Organ Failure and Patient Survival

Task 4: *Assess current policies and the potential impact of the Final Rule on patient survival rates and organ failure rates leading to retransplantation, including variances by income status, ethnicity, gender, race, or blood type.*

Abstract. **The effects of solid organ ischemic times on transplant outcomes has not been rigorously evaluated in the past. The committee reviewed existing literature and made judgments based on this information that are in general agreement with current practices. Data analysis also supports the previously reported association between volume and outcome—in this case, larger OPOs are associated with decreased mortality rates following transplantation.**

A number of biological factors can influence both short-term and long-term function of transplanted solid organs. The function of the liver, kidney, heart, lung, and pancreas depends on the continuous flow of blood through them. *Ischemic time* refers to the amount of time that elapses when blood flow to an organ is interrupted (e.g., when the organ is removed for transplantation).

Some organs appear more sensitive to ischemic damage than others. For example, with current technology, common general practice suggests that acceptable clinical results cannot be obtained with heart grafts exposed to much more than 4 hours of ischemia. Livers have longer acceptable ischemic times, and kidneys even longer, using preservation fluids such as University of Wisconsin solution and technologies such as pulsatile perfusion.

The duration of ischemic time is highly, positively correlated with the incidence *of primary nonfunction* (failure to function after a transplant). A lengthy ischemic time may also impair long-term graft function. Increased donor age and other aspects of the donor's health status, such as condition of the organ, can accentuate the impact of ischemic time on primary graft nonfunction.

Primary nonfunction refers to a situation in which the organ, after it has been transplanted, fails to function and must be replaced. For kidney graft failure, dialysis is available as a backup. For failing hearts, ventricular assist devices may be used, at least for short periods of time. With lungs and livers, no substitute is available as a therapeutic bridge. As a result, the recipient of a failed or failing transplanted lung or liver, for example, is at risk of death if he or she does not receive a replacement. However, replacement of the failed organ with a second transplant (i.e., retransplantation) means that an organ has been used that could potentially have saved the life of another individual.

Strategies that minimize the number of organs lost to primary nonfunction are essential. This goal may be accomplished by technological advances that extend maximal achievable and, in turn medically acceptable, ischemic time. Alternatively, the more immediately available approach is to minimize ischemic time. For example, it has been suggested that the rates of primary nonfunction after liver transplantation double from approximately 4 to 8 percent when cold ischemic time is extended beyond 12 hours (Ploeg et al., 1993).

Longer ischemic time is also associated with an increased rate of *delayed graft function*, i.e., a situation in which the graft eventually functions, but only after a prolonged period of time. Delayed graft function, in turn, is associated with longer hospital stays, a higher rate of morbidity and mortality in the recipient, and a higher rate of late graft loss.

An approximate 4.2 percent reduction in primary graft nonfunction, achieved by eliminating severely steatotic (i.e., "fatty") livers, reducing ischemic times, and using selected patients has been reported to reduce the need for retransplantation due to primary nonfunction or initial poor function (D'Allesandro et al., 1998). Extrapolating these data to the 4,000 transplants performed nationally would mean that 170 additional patients could receive a liver transplant. This compares favorably with the increase in recovered cadaveric livers of only 231 between 1997 and 1998. This example does not prove that this strategy is correct or should be universally adopted. Rather, the example illustrates how careful scrutiny of procurement and utilization practices and subsequent clinical outcomes may be used to model and then measure optimal management of a scarce human resource.

ORGAN PRESERVATION AND DONOR INFLUENCES

In the early days of transplantation, the optimal approach to preserve and protect the function of organs deprived of their blood flow had not been well explored. As a result, the donor and recipient had to be located very close to each other to minimize ischemic time. Methods to improve the medically acceptable ischemic time became an intense focus of research that continues. As organ preservation and technical aspects of transplantation improve, the geographic limitations for organ transport have been eased, but not totally eliminated.

The medical literature addressing the impact of cold ischemic time on outcome is expanding but is not yet sufficiently developed to state with certainty the optimal times on an organ-by-organ basis. Even the basic criteria by which viability and function are judged in laboratory-based studies are subject to scientific debate. More to the point, the number of patient and donor variables that confound the interpretation of clinical transplant results is large. Moreover, variability among transplant programs in their philosophy regarding the use of extended criteria donors and organs, as well as the role of retransplantation, significantly affects the results produced in any series.

In addition to ischemic time, several donor factors also influence graft survival. As a result of the shortage of organs for transplantation, the criteria for organ donation have been expanded to include marginal donors (i.e., extended criteria donors) for those candidates awaiting a transplant who could face death if a donor does not become available within a limited time. Donor age, health at the time of donation, and the presence of fatty change on donor liver biopsy are all representative of donor and donor organ characteristics that may influence graft survival.

The transplant team needs to have the flexibility to apply medical judgment in selecting extended criteria donors for candidate recipients with life-threatening organ failure. These decisions may relate solely to the donor source or to the recipient's medical status, and the results of such transplantation decisions must be weighed in clinical context. As an example, approximately 50 percent of candidates for a cardiac transplant die before a donor becomes available. In this circumstance, a 10–15 percent risk of primary graft nonfunction, hypothetically, might be acceptable if the patient was medically decompensating and likely to die if no donor were available. However, the increased use of non-heartbeating donors and other extended criteria donors must be prospectively evaluated within the context of current and novel technology. The impact on total organ allocation among potential recipients must also be assessed. These analyses must be formulated in a manner that recognizes that clinical and programmatic philosophies will influence perceived differences in outcome.

