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Review: Which Practices are Evidence Based in Regards to Lung Transplantation

[or... what can we stop avoiding because it
may not be as bad as we were told]

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 Brigham and Women's Hospital  Harvard Medical School

NATCO 2010 Symposium for Advanced Transplant Professionals

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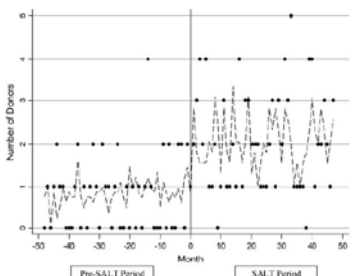
Topics of Discussion

- Donor Management Protocols
- Ischemic Time for Donor Lung
- Donor and Recipient Age
- Cause of Death
- Oxygenation
- CXR usefulness
- Gram Stain and BAL
- Smoking and Substance abuse
- Social History
- Infections impact on outcomes
- Use of Marginal vs. Standard Donor
- Center Volume

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Protocols for Donor Lung Management



The graph plots the 'Number of Donors' on the y-axis (ranging from 0 to 10) against 'Months' on the x-axis (ranging from -50 to 50). A vertical line at month 0 separates the 'Pre-SALT Period' (months -50 to 0) and the 'SALT Period' (months 0 to 50). In the Pre-SALT period, the number of donors fluctuates between approximately 0 and 4. In the SALT period, there is a significant increase, with the number of donors frequently reaching 6, 7, 8, and 9, and peaking at 10 around month 40.

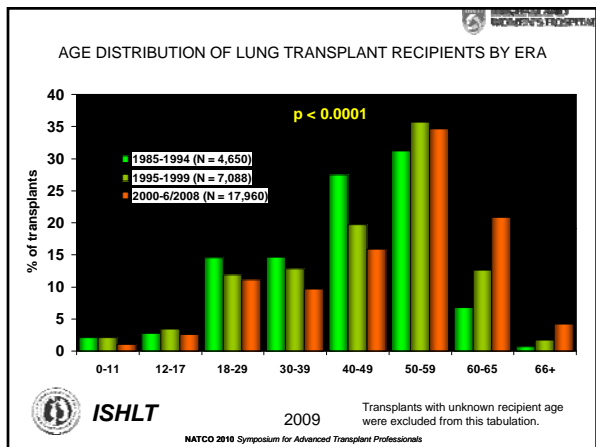
AJRCCM 2006; 174: 710-716

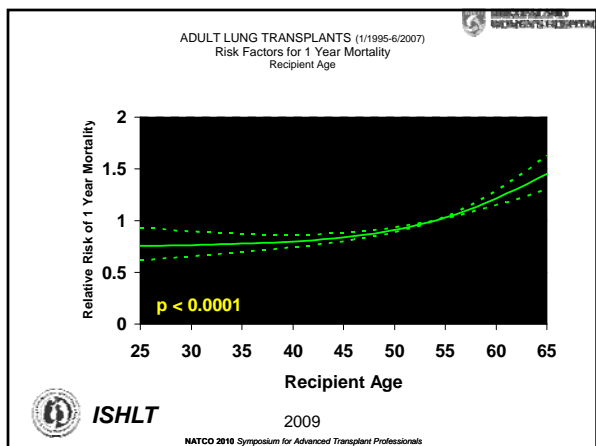
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Protocols

- Protocols for Donor Management Improve Transplant Outcomes
- Protocols Improve ECD Donor Outcomes

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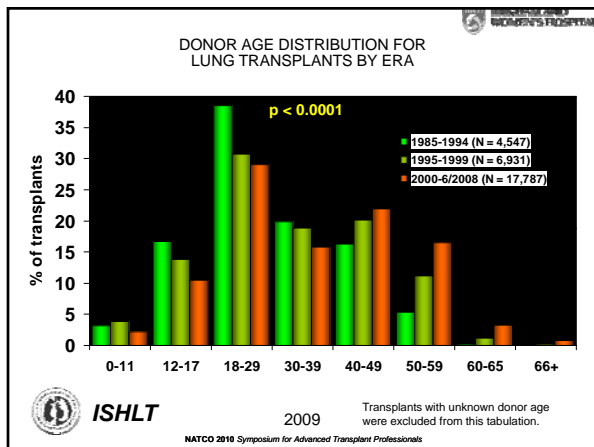


