibody (PRA) level, frequency of human lymphocytic antigen (HLA) alleles (with scarcity defined as a frequency <3% among all registered patients), time on dialysis at registration, year of registration, ESRD treatment modality at registration, waiting time before transplantation, HLA mismatching (0–6), cold ischemia time, gender and blood group matching, donor age, gender, blood group, and cause of death.

Statistical analysis

The effect of ESRD treatment modality was evaluated on two main outcomes: likelihood of transplantation was assessed through the analysis of waiting time to transplantation and transplant outcome through the analysis of patient and graft survivals.

Differences among categorized patient's characteristics were tested by chi-square test for discrete variables, and analysis of variance (ANOVA) for continuous variables.

To estimate waiting time to transplant, time on the national kidney transplant waiting list was calculated for each patient. The event of interest is transplant, with patients dying on the list censored at date of death. Patients removed from the list were censored at the date of removal, and those still awaiting a transplant at the end of the analysis period were censored at that time. To estimate graft survival after transplant, defined as a patient alive with a functioning graft, end point was defined as either death or graft failure. Kaplan-Meier estimators were used to determine waiting time and graft survival.

Cox proportional hazard regression was used to analyze the effect of ESRD treatment modality on waiting time and on graft survival adjusted on all risk factors associated with each outcome in the univariate analysis, with a P value <0.2.

The final multivariable model is adjusted on centers after investigation of a possible association between ESRD treatment modalities and center waiting times. Statistical significance was accepted at $P < 0.05$.

All statistical analyses were performed using SAS software package, version 8.1 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Likelihood of transplantation

The characteristics of patients at registration are summarized in Table 1. A total of 6240 registrations on the waiting list were included: 647 (10.1%) PD, 5190 (80.8%) HD, and 583 (9.1%) Pre-T. The number of new yearly registrations according to ESRD treatment modality differed between 1997 and 2000 ($P < 0.0001$). Registration of patients treated by PD increased in time, from 128 (8.5%) in 1997 to 177 (10.8%) in 2000, as well as Pre-T registrations from 106 (7.2%) in 1997 to 189 (11.3%) in 2000, while HD decreased (84.3% in 1997 to 77.9% in 2000).

Table 1. Characteristics of patients registered on kidney waiting list according to the ESRD treatment modality

	PD ($N = 647$)	HD ($N = 5190$)	Pre-T ($N = 583$)	P value
Female gender%	267 (41.3)	1910 (36.8)	248 (42.5)	0.004
Age *years*	44.8 ± 13.2	46.2 ± 12.8	44.8 ± 12.2	0.04
Diabetes mellitus%	17 (2.6)	227 (4.4)	22 (3.8)	0.1
Year of registration%				
1997	128 (19.8)	1255 (24.2)	106 (18.2)	<0.0001
1998	167 (25.8)	1284 (24.7)	113 (19.4)	
1999	175 (27.0)	1388 (26.7)	175 (30.0)	
2000	177 (27.4)	1263 (24.3)	189 (32.4)	
Time on dialysis at registration *months*	11.4 ± 11.8	19.5 ± 34.8	0	<0.0001
Blood group%				
A	289 (44.7)	2173 (41.9)	273 (46.8)	0.22
AB	24 (3.7)	209 (4.0)	26 (4.5)	
B	65 (10.0)	563 (10.9)	63 (10.8)	
O	269 (41.6)	2245 (43.2)	221 (37.9)	
HLA alleles frequency (<3%)%				
0	179 (27.7)	1424 (27.4)	184 (31.6)	0.02
1	258 (39.9)	1924 (37.1)	215 (36.9)	
2	149 (23.0)	1257 (24.2)	136 (23.3)	
3	54 (8.4)	450 (8.7)	44 (7.5)	
≥ 4	7 (10.0)	135 (2.6)	4 (0.7)	
Peak PRA level%				
0–14	598 (92.4)	4755 (91.6)	542 (93.0)	0.6
15–69	36 (5.6)	306 (5.9)	32 (5.5)	
70 and above	13 (2.0)	129 (2.4)	9 (1.5)	

Abbreviations are: PRA, panel reactive antibody; Pre-T, preemptive transplantation. For continuous variables, data are expressed as mean ± SD.

Significant differences between patients according to ESRD treatment modalities were observed for gender ($P = 0.004$) and age at registration ($P = 0.04$). More precisely, PD and Pre-T patients were more often women, and were registered at a younger age.

The overall waiting time curves differed significantly ($P < 0.0001$) between ESRD treatment modalities (Fig. 1), with 13.5 months median waiting time for HD, 9.4 for PD, and 11.7 for Pre-T patients ($P < 0.0001$).