REVIEW OF LITERATURE

As the science of organ preservation continues to advance, the duration of tolerable ischemic time from organ procurement to organ transplantation may increase. An important distinction must be made, for purposes of this analysis, between what might be labeled "maximal achievable cold ischemic time" (i.e., the longest duration of cold storage to which an ideal organ can be exposed and still have some measurable chance of functioning when reanastomosed to a blood supply) and "medically acceptable ischemic time" (i.e., the duration of cold ischemia that has been associated in clinical experience with an appropriate and acceptable percentage of acute and long-term organ survival). These times may differ significantly. Improvements in the former rely primarily on advances in technology, which are then explored in clinical studies to determine the rates of acute and long-term graft function. In addition, although the maximal achievable ischemic time may be an absolute, the medically acceptable ischemic time will differ depending on the relative scarcity of the organ, the opportunities for retransplantation, the condition of the patient, and increasing knowledge of synergistic variables that influence ultimate organ survival.

Based on a review of the existing literature on organ preservation and patient survival, outlined in Tables 6-2 through 6-6, the committee generated a summary of its findings, which are presented in Table 6-1. The figures presented

in Table 6-1 are not meant to be standards of practice, but rather approximations that will vary as a function of other factors (described above). Although these findings should not be interpreted as absolute standards, they tend to agree in general with the current practice among transplant professionals.

ASSESSING THE IMPACT

Any strategy to expand organ allocation areas, for example, as described in this report, would have to take into account the very significant efforts devoted to matching a suitable donor with a suitable recipient, including the mechanisms currently used by the OPO system to expedite organ recovery and distribution. Given current biological constraints, any format must have as a central goal an organ allocation policy that serves to minimize ischemic time within reasonable limits in locating a potential recipient. That this function can be performed for some organs on a large geographic basis with some efficiency is attested to by current practice nationwide as well as the results within regional sharing programs.

Health outcomes data of several different types will be needed to assess and monitor the impact of biological factors on the organ distribution and allocation system. The data collected should inform the evaluation of minimum performance criteria for the organ procurement process and the transplantation process itself because they may have an impact on organ viability. Rigorous evaluation of the procurement process would appear to be a sound principle.

TABLE 6-1 Summary of Literature on Cold Ischemic Time for Solid Organs

Organ	Medically Acceptable Cold Ischemic Time* (simple cold storage using appropriate preservation fluids) (hrs)
Liver	12
Pancreas	17
Kidney	24
Heart	4
Lung	6–8

*The committee defines medically acceptable cold ischemic time as the duration of cold ischemia that has been associated in clinical experience with an appropriate and acceptable percentage of acute and long-term graft function and survival. The times presented in this table are based on the committee's review of peer reviewed literature. Longer times are sometimes reported in clinical practice with acceptable outcomes. Outcomes vary as a function of many other factors, including age of donor and quality of organ.

Data provided by the United Network of Organ Sharing (UNOS) suggest that between 450 and 550 (or 10–13 percent) of livers recovered per year (1994–1998) are not transplanted. It is difficult to ascertain the exact reasons for this, although possibilities include a marginal donor, difficulty in finding a second center in a timely manner after the first choice rejects the organ, or the finding of extensive steatosis or hepatitis in the donor organ. Each of these losses may be unavoidable. Alternatively, many of these lost opportunities might be avoided by improved communication and tracking—for example, data on the time from notification of a possible donor to the time that formal contact between the OPO and family is established; time to obtain permission for donation; time to scheduling of organ harvest; duration of the organ harvest procedure; number of organs procured but not used; and cold ischemic time of procured organs stratified by appropriate geographic criteria (e.g., miles traveled).

Transplant center-based measures would likely include the number of delivered but discarded organs; number of transplanted organs with primary nonfunction or delayed graft function; and the number of patients requiring retransplantation. Both acute and chronic organ survival could be followed and analyzed by appropriate demographics to suggest where more efficient organ allocation might be implemented to maximize organ utilization. A method to ensure the accuracy of data reporting as well as the timely availability of data is essential.

Despite the variable nature of patients and donors, other parameters that are well within the control of the system may be associated with divergent results. Appropriate and timely data analysis will strengthen the ability of the medical and allied communities to make strategic decisions in this regard. Promulgation and enforcement of minimum performance guidelines should help optimize graft survival of the overall population. Given the critical nature of this system, all involved parties should be monitored for quality control and quality assurance and for compliance with recommended methods and processes. Lastly, appropriate measures are needed to assess the impact of the Final Rule on the biological and practical measures that affect organ failure and patient survival. It must also be recognized that as methods for preservation or other technologies change, the system must be flexible enough to incorporate new data. The National Marrow Donor Program is offered as an example of a system that has operated well with respect to many of these factors (see Box 6-1).

Computer Simulation Models

Historically, the primary approach to exploring the impact of various changes on the allocation system has been through the use of computer simulation models. These models allow the user to input various characteristics of the organ allocation system (e.g., initial waiting list composition, recipient stream, status changes, donor stream, allocation policy, liver offer/acceptance process, post-transplant relisting/mortality) and then simulate the impact that various changes in organ allocation policies have on relevant outcomes (e.g., numbers of

primary and repeat transplants; distribution of transplants by medical urgency status; posttransplant survival rates; percentage of transplants performed locally, regionally, and nationally; cost-related measures; and, waiting times).

As an illustration, change from the current allocation policy to a system using expanded allocation areas is generally expected to increase the number of status 1 patients receiving liver transplants and decrease the number of status 3 patients receiving transplants. Depending on the assumptions of the model, this change can lead to either increased or decreased posttransplant survival. The outcomes and conclusions of the simulation models are highly dependent on the assumptions upon which they are based.