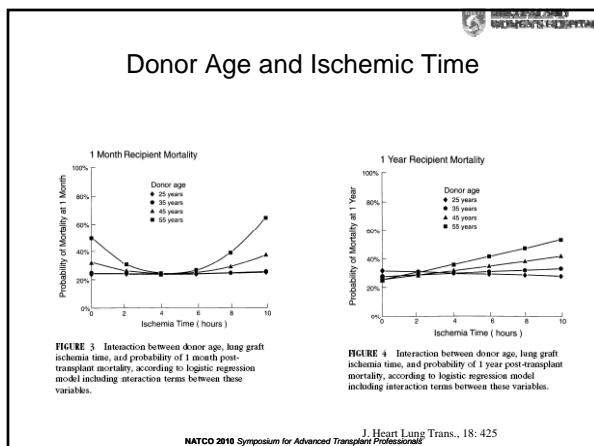


Age

- Increased in average age of recipient.
- Over 55 is associated with slightly worse survival
- When looked at by age blocks, most of effect is in patients 70 or greater
- Properly screened older recipients have good outcomes

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Donor Age

- Largest body of literature.
- Age alone not shown to have significant impact on survival.
- Possible increased incidence of BOS with older donors.

- Donor age > 50-55 years combined with ischemic time > 6-7 hours confers increased risk of 1 and 5 year survival.
- Confirmed on largest available cohort from ISHLT registry data.

J. Thor CV Surg, 133: 525
 J. Heart Lung Trans., 18: 425
 J. Thor CV Surg; 129: 919

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Cause of Death

- Postulated differences in catecholamine surge and cytokine release depending upon cause of donor death.
- Retrospective analysis of 500 donors at a single institution did not confirm difference in outcomes.
- ? Association of traumatic brain injury with increased AR and BOS risk.

- In the end, DCD may be one of the safest pools of donors

J. Thor. CV Surg., 123: 429

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Oxygenation

- Small studies suggesting limited risk to use of donors with P/F > 225-250.
- Thabut, et al: retrospective review of donors at 7 French centers.
- Donor gas exchange associated with duration of MV and long-term survival.

- Think Lung Math:
- $100 + 400 / 2 = 250$
 - When is 250 not really 250

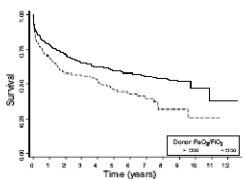


Figure 1. Graft survival according to donor PaO₂/F_iO₂ before harvest <350 (n = 111) and >350 (n = 584). Survival is adjusted for recipient age, underlying disease, and graft ischemic time.

J. Heart Lung Trans., 24: 1347

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Chest Xray

- No studies directly examining impact of donor CXR findings on recipient outcomes.
- No data on role of chest CT in evaluation of donors.
- Numerous studies describe CXR abnormalities in donor cohorts.
- Abnormalities: edema, atelectasis, contusion, pleural effusion.

Chest Surg Clin N. Am., 13: 429
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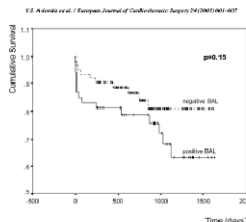
Donor Gram Stain

- Weill, et al, reviewed gram stains of 90 lung transplants from 60 consecutive donors.
- Recipient prophylaxis with vanc/3rd gen ceph.
- Compared incidence of pneumonia in recipients with and without positive donor gram stain – no difference observed.
- No difference in length of MV or mean post-op P/F ratio.

J. Heart Lung Trans., 21: 555
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Donor BAL


- 115 consecutive lung transplants in 114 patients.
- Prophylaxis with flucloxacillin alone.
- Analysis of donor BAL cultures and survival.