Using the proportional hazard regression model, we found a number of variables to be significant in univariate analysis for their effect on waiting time before transplantation (Table 2). An increased risk was observed for female gender (RR = 1.1, $P = 0.0003$), O and B blood groups [RR = 1.83, $P < 0.0001$, peak PRA level between 15% and 69% (RR = 1.42, $P < 0.0001$) and 70% and more (RR = 2.06, $P < 0.0001$), and an increased number of infrequent HLA alleles (RR = 1.2, $P < 0.0001$)]. On the contrary, patients of less than 30 years at registration (RR = 0.81, $P = 0.0001$), or 60 years and above (RR = 0.87, $P = 0.01$) had a reduced waiting time.

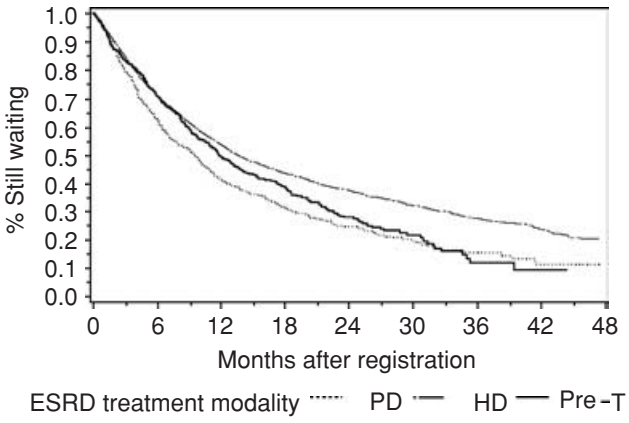


Fig. 1. Kaplan-Meier plots of waiting time to transplant by ESRD treatment modality (log-rank, $P < 0.0001$).

ESRD treatment modality at registration had a profound impact on waiting time, with a risk ratio of 0.71 ($P < 0.0001$) for PD and 0.83 ($P = 0{,}002$) for Pre-T patients compared to HD patients. As allocation rules in France do not take into account the modality of ESRD treatment, this prompted us to investigate the potential relationship between waiting time and percentage of PD patients on the waiting list in individual transplant centers. Results are shown in Figure 2, and clearly show that PD patients are more likely to be registered in centers with the shortest waiting times. Indeed, centers with a median waiting time of less than 10 months have the highest percentage of PD patients on list (16%) compared to the longer waiting centers, averaging only around 5% PD patients on list. After adjustment on all risk factors described above and adjustment on centers, no effect of ESRD treatment modality was observed any longer, with a risk ratio of 1.0 ($P = 0.95$) for PD modality (Table 2).

Two-year graft survival after transplantation

The characteristics of donors and recipients at transplantation are summarized in Table 3. Of the 3464 transplant patients, 400 (11.5%) were treated by PD at registration, 2738 (79.1%) by HD, and 326 (9.4%) by Pre-T. The same differences seen in registered patients in terms of age and gender between ESRD treatment modalities are again observed in transplanted patients (Table 1). The unadjusted overall graft survival differs significantly ($P = 0.003$) according to ESRD treatment modality (Fig. 3). Pre-T graft survival was significantly higher when compared to HD ($P = 0.0009$) and to PD graft survival ($P = 0.02$). No difference was observed between HD and PD populations ($P = 0.31$).

Using the proportional hazard regression model, we found different variables to be significant in univariate analysis for their effect on graft survival (Table 4), such as donor age above 54 years (RR = 1.66, $P < 0.0001$), recipient age above 60 years at transplantation (RR = 2.13, $P < 0.0001$), months on dialysis before transplantation (RR = 1.003, $P = 0.003$), and cold ischemic time (RR = 1.02, $P = 0.004$). Pre-T compared to HD was found to be the only treatment modality significantly linked with better graft survival, and no significant effect on graft survival was observed for any dialysis modality.

After adjustment for risk factors linked with graft survival in univariate analysis ($P < 0.2$), PD (RR = 0.90, $P = 0.52$) had no effect on graft survival, but Pre-T (RR = 0.46, $P = 0.005$) was still found to be associated with a decreased risk of graft failure.

Concerning patient survival, no difference was found between the different groups of patients (Fig. 4).