This has largely been the case for the two major simulation models used in this area; the Pritsker model used by UNOS and the CONSAD model used by the University of Pittsburgh. In general, the Pritsker model shows that national organ sharing will result in more repeat transplants and poorer posttransplant survival than will the current system (Edwards and Harper, 1995). Although there is some evidence of reduced pretransplant mortality, it is at the expense of increased posttransplant mortality.

The CONSAD model also shows a decrease in pretransplant deaths but an increase in posttransplant deaths (CONSAD, 1995). The two models differ slightly because the CONSAD model assumes that, under a national sharing system, status 3 patients are at increased risk of death following transplant. The CONSAD model also shows a larger number of status 1 patients would die under a national system than does the Pritsker model.

Those developing the Pritsker model had an advantage over the CONSAD model because of their complete access to all center-level data from UNOS. Furthermore, they were able to validate their simulation model results using the rates actually observed in the population of transplant patients over time.

POSTTRANSPLANT PATIENT SURVIVAL

In an effort to better understand the determinants of organ failure and posttransplant survival, the committee examined posttransplant mortality data for liver transplant recipients who were transplanted in 1998 and 1999, using the data provided to this committee by UNOS. Attention was restricted to this more current period because of the change by UNOS in 1998 to the definitions of medical urgency status categories. This time restriction severely limits both the length of follow-up and the number of transplanted patients for which follow-up information was available. Therefore, this analysis should be replicated as more follow-up data under the new status system become available.

BOX 6-1 National Marrow Donor Program

The National Marrow Donor Program (NMDP) is a nonprofit organization that has a cooperative agreement with the Department of the Navy and a competitively renewed contract with the Health Resources and Services Administration. The mission of NMDP is to identify hematopoietic stem cell donors and then procure and deliver stem cell transplants to patients who do not have a suitably matched family member donor. This organization has a clearly stated set of minimum performance criteria for both donor harvest (procurement) and transplant centers. NMDP has also developed criteria that govern allocation (e.g., donors must match at five or more of six prescribed histocompatibility loci), and there is centralized training and retraining of personnel involved in the donor search process (which is the closest analogue of the solid organ allocation process). There is a requirement that any change in the ability of the center to meet any of the above as well as many other criteria must be reported immediately. Acceptance as a center of any sort (transplant, donor harvest) is dependent on having appropriate computer and communication software and hardware on-site and operational. Strict time criteria exist for merging data with the NMDP central data file. For example, donor recruitment centers must merge these data at least monthly and must use either NMDP-developed software or other software that meets NMDP standards. All centers must meet or exceed the NMDP continuous process improvement indicators. Centers are given frequent feedback on task-appropriate indicators. Data are analyzed centrally, not locally, and feedback enables the center to measure its own performance as well as compare its performance to that of other centers. In addition, an NMDP statistician analyzes the aggregate data to ascertain whether there is systematic improvement or deviation from standards and then recommends actions.

There are significant medical differences between solid organ and bone marrow transplantation, as well as many differences in the processes of donor recruitment and organ procurement. However, there are also significant commonalties in making a scarce human resource available to critically ill individuals in a reproducible, effective, and safe fashion. Many of the issues that concern access for the socioeconomically underserved as well as the particular biologic issues that influence organ availability for minority populations are common to both groups. Thus, with due acknowledgment of the divergence between these disciplines, NMDP serves as an illustration of a federally funded organ procurement and allocation organization with a highly regulated set of performance standards for itself and its participating centers. This program demonstrates that a sophisticated data monitoring process that includes a significant quality assurance–quality improvement component can serve a diverse national constituency of small to large procurement and transplant centers. Central data analysis and analyses performed after application by interested parties are made available to the community in a timely fashion. This and other models, thoughtfully adjusted for discipline-specific issues, may provide practical tools to improve and enforce more regularized practice in the area of solid organ procurement, allocation, and transplant.

The sample was comprised of 1,095 transplanted patients in status categories 1, 2B, and 3. The follow-up period ranged from 0.03 month to 17.83 months, with an average follow-up of 3.30 months. The committee examined blood type (O and B versus A and AB), age (0–5, 6–17, and 18 and older), gender, race (black versus other), status (1, 2B, and 3), OPO volume (small, medium, and large),[*] and follow-up time as potential predictors of patient survival. In addition, OPO-specific effects were included as a random effect in the model. A mixed-effects "person–time" logistic regression model was used to analyze these data and follows directly from the previously described mixed-effect multinomial logistic regression model, where interest is restricted to only two outcomes (i.e., dead or alive).

Results of the analysis revealed that risk of posttransplant mortality for status 1 patients significantly decreased over time ([MMLE] = –0.58, SE = 0.089, $p < .001$). Similarly, patients transplanted in status 2B (MMLE = –0.74, SE = 0.298, $p < .01$) and status 3 (MMLE = –1.37, SE = 0.529, $p < .01$) both had decreased risk of mortality relative to patients transplanted in status 1.

The analysis also showed that patients located in smaller-volume OPOs had increased risk of posttransplant mortality relative to those in larger-volume OPOs (MMLE = 0.79, SE = 0.323, $p < .01$). These results are not readily explainable. Because smaller OPOs have a larger proportion of status 2B and status 3 patients receiving transplants than larger OPOs, smaller OPOs should be expected to have lower mortality rates. The results found may be explained with the fact that, as a general rule, smaller OPOs are serving lower volume transplant centers. There is considerable health services research indicating that, for a variety of other surgical procedures, there is a positive correlation between volume and patient outcomes (Hannan, 1995; Hosenpud, 1994). Although the committee did not find comparable research for liver transplantation, it did find that the 1997 Report of Center Specific Graft and Patient Survival Rates, produced by UNOS (UNOS, 1997), contains a table showing that several of the transplant centers doing 25 or fewer liver transplants had 1-year graft survival rates significantly lower than expected, given the health status of their patients (See Fig. II-2, pg. 15, UNOS, 1997). Further research is needed before any definitive conclusion can be drawn. Therefore, the committee is reluctant to draw any inference as to whether or how graft and patient survival might be affected by the broader sharing of organs.