V.S. Akintola et al. / European Journal of Cardiothoracic Surgery 24(2007)601-607

Fig. 1. Kaplan-Meier survival curves for the groups with positive and negative donor BAL. CI and σ mark censored cases.

Eur. J. CT Surg., 24: 601
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Bronchoscopy

- Considered obligatory.
- Limited data suggest increased early mortality with donor bronchoscopy demonstrating purulence.
- ISHLT: no definitive recommendation.

Chest Surg Clin N. Am, 13: 429
Transplantation, 82: 1273
J. Heart Lung Trans., 22: 1183

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Substance Use - Tobacco

- Retrospective study of lung and heart-lung transplant recipients.
- Divided into never smokers, ever smokers, and current smokers.
- Subdivided by number of pack years and current number of cigarettes.

Transplantation, 78: 599

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Substance Use - Tobacco

- Current and cumulative dose impacted upon post-op P/F ratio, MV time, and ICU LOS.
- Significant increased risk with > 20 py, but more so with > 25 cigarettes/day current smoking.
- No difference in 3 year survival.
- Cancer Risk?
 - Majority of reports of post-transplant lung cancer are from native lung/explant.

Transplantation, 78: 599

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Substance Use - Other

- Retrospective review of all lung transplants at single institution comparing outcomes with standard and ECD's.
- Included donor use of inhaled cocaine or marijuana (n unknown).
- No difference in early or late outcomes with 1 year f/u.

J. Heart Lung Trans., 19: 1199

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Hepatitis Infection

- No difference in survival for HB group, no evidence of HBcAb conversion or + HBV DNA detection.
 - Theoretical risk
 - Risk is neutralized with Hep B immunization
- Hep C Donors:
 - All patients in HC group developed RNA positively with one death of liver failure.
- Hep C Recipients:
 - If no evidence of advanced liver injury and no viral load, NO significant risk for conversion and worse outcomes due to Hep C
 - If treated and no viral load after 6 months, Same as above

Transplantation, 80: 320

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Extended Donor Criteria

- Age < 65
- No proven impairments after tob > 20 py
- No parenchymal destruction after chest trauma
- **Unilateral infiltrate, aspiration, trauma – use of contralateral lung**
- Reduced arterial oxygenation – evaluation of potential non-pulmonary cause
- Active donor management

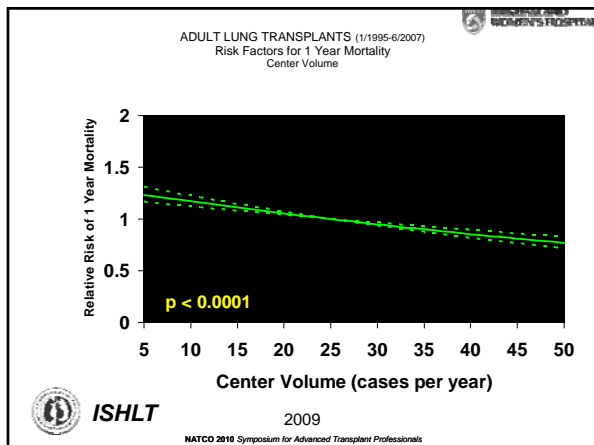
Aigner, et al, Chest Surg Clin N. Am. 2003

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Results of ECD Use

- Reported possible complications:
 - Increased need for CPB
 - Increased incidence PGD
 - Longer ICU course
 - Prolonged hospital stay
 - Lower PFT's at 1 year
 - Increased early mortality (BLT)
- Guided use of ECD helps neutralize possible increased risk
- Increased risk may be most appropriate in patients with least options

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Thank You for Your Time and Consideration!


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Questions?



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Evidence-Based Practice in Cardiothoracic Transplantation

A Literature Review for Heart and Lung Procurement (2008-2009)

Tina Abdelnour
NATCO Symposium for Advanced Transplant Professionals (January 2010)

Infectious Disease: Implications for heart & lung transplant...