DISCUSSION

Peritoneal dialysis is still used in a minority of patients needing renal replacement therapy. The rates range from 45% in the United Kingdom to 8% in Germany [2], as compared to 13% in the United States [11]. However, the percentage of patients waiting for a kidney transplant treated by PD may be different, depending on the characteristics of the patients such as age or comorbidities. In France, no such difference exists, as the percentage of ESRD patients treated by PD is 10%, and the percentage of patients on the transplant waiting list treated by PD is exactly the same. Transplants from living donors represent less than 5% of all kidney transplantations performed in France. The proportion of patients registered on the waiting list and expecting a living donor transplant and treated by PD in France is 9%, which is comparable to the percentage of patients registered on the waiting list for a deceased donor. Moreover, the analysis of graft survival was performed on the cohort of patients finally transplanted among the cohort of patients included in the analysis of time to transplant and, therefore, did not include the effect of the donor type.

Small differences, however, exist in terms of age at registration and female gender between HD and PD patients (see Table 1). PD patients are more likely to be female and younger, as seen in the United States [8].

The likelihood of transplantation for PD patients has recently been reported as 1.39 times greater than HD patients in a retrospective analysis of the UNOS database [11], even after considering clinical differences between HD and PD patients, such as sex, race, age, BMI, and comorbidities. Likewise, in our analysis, we found a reduced median waiting time to transplantation for PD patients (Fig. 1) that persisted after taking into account such variables as gender, age, or PRA level. However, this result could not be easily explained, as kidney allocation rules in France are blind to dialysis modality. As the median waiting time differs significantly between transplant centers in France [12], we hypothesized that a center effect

Table 2. Cox univariate and multivariate analysis of waiting time to transplant ($N = 6420$ registrations)

	Univariate		Multivariate		Multivariate (adjusted on center effect)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Year of registration (1997, referent)	1.06 (1.02, 1.01)	0.001	1.08 (1.04, 1.12)	<0.0001	1.08 (1.04, 1.1)	<0.0001
Female gender	1.1 (1.06, 1.2)	0.0003	1.1 (1.00, 1.15)	0.053	1.056 (0.99, 1.14)	0.08
Age at registration *years*						
16–29	0.81 (0.73, 0.9)	<0.0001	0.83 (0.75, 0.9)	0.0004	0.89 (0.8, 0.99)	0.03
30–44, referent						
45–59	0.95 (0.82, 1.03)	0.2	0.96 (0.89, 1.04)	0.33	0.95 (0.88, 1.03)	0.22
60 and older	0.87 (0.78, 0.87)	0.01	0.87 (0.78, 0.97)	0.01	0.9 (0.80, 0.99)	0.04
Blood group (O and B)	1.83 (1.65, 1.87)	<0.0001	1.84 (1.72, 1.97)	<0.0001	1.96 (1.84, 2.10)	<0.0001
Peak PRA level%						
0–14, referent						
15–69	1.42 (1.23, 1.65)	<0.0001	1.40 (1.20, 1.63)	<0.0001	1.7 (1.46, 1.98)	<0.0001
70 and above	2.06 (1.6, 2.68)	<0.0001	2.11 (1.6, 2.75)	<0.0001	3.0 (2.3, 3.97)	<0.0001
HLA allele frequency <3%	1.2 (1.14, 1.22)	<0.0001	1.2 (1.13, 1.21)	<0.0001	1.2 (1.13, 1.21)	<0.0001
Time on dialysis at registration						
<19 months, referent						
≥19 months	1.1 (1.03, 1.2)	0.009	1.02 (0.94, 1.1)	0.58	1.03 (0.95, 1.12)	0.45
ESRD treatment modality						
Hemodialysis, referent						
Peritoneal dialysis	0.71 (0.64, 0.79)	<0.0001	0.71 (0.64, 0.79)	<0.0001	1.00 (0.90, 1.12)	0.95
Preemptive transplantation	0.83 (0.74, 0.94)	0.002	0.86 (0.76, 0.96)	0.009	0.92 (0.81, 1.03)	0.15

Abbreviations are: PRA, panel reactive antibody; HR, hazard ratio.

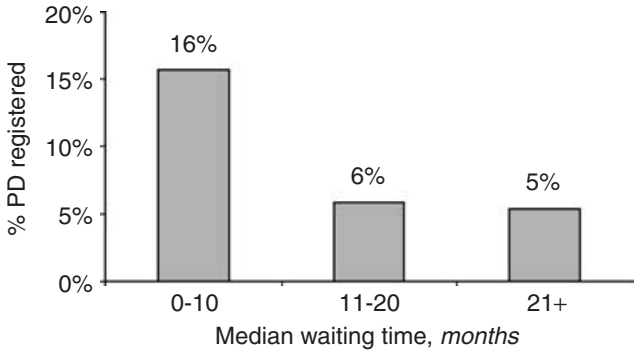


Fig. 2. Proportion of PD registrations according to median waiting time to transplant.