CONCLUSIONS

Ischemic times for solid organs have not been rigorously evaluated in the past and they are an important factor in the calculus of allocation. The committee re-

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[*]OPOs were split into three groups (17, 17 and 18 for large, medium and small OPOs respectively) on the basis of number of transplants performed during 1995-1998. In general this breakdown corresponded to the following definitions: small (S) OPOs performed < 150 transplants during the period 1995–1999; medium (M) OPOs performed 150–300 transplants in the same period; and large (L) OPOs performed > 300 transplants.

viewed existing literature and made judgments based on this information that are in general agreement with current practices. Data analysis also supports the previously reported association between volume and outcome—in this case, larger OPOs are associated with decreased mortality rates following transplantation.

TABLE 6-2 Heart: Summary of Literature on Cold Ischemic Times

Source	Solution	No. of Transplants	Preservation Time	Comments
Korner et al., 1997	HTK solution (Bretschneider), University of Wisconsin Solution (UW)	100	> 4-hr CIT vs. < 4-hr CIT	• Retrospective Evaluation • A preservation time of up to 5.5 hrs using HTK-solution satisfies early and long-term survival rates compared to heart transplants with ischemic times of < 4 hours. • Demonstrated no survival differences in either the short term or long term.
Briganti et al., 1995	Euro-Collins	151	< 4 hrs, 4–5 hrs, > 5 hrs	• Short and Long-Term Outcome Study • An increase in the available donor pool has been facilitated by the use of allografts with prolonged ischemic time (>4 hrs). • No difference in allograft functional capacity, development of transplant-associated coronary disease, or actuarial survival in the short and the long term. • Conclusion: Improved population treatment with prolonged ischemic time cardiac allografts can be safely undertaken without long-term risk to heart transplant recipients. • Intermediate- and long-term survival has not been compromised by the use of cardiac allografts with ischemic times up to 441 minutes. • Prolonged ischemic time cardiac allografts (> 5 hrs) can be successfully used in clinical heart transplantation with acceptable outcome.

Young et al., 1994	1,719	• Consecutive Primary Transplantation
		• Probability of death within one moth increases with longer ischemic time (i.e., > 4 hrs).
		• Transplants were performed at 27 institutions between Jan. 1, 1990, and June 30, 1992, were analyzed.
		• Mean follow-up of survivors was 13.9 months, and actuarial survival was 85% at 1 year.
		• Most common causes of death were infection (22%), acute rejection (18%), and early graft failure (18%). Forty-five percent of the deaths occurred within 30 days of transplantation.
		• The risk of failure increases with donor age and the interaction of advanced age with other risk factors.
		• Mean follow-up of survivors was 13.9 mos., and actuarial survival was 85% at 1 year.

CIT = Cold ischemic time.

TABLE 6-3 Kidney: Summary of Literature on Cold Ischemic Times

Source	Solution	No. of Transplants	Preservation Time	Comments
D'Alessandro et al., 1991	UW	68	Mean 18.3 ± 4.3 hrs, range 6–28 hrs	• Retrospective Analysis • Actuarial renal allograft survival as 97.8% and 86.6% at 1 month and 2 years, respectively.
Belzer et al., 1992	UW	163	Kidney: 19.2 ± 4.3 hrs, range 4–27 hrs	• Retrospective Analysis • Time period: May 1997-November 1991. • Simultaneous pancreas–kidney transplants. • No differences in allograft function or graft-related complications in organs preserved for <12 or >12 hrs. • Liver, kidney, and pancreas can be safely preserved for times that currently meet most clinical needs (i.e., 24–40 hrs). • After transplant pancreas/kidney , the actuarial patient survival was 97.5% and 96.8% at 1 month, and 83.0% and 83.4% at 4 years, respectively.
Lange and Kuhlmann, 1998				• Literature Review • No correlation between CIT and histopathological changes or serum creatinine levels. • Conclusion: Immunological factors such as human leukocyte antigen mismatches, preformed cytotoxic antibodies, and the number of previous grafts have had a greater impact on graft survival than CIT. • Conclusion: Organ sharing would be almost completely abandoned and HLA mismatch rate would increase tremendously with the introduction of ultrashort CIT (<6 hrs) into clinical practice.

Offermann, 1998			• Literature Review • Long-term graft outcome clearly depends on the length of CIT, with significantly inferior results after CIT > 36 hrs. • A reasonable CIT (<18–24 hrs) allows surgery to be performed during the day.
Opelz, 1998	UW	• Group 1: 7 to 12 hrs • Group 2: 13 to 24 hrs • Group 3: 0 to 6 hrs	• Collaborative transplant study • Time period: 1986–1996. • Group 1 had the best long-term survival (75% at 5 years); Group 2 was slightly worse; Group 3 was worst (65% at 5 years). • Conclusion: No clear relationship between the length of warm ischemia and graft outcome. • Decrease in the success rate as cold ischemia increased from 7 to 12 hrs to 37 to 48 hrs. • Some centers believe that short ischemia times eliminate the need for HLA matching. • Only kidneys preserved with the cold storage method were analyzed: machine perfused kidneys were excluded.
Shaheen et al., 1994	CyA (cyclosporine)	Mean CIT: 46 hrs, range: 18–72 hrs	• Time period: 1983–1987. • Patients received kidneys from Eurotransplant. **Actuarial graft survival:** • 1 year: 88.6% • 3 years: 70.2% • 5 years: 58.4% • 7 years: 55.1%