Use of hearts from donors with severe sepsis and infectious deaths

- 9 Donors
- Donor infection:
 - Pneumococcal meningitis, pneumonia, and/or shock(4)
 - meningococcal meningitis(2)
 - streptococcal brain abscess, pneumonia(2), and/or shock
 - gram+ bacterial meningitis(1)
- Antibiotic coverage 32-96 hours (admit to procurement)
- Normal cardiac function in all
- “No evidence of donor-transmitted infection, sepsis, or rejection was observed, and long-term function remained excellent;”

Kubak, J Heart Lung Transplant 2009;28;3:260-265

Intrathoracic organ transplantation from donors with meningitis

- 39 Recipients, single-center (15 Htx, 12 Ltx, 12 HLtx)
- Donor infection:
 - All donors with bacterial meningitis with positive blood or CSF culture and s/s
 - *Neisseria meningitidis* (n = 21; 53.8%), *Streptococcus pneumoniae* (n = 16; 41%), and *Haemophilus influenzae* (n = 2; 5.2%)
- Hospital mortality 10%, none infection-related
- "Intrathoracic organ transplantation using donors with bacterial meningitis is an acceptable strategy. No organism (*Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*) could be identified as contraindication because no recipient died of infectious-related diseases."

Bahrami, Ann Thoracic Surg 2008;86;1554-1556

Infectious Complications in Extended Criteria Heart Transplantation

- Extended Criteria donor characteristics: ventricular dysfunction, CAD, LVH, hepatitis positive, high-risk donor behavior
- Recipients also "extended," (not suitable for standard listing)
- "...although overall survival among patients in the SL group was not influenced by the occurrence of a major infectious complication, survival in the extended criteria group was significantly impacted by major infectious complications ($p < 0.001$)."

Rajagopal, J Heart Lung Transplant 2008;27;11;1217-1221

Impact of Hepatitis B Core Antibody Positive Donors on Lung & Heart-Lung Transplant

- UNOS Database analysis
- Adjusted one-year and five-year survival no different for recipients of HBcAb positive donors
- On multivariate analysis, recipient and donor age, procedure type, era of transplant, baseline medical condition, diagnosis, and donor HcAb status impacted 1- and 5-year survival
- "Lung and heart-lung allografts from HBcAb positive donors may be safely used, which would increase the number of transplants performed without compromising recipient outcomes."

Dhillon, J Transplantation 2009;88;6;842-846

**Donation after Cardiac Death:
Implications for
heart & lung transplant...**

**Ethics of declaring death and
DCD heart transplant**

- In other words, in the setting of such a protocol, "cardiac death" should be intended as death of the patient certified on cardio-circulatory criteria while the cardiac muscle is still viable (and the brain and the rest of the organism as well). We argue that the correct term would be "donation after circulatory arrest" (DCA) rather than "donation after cardiac death." This term would not imply that the heart has died. The heart could then, like other organs, be transplanted, admitting that heart retrieval is permissible in such a context.
Zamperetti, Intensive Care Medicine, 2009;35:1673-1677
- Reflecting on these discussions, there is **perhaps a need for a new term** to describe this whole area because DCD and non-heart-beating donors both struggle when referring to heart transplantation that follows death as defined by clinical cessation of the donor's circulation.
Snell, Transplantation, 2009;88;2:147-148

**Lung Transplantation
from DCD Donors "shows promise"**

- Through late 2007:
 - 47 transplants in North America
 - 29 in Europe & Australia
 - 28 in Spain (many of these "uncontrolled")
- "Early results have been good, with an almost complete absence of primary graft dysfunction, usually expected in 10% to 20% of patients. At an earlier stage it was feared these would be marginal donors, with frequent lung injury. The consensus of those in the field is the opposite, with a general view that these lungs are "better" than those retrieved from standard cadaveric, brain-stem dead donors."

Dark, Transplantation, 2008;86:200-201

DCD Lung Transplant Outcomes to 5 years

- 17 Patients at single-center (1993-2007 University of Wisconsin)
- Patient survival at 1, 2, & 5 years: 88%, 88%, 80%, respectively
- “Our data shows that the long term patient survival after DCD LTx was equivalent to that after BDD LTx. Although the number is small and further evaluation is necessary to confirm our findings, our data substantiated excellent short-term survival.”