Table 3. Characteristics of donors and recipients according to ESRD treatment modality ($N = 3464$ recipients)

	Peritoneal dialysis ($N = 400$)	Hemodialysis ($N = 2738$)	Pre-T ($N = 326$)	*P* value
Donor age *years*	40.8 ± 13.8	40.77 ± 14.5	39.6 ± 15.3	0.4
HLA mismatches	3.2 ± 1.2	3.1 ± 1.22	3.0 ± 1.2	0.14
Cold ischemic time *hours*	20.5 ± 8.1	22.4 ± 8.3	22.5 ± 8.4	<0.0001
Female gender	156 (39.0)	966 (35.3)	141 (43.2)	0.01
Recipient age *years*	45.2 ± 13.1	46.6 ± 12.9	44.8 ± 12.4	0.012
Time on dialysis *months*	18.6 ± 13.0	26.7 ± 33.9	–	
Diabetes mellitus	9 (2.3)	101 (3.7)	11 (3.4)	0.3
Peak PRA level%				
0–14	380 (95)	2548 (92.9)	304 (93.3)	0.5
15–69	13 (3.3)	146 (5.3)	18 (5.5)	
70 and above	7 (1.6)	44 (1.6)	4 (1.2)	

Abbreviations are: PRA, panel reactive antibody, Pre-T, preemptive transplantation. For continuous variables, data are expressed as mean ± SD.

could be responsible for this apparent difference in waiting time between PD and HD patients. We, thus, divided the transplant groups into short, medium, or long waiting time, and assessed the proportion of PD patients registered in those three types of centers (Fig. 2). There is a striking difference, with a much higher proportion of PD patients in the centers with the lowest median waiting time. We then estimated waiting time integrating the center as a variable, which became strictly identical between dialysis modalities. This potential bias could cast a doubt on previous publications, demonstrating a shorter waiting time of PD patients.

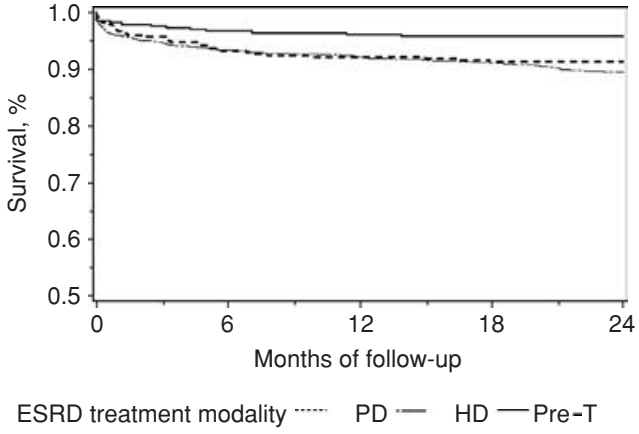
Our analysis points out to another potential bias, namely pretransplant dialysis duration. Indeed, it has been demonstrated that dialysis duration impacts negatively on graft survival [13]. This period of time is, in fact, the sum of the time spent on dialysis before registration and the actual waiting time for transplant. In our series, PD patients were registered significantly earlier than other patients (11.4 vs. 19.5 months, $P < 0.0001$). This leads to a shorter dialysis time for PD patients, even with equivalent waiting times. This might explain the results of previously published studies with longer dialysis duration for HD patients [6, 10, 14].

Graft survival in our analysis does not depend on dialysis modality, but is strongly enhanced by preemptive transplantation, in accordance with previously published studies [15–17]. Although our database does not include complications such as thrombosis or rejections, the similar survival suggests that any potential complication