Continued

TABLE 6-3 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Shaheen et al., 1994 (*continued*)				**Actuarial patient survival:** • 1 year: 94.3% • 3 years: 91.4% • 5 years: 88.5% • 7 years: 88.5% • Good prognosis for patients with prolonged CIT (even when immunosuppressed with CyA). • 35 patients whose grafts survived for > 6 months. • Long-term results unknown.
Pita et al., 1997	UW	858	• Group 1: 0–24 hrs • Group 2: >24 hrs	• Used consecutive patients in a Spanish hospital Cadaveric Kidney Transplants **Graft survival, Group 1:** • 1 year: 86.4% • 2 years: 83% • 3 years: 80% • 5 years: 72.8% **Graft survival, Group 2:** • 1 year: 77.9% • 2 years: 73.5% • 3 years: 65.1% • 5 years: 58.7% • CIT > 24 hrs vs. 0–24 hrs has an RR = 1.75 (95% CI: 1.052–2.91); prolonged CIT (>24 hrs) exerts an independent adverse effect on graft survival.

NOTE: CI = confidence interval; CIT = cold ischemic time; RR = relative risk; and UW = University of Wisconsin solution.

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TABLE 6-4 Liver: Summary of Literature on Cold Ischemic Times

Source	Solution	No. of Transplants	Preservation Time	Comments

Kalayoglu et al., 1988	UW	17 transplants, 13 with storage > 8 hrs	• Group 1: 8 livers ≤10 hrs (mean 8 hrs)
			• Group 2: 9 livers >10 hrs (mean 12.7 hrs; range 11–20 hrs)
			
			Total Preservation time: 6–20 hrs (mean: 10.5 hrs)
				• All had good liver function, even when preservation time > 10 hrs (mean 12.7 hrs, range 11–20 hrs).
				• No differences between groups in:
				  – total bilirubin concentration in the first postoperative week,
				  – serum aspartate aminotransferase,
				  – prothrombin, and
				  – partial thromboplastin time.
				• Other liver enzymes showed normal levels within 5 days.
				• All patients discharged with normal liver function and enzyme values.
				• Acceptable liver function when preservation ≤ 8 hrs

Todo et al., 1989	UW, 4–24 cadaveric liver homografts: 185 (mean 10.1 ± 5.0) Euro-Collins solution 3–9, 5 hrs: 180 (mean 5.9 ± 1.4 hrs)	UW: 185 cadaveric liver homografts Euro-Collins: 180 grafts	• With UW: 4–24 hrs • With Euro-Collins: 3–9.5 hrs	• Comparison between liver preserved with UW and Euro-Collins solution. • UW-preserved grafts survived at higher rate. • Permitted equal patient survival. • Lower rate of primary nonfunction. • Reduced need for retransplantation. • Lower rate of hepatic artery thrombosis—no correlation between time of preservation with UW preserved grafts up to 24 hrs and liver function abnormalities in the first postoperative week • Maximum increase in serum aspartate aminotransferase and serum alanine aminotransferase in first week was not greater than with Euro-Collins-preserved livers. • No differences in prothrombin for UW livers.

				• Livers preserved with Euro-Collins solution for >5 hrs had significantly increased perturbation of hepatic function tests (significant increases in serum aspartate aminotransferase and serum alanine aminotransferase levels).
D'Alessandro et al., 1991	UW	181	Mean 12.6 ± 4.5 hrs, range 2–24 hrs	• Retrospective Analysis • Time period: May 1987 to June 1990 • No differences in primary nonfunction or hepatic artery thrombosis were seen for those preserved <6 hrs, 6–12 hrs, or >12 hrs. • Serum aminotransferase levels and prothrombin times were lower on the first postoperative days in livers preserved for <6 hrs when compared to 6–12 hrs or >12 hrs. • Comparison of rates of PNF for reduced and nonreduced liver transplantation also failed to demonstrate a statistical difference. Likewise, the length of preservation for up to 4 hours did not impact on the development of PNF. • The actuarial 1-month patient survival for liver transplant was 91.5%. Actuarial 1-month allocation survival for liver transplants was 83.0%.
Belzer et al., 1992	UW	288	Mean 12.7 ± 4.4 hrs,	• Retrospective analysis from May 1987 to Nov. 1991 • No differences in allograft function or graft-related complications in organs preserved for <12 hrs or >12 hrs; no differences in rates of PNF, hepatic artery thrombosis, or bile duct stenosis for < 12 hrs or > 12 hrs preservation. • Grafts preserved for <6 hrs: less hepatocellular injury (lower serum enzymes including aminotransferases and lactate dehydrogenase). *Continued*

TABLE 6-4 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Belzer et al., 1992 (*continued*)				• Length of stay in intensive care unit after liver transplantation did not correlate with length of preservation but appeared to correlate with the patient's condition before transplant. • One-month patient and graft survival was 91.4% and 80.2% respectively.
Porte et al., 1998	UW	315		• Retrospective European multi-center analysis • Overall patient survival: 3 months, 83%; after 6 years, 63%. • Median CIT was significantly longer in grafts with primary nonfunction (PNF) compared to initial poor function (IPF) or immediate function. • Long-term graft survival was significantly influenced at a lower CIT threshold, with a 6-year graft survival of 67% for CIT of 16 hrs compared to 46%% for CIT > 16 hrs. • Patients with PNF but not IPF have significantly lower CITs. • There is a definitive effect of length of CIT on graft survival. • Follow-up analysis after 3 months indicates that preservation times up to 18 hrs with UW are without adverse effects on long-term graft survival after transplantation. • Long-term data with a 6-year follow up indicate that CIT should be kept to <16 hrs to avoid detrimental effects on graft survival.

- Complete follow-up of at least 6 years was available for 296 grafts in 277 patients.
- Patients with IPF had a 34% lower GS at 3 months than those with immediate function.
- 315 transplants were performed in 288 patients in participating European centers.

Furukawa et al., 1991	593	Groups (CIT):	

Groups (CIT):
- 1: <10 hrs, $N =$ 223;
- 2: 10–14 hrs, $N =$ 188;
- 3: 15–19 hrs, $N =$ 101;
- 4: 20–24 hrs, $N =$ 52; and
- 5: ≥25 hrs, $N =$ 29.

Mean CIT: 12.8 hrs, range 2.4–34.7 hrs

- 13–32 Months of post-transplant observation
- Cadaveric livers were used for primary liver transplant between Oct. 1987 and May 1989 at the University of Pittsburgh
- No difference among the five groups in 1-year patient survival; highest serum glutamic oxaloacetic transaminase (SGOT) occurred in the first week after operation and the highest SGOT and total bilirubin during the first month after operation.
- However, the retransplantation rate and primary nonfunction rate rose significantly as CIT increased (using a logistic regression model).
- Equivalency of patient survival was increasingly dependent on aggressive retransplantation.
- Results reported caution against undue procrastination in the use of these livers.
- Most of the organs preserved for ≥20 hrs were satisfactory, attesting to the efficiency of the method used. The necessity for life-saving retransplantation because of primary graft nonfunction or other reasons became progressively more frequent.
- Effective use of retransplantation prevented a commensurate increase in mortality.

Continued

TABLE 6-4 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Furukawa et al., 1991 (*continued*)				Policy formulated from findings of the study: • Need to revascularize liver grafts within 20 hrs because the early graft failure rate was increasingly nonlinear beyond this time. • Patient survival was 77.2% at the end of 1 year; there was no difference in patient survival between the different CIT groups. • Differences existed in early graft survival. • When the CIT was less than 10 hrs, the retransplantation rate was 5.4%, whereas it was double, triple, or quadruple, this rate with successively longer preservation times. • Primary nonfunction was the principal course of graft loss during the first 2 weeks no matter what the CIT, and rejection was the lest important factor.
Rossi et al., 1993	UW	62	Mean: 12.6 hours Range: 6–20 hours	• In 51.5% of cases with CIT > 12 hrs, incidence of delayed liver function (DLF) has not exceeded 29.5%, as retransplantation due to PNF or technical failure has never been required. • Results may be partially attributed to homogeneous, careful donor selection and liver harvesting procedures. • Even if UW allows one to safely extend liver preservation up to 24 hrs, such a prolonged CIT is associated with an increased incidence of delayed liver function; thus, concluded that these organs should not be transplanted into marginal recipients, but only into those who could tolerate a more complicated postoperative course.

| Marino et al., 1997 | UW | 2,376 | Transplantations performed from November 1987 to December 1993. Purpose of the study was to identify the risk factors associated with an unfavorable outcome following orthotopic liver transplantation (OLTx). Total ischemic time was found to be associated with outcome of liver transplant (graft failure): Odds ratio = 1.3 for each 6-hr increase in CIT after the first 8 hrs; 95% CIT 1.1–1.5. Three donor variables (donor age, female donor sex, and total CIT) and 7 recipient variables (recipient age, indication for OLTx, history of prior OLTx, need for preoperative mechanical ventilation, preoperative bilirubin and creatinine, type of primary immunosuppressant) were foundt to be independently associated with graft failure. Number of successful transplants: 1,635 Number of transplants that failed: 741 |
| Haller et al., 1995 | UW (for majority of grafts: 433 of transplants, or 95.8%) | 452 | Transplantation occurred between September 1988 and December 1993 in 414 patients. Grafts developing primary dysfunction (PDF) had significantly longer CIT: 12 hrs for PDF vs. 10 hrs for initial function (IF). Donor age was significantly higher: PDF, 38 years; IF, 29 years. One-year graft survival was 88.0% in the IPF group and 85.1% in the IF group. The extent of CIT was the most important risk factor leading to PDF in this population. Concluded: CIT should be kept below 12 hrs whenever possible to avoid the development of PDF.   *Continued* |

TABLE 6-4 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Adam et al., 1995	UW, Euro-Collins	789		• Retrospective analysis of implants at one center • Study conducted: November 1984– March 1992 • Compared survival of livers from donors of different age groups: – Group 1: <30 years (281 livers) – Group 2: 30–49 years (206 livers) – Group 3: ≥50 years (51 livers) • Graft survival was comparable among groups both within 1 month and 1 year after liver transplant. • However, as far as grafts preserved for an ischemic time exceeding 12 hrs, maximal alanine transaminase levels were higher and PT and bile output decreased with increasing time. • No difference in 1-month graft survival was noted, but a difference in graft survival existed at 1 year when CIT > 12 hrs. • Liver grafts from donors > 50 years old and submitted to CIT exceeding 12 hrs demonstrated increased transaminase levels, lower PT, and lower bile output as compared to young livers. • 1-year survival of grafts also decreased with increasing age. • Cumulative effects of advanced age and extended ischemia may be deleterious.
Deschenes et al., 1998	Retrospective analysis of transplants at 3 centers	710		• Authors evaluated the incidence of early allograft dysfunction (EAD), its effect on long-term allograft survival, and factors contributing to this. • EAD occurred in 23% of recipients who had a worse clinical outcome. • Those with EAD had worse 3-year graft survival (68% vs. 83%). • EAD was independently associated with CIT ≥ 15 hrs.