Table 4. Univariate and multivariate analysis of graft survival

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Predictor				
Donor age *years*				
0–15	1.24 (0.66, 2.34)	0.5	1.23 (0.64, 2.34)	0.53
16–54, referent				
55 and older	1.66 (1.29, 2.12)	<0.0001	1.45 (1.1, 1.91)	0.008
Donor death: CVA or stroke	1.16 (0.93, 1.44)	0.19	1.02 (0.80, 1.28)	0.89
Time on dialysis *months*	1.003 (1.001, 1.005)	0.003	1.002 (1.00, 1.004)	0.09
Cold ischemic time *hours*	1.02 (1.01, 1.03)	0.0042	1.016 (1.003, 1.03)	0.001
Recipient-donor blood group mismatch	1.47 (0.86, 2.5)	0.16	1.53 (0.88, 2.65)	0.13
Number of HLA mismatches (A-B-DR)	1.05 (0.96, 1.5)	0.26	1.06 (0.9702, 1.16)	0.22
Female donor to male recipient	1.08 (0.84, 1.40)	0.56	-	
Recipient age at transplantation *years*				
16–29	1.17 (0.8, 1.7)	0.42	1.21 (0.83, 1.78)	0.32
30–44, referent				
45–59	1.2 (0.90, 1.61)	0.22	1.13 (0.84, 1.51)	0.44
≥60	2.13 (1.54, 2.9)	<0.0001	1.85 (1.32, 2.56)	0.0003
Diabetes mellitus	1.20 (0.69, 2.08)	0.5	-	
Peak PRA level%				
0–14, referent				
15–69	1.47 (0.96, 2.25)	0.076	1.40 (0.91, 2.14)	0.134
70 and above	0.99 (0.41, 2.38)	0.97	1.0 (0.996, 2.46)	0.99
Dialysis modality				
Hemodialysis, referent				
Peritoneal dialysis	0.83 (0.58, 1.19)	0.31	0.90 (0.62, 1.28)	0.52
Preemptive transplantation	0.413 (0.242, 0.71)	0.0013	0.46 (0.27, 0.79)	0.005

Abbreviations are: PRA, panel reactive antibody, HR, hazard ratio.



Months after transplant	% Survival (number of events)		
3 months	95.7 (17)	94.6 (145)	97.5 (8)
6 months	93.1 (27)	93.3 (181)	96.6 (11)
12 months	92.1 (31)	92.1 (212)	96.0 (13)
24 months	91.3 (34)	89.5 (275)	95.6 (14)

Fig. 3. Kaplan-Meier plots of kidney graft survival by ESRD treatment modality (Log Rank, $P = 0.003$).

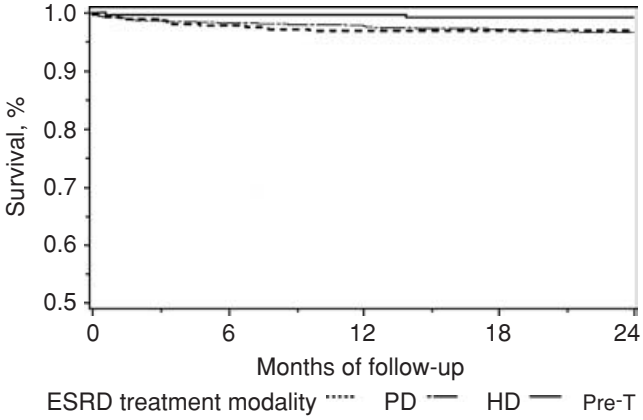


Fig. 4. Kaplan-Meier plots of patient survival by ESRD treatment modality (Log Rank, $P = 0.09$).

arising in the PD patients has no detrimental effect on patient or graft survival at two years [6, 11].

CONCLUSION

Our study supports the concept that the choice of dialysis modality does not influence either the patient waiting time for transplantation or patient and graft survival.

ACKNOWLEDGMENTS

The authors would like to thank the kidney transplant teams of the following hospitals for providing us their data: Hôpital Sud, Amiens, Hôpital Hôtel-Dieu, Angers, Hôpital Saint-Jacques, Besançon, Hôpital Pellegrin, Bordeaux, Hôpital la Cavale Blanche, Brest, Hôpital Clemenceau, Caen, Hôpital G. Montpied, Clermont-Ferrand, Hôpital du Bocage, Dijon, Hôpital Necker, Paris, Hôpital Tenon, Paris, Hôpital Saint-Louis, Paris, Hôpital A. Michalon, Grenoble, Hôpital C. Huriez, Lille, Hôpital Dupuytren, Limoges, Hôpital E. Herriot, Lyon, Hôpital Lyon-sud, Lyon, Hôpital de la Conception,

Marseille, Hôpital Lapeyronie, Montpellier, Hôpital Brabois, Nancy, Hôpital Pasteur, Nice, Hôpital Hôtel-Dieu, Nantes, Hôpital Foch, Suresnes, Hôpital Européen G. Pompidou, Paris, Hôpital H. Mondor, Créteil, Hôpital de la Pitié-Salpêtrière, Paris, Hôpital de Bicêtre, Kremlin Bicêtre, Hôpital J. Bernard, Poitiers, Hôpital F. Guyon, La Réunion, Hôpital de Pontchaillou, Rennes, Hôpital Maison Blanche, Reims, Hôpital C. Nicolle, Rouen, Hôpital Nord, Saint-Etienne, Hospices Civils, Strasbourg, Hôpital Rangueil, Toulouse, Hôpital Bretonneau, Tours.

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