Ploeg et al., 1993	UW (n = 277) Euro-Collins (n = 46)	323	• Group 1: 1–6 hrs • Group 2: 6–12 hrs • Group 3: 12–17 hrs • Group 4: > 17 hrs	• Retrospective analysis • Analysis conducted: November 1984 to March 1992 • This series reviewed 323 orthotopic liver transplants to identify possible risk factors for 2 forms of primary dysfunction (PDF) of the liver: primary nonfunction (PNF) and initial poor function (IPF). • Group 1: 83% IF (initial function), 14% IPF, 3% PNF • Group 2: 83% IF, 13% IPF, 4% PNF • Group 3: 74% IF, 18% IPF, 8% PNF • Group 4: 62% IF, 27% IPF, 11% PNF • Occurrence of both IPF and PNF resulted in a higher graft failure rate, retransplantation rate, and patient mortality within the first 3 months after liver transplantation. • Multivariate analysis of potential risk factors showed that reduced-size liver, fatty changes on donor liver biopsy, older donor age, retransplantation, renal insufficiency, and prolonged ischemia times were independently associated with a higher incidence of IPF and PNF. • Post liver transplantation: PDF was 22% (73/323), PNF occurred in 6% (20/323), and 16% (53/323) IPF found. **Risk factors for the development of PDF included:** • older donor age (>49 years), • longer donor hospitalization (>3 days), • extended preservation times (>18 hrs), • fatty change on donor biopsy, • renal insufficiency, • reduced liver size, and • younger recipient age.

TABLE 6-4 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Ploeg et al., 1993 (*continued*)				**No significant correlation was observed between:** • etiology of end-stage liver disease, • nutritional status of patient, • UNOS status, • child's (Child-Pugh) classification, and • PDF. • Note: the lack of statistically significant correlation between some of these factors and IPF or PNF does not necessarily prove lack of relationship between these variables and PDF. **Conclusions:** • Results of study highlight the importance of IF of the liver after transplantation. • Impact of PNF and IPF are significant as 2 separate forms of PDF. • IPF of livers should be recognized as a separate clinical entity with its own significant effects.
Kadmon et al., 1993	UW	59	Range: 4–22 hours; used a cut-off time of 10 hrs	• The objective in this report was to examine the possibility that long CIT has an adverse effect on the biliary system in allografts not damaged by ABO incompatibility or thrombosis. • 59 Patients were identified using 10 hrs of CIT as the cutoff; unknown etiologies for biliary complications occurred in 7% of patients with <10 hrs of CIT and 27% of patients with >10 hrs of CIT. • Conclusion: cold preservation appears to represent the major causative explanation for bile complications occurring after CIT of longer than 10 hours.

| Sanchez-Urdazpal et al., 1992 | UW (91) Euro-Collins (97) | 188 | • UW: 5–19 hrs
 • Euro-Collins: 4–9 hrs | • Retrospective study of transplants at one center
 • Purpose: To evaluate risk factors for ischemic-type biliary complications (ITBC) (excluding ABO incompatibilities, chronic rejection, and hepatic artery thrombosis).
 • Results: 17% of these patients had ITBC. With UW, grafts with ischemic times of <11.5 hrs had 2% ITBC; in contrast, grafts with ischemic times of >11.5 hrs had 35% ITBC. With Euro-Collins, ischemic time < 6.5 hrs had 2% ITBC; ischemic time >6.5 hrs yielded 24% ITBC.
 • Prolonged CIT may cause either direct ischemic injury or predisposes to reperfusion injury. |
| Mor et al., 1993 | UW | 419 | < 12 hrs
 > 12 hrs | • Retrospective study of transplants at one center
 • Authors evaluated the incidence of hepatic artery thrombosis (HAT) with prolonged preservation with UW; background for this study included prior work showing that prolonged preservation with Euro-Collins is associated with HAT.
 • 12 patients (3.3%) developed HAT.
 • Results: Graft survival after HAT is 33.3%, with patient survival at 75% in this population.
 • 7 Out of 165 patients with CIT > 12 hrs developed HAT.
 • 3 Out of 234 patients with CIT < 12 hrs developed HAT.
 • Warm ischemic time was the same in patients who developed HAT and those who did not.
 • Conclusion: This is the first study to report an association between UW and HAT similar to that seen with Euro-Collins solution; a possible explanation for this finding is that a disturbance of the vascular microcirculation due to endothelial damage during CIT may activate coagulation factors predisposing to thrombosis. |

Continued

TABLE 6-4 *Continued*

Source	Solution	No. of Transplants	Preservation Time	Comments
Strasberg et al., 1994	Not applicable	Not applicable		• Literature Review • Injury is a microvascular injury; it appears to be delayed rather than changed by UW. • CIT of 30 hrs seems to be *absolute risk factor* for development of PNF using UW. • Two large studies identified CIT = *12 hrs as a relative risk factor* for IPF. • It is not yet clear how long the period of cold preservation must be to lead to increased relative risk; shortest cold preservation time to be a relative risk factor has not been established.
Angelescu et al., 1999		44	• No injury mean = 10.1 hrs • Moderate injury mean = 14.9 hrs • Severe injury mean = 12.9 hrs	• Histologic examination of graft biopsies obtained 1 hr after graft revascularization • Associated with CIT (≤12 hrs); increased damage to the liver allograft as demonstrated by propagation of intrasinusoidal granulocytes. • Evaluated histologically the outcome of orthotopic liver transplants after prolonged ischemic times

NOTE: CIT = cold ischemia time; IF= immediate function; IPF = initial poor function; ITBC = ischemic-type billary complication; PNF = primary nonfunction; PT = prothrombin time; and UW = University of Wisconsin solution.

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TABLE 6-5 Lung: Summary of Literature on Cold Ischemic Times

Source	Solution	No. of Transplants	Preservation Time	Comments
Kirk et al., 1993				• Literature review • Authors reviewed 10 years of pulmonary transplantations and reviewed the relative merits of current preservation techniques of core-cooling and single flush perfusion. • Solution most commonly used for flushing is Euro-Collins; clinical experience with single flush perfusion is greatest with this solution. • Steroids are used widely as an adjunct to preservation. • Ischemia of the lung is better tolerated in conditions of hypothermia than normothermia; it is common practice to flush lungs with a solution at 4ºC and to store and transport them at 4ºC on ice. • Preservation of the lung is better when it is inflated. • The optimal gas mixture with which to ventilate and store lungs is not known. • Double lung transplantation is perhaps the ideal model for assessing lung preservation, but operative mortality is high. • Concluded that safe limits of such techniques extend only to 6 hours of ischemia.
Wahlers et al., 1991	First four patients: core cooling of the donor; for the rest: modified Euro-Collins and prostacyclin	44	Mean: 241; 176–390 minutes Range: 3–6.5 hours	• Prospective single-, double-, or heart–lung transplants • December 1987 to February 1991: 44 patients underwent either single-, double-, or heart–lung transplantation. • Authors concluded that lung preservation with modified Euro-Collins solution and prostacyclin for flush perfusion of the pulmonary artery will result in excellent lung function early postperatively with ischemic times up to 6.5 hrs.

Grover et al., 1997		• Review of studies for the past 10 years • Review covering the history of and recent advances in lung transplantation. • Article reviewed the results of single, double sequential, and heart–lung transplantation over the past 10 years as reported by the International Society for Heart and Lung Transplantation Database; also reviewed the statistics of the lung and heart–lung tranplantation program at the Univ. of Colorado Health Sciences Center. • Lung preservation techniques are now capable of preserving lung for up to 8 hours of CIT, utilizing cold modified Euro-Collins pulmonoplegia and intravenous PGE to the donor. • Concluded: during the past decade, significant improvements have resulted in single and double-sequential lung transplants. • Areas for continuing and future investigation: living related lobar transplantation, new antirejection agents, chimerism, and xenograft transplantation.
Hopkinson et al., 1998	UW, Euro-Collins, and Papworthy	• Survey • Worldwide survey of the 125 centers performing lung transplantation was conducted by questionnaire; 112 (90%) replies were received. • Maximum ischemic period accepted by centers varies from 4 to 12 hrs, with median periods of 8, 7, 6, and 6 hrs for the UW, Euro-Collins, Papworth, and donor core-cooling centers, respectively. • Beginnings of a trend toward the use of UW and a slightly warmer storage temperature. • Conclusion: there has been a trend toward the use of UW solution and a slightly warmer storage temperature. However, for most centers, graft storage techniques have changed little over the past decade.

NOTE: CIT= cold ischemic time.

TABLE 6-6 Pancreas: Summary of Literature on Cold Ischemic Time

Source	Solution	No. of Transplants	Preservation Time	Comments
D'Alessandro et al., 1991	UW	92 (combined pancreas–kidney)	Mean 16.7 ± 4.4 hrs, range 4–27 hrs	• Retrospective analysis • Analysis conducted: May 1987 to June 1990. • Early pancreatic allograft function was excellent for up to 24 hrs of cold storage preservation. • No differences in pancreatic function were noted for organs that were preserved for <6 hrs, 6–12 hrs, or >12 hrs.
Belzer et al., 1992	UW	163 (simultaneous pancreas–kidney transplants)	17.2 ± 4.4 hrs, range 4–27 hrs	• Retrospective Analysis • Analysis conducted: May 1987 to Nov. 1991. • No differences in pancreas allograft function or rate of graft-related complications in organs preserved for <12 hrs or >12 hrs. • After combined pancreas/kidney transplantation, there was one initial nonfunction (0.6%) and 2 episodes of vascular thrombosis (1.2%). • Pancreatic allograft survival at 1 month and 4 years was 97.5% and 83.0%, respectively.
Stratta, 1997		134 (combined kidney–pancreas transplants)	< 20 hrs (mean CIT 15.3 hours) and ≥ 20 hrs (mean CIT 21.9 hours)	• Retrospective Analysis • Combined kidney–pancreas transplants • In this study, donor age above 45 years and CIT above 20 hours were both associated with a significantly increased incidence of posttransplant dialysis and early technical problems/pancreatitis. However, neither of these factors had an adverse effect on patient survival or early graft survival. • Results suggest that the outcomes of simultaneous kidney–pancreas transplantation from older donors can be optimized when experienced surgeons perform the organ retrieval with short CIT.

		253 (combined pancreas–kidney transplants)	Average preservation time: 17 hrs	• Safe preservation time with UW for up to 30 hrs without any obvious deleterious effects on immediate pancreas function. • Concluded: preservation with the UW solution is safe, effective, and virtually meets all clinical needs.
Belzer et al., 1994	UW			

NOTE: CIT = cold ischemic time, and UW = University of Wisconsin solution.