Patients at risk	1 year	3 year	5 year	7 year
DCD	17	8	3	1
BDD	292	207	139	94

Osaki, European J Cardiothoracic Surgery, 2009; Elsevier online

DCD Lung Transplant Early Outcomes

- 8 Recipients: All survive at a mean of 311 days (10-573) with good performance status and lung function; all bilateral LTx; mean WIT 38.4 min; ICU stay 9.5 (2-21) days
Snell, American J Transplantation, 2008;8:1282-1289
- 9 Recipients: 30-day mortality 0%; 90% alive at median 270 days (range 47-798); ICU stay 3.5 days (range 2-21); acute rejection 2 patients, no early BOS
Cypel, J Heart Lung Transplant, 2009;28:753-758
- 11 Recipients: 2 in-hospital deaths; 64% survival at median follow-up 32 months; 4 deaths versus non-deaths had longer ischemia times (293 vs. 392 min); all bilateral LTx
- “At our center, early outcomes after DCD lung transplantations are somewhat inferior to those of series from other centers but approach national averages for conventional lung transplantation.”
Puri, Annals Thoracic Surgery, 2009;88:1609-1615

DCD Lung Transplant Early Outcomes

- 36 Recipients: 27 bilateral LTx, 9 single LTx; Unadjusted survival at 1, 6, 12, and 24 months was 94%, 94%, 94%, and 87%, respectively, for DCD donors versus 92%, 84%, 78%, and 69%, respectively, for brain death donors ($P=.04$). Adjusted survival for double LTx, DM, lower FEV1, and longer CIT better than BD ($P=0.6$)
- “DCD as practiced in the United States results in survival at least equivalent to that after brain death donation. It also demonstrates selection bias, particularly in performing double lung transplantation, making generalization regarding survival difficult. Nevertheless, the data support the expanded use of DCD.”

Mason, J Thoracic & Cardiovascular Surgery, 136:1061-1066

**Donor-related variables
that impact
heart & lung transplant
outcomes...**

Effects of naloxone administration on gas exchange in brain-dead organ donors

- 19 Donors (17 donors excluded due to ABGs not collected)
- Naloxone (mean dose 8.1 mg IV) administered after brain-death; ABGs within 1-4 hours and 8-12 hours post-infusion
- PaO2 not significantly increased from baseline at first measurement (PaO2 increased in 13 patients, decreased in 6 patients)
- PaO2 increased at second measurement from 329 to 416 ($P<0.1$); (PaO2 increased in 15 patients, decreased in 4 patients)
- TV was significantly higher than baseline ($P=.01$)
- No multivariate analysis performed

• "This preliminary observational study suggests that some brain-dead organ donors may have significant improvement in oxygenation after administration of naloxone."

Eagan, Progress in Transplantation, 2009;19;3:267-271

Life years gained by reducing donor heart ischemic times

- 2271 Htx recipients studies, median post-tx time 10.4 years
- FOR EACH HOUR OF DONOR ISCHEMIC TIME, RECIPIENTS HAD A 25% INCREASED RISK FOR DEATH IN THE FIRST YEAR POST-TRANSPLANT, AND 5% INCREASE THEREAFTER ($P<0.001$)
- Limiting ischemic time to 1 hour post-transplant has the potential to significantly increase life-years after heart transplantation

• "Use of cardiac donor organ maintenance systems has the potential to increase post-transplantation survival."

Goldsmith, Transplantation, 2009;87:243-248

Relationship of hormonal resuscitation therapy and CVP on increasing organs for transplant

- Hormonal resuscitation therapy ≥ 15 hours increases hearts transplanted
- CVP < 10 mmHg increases hearts, lungs, and kidneys transplanted
- HRT ≥ 15 hours AND CVP < 10 mmHg increases hearts, lungs, and pancreata transplanted
- Heart and lung patient and graft outcomes superior to national averages

- "The use of hormonal resuscitation therapy and management of fluid status are two practices that should be a focus of any donor management protocol."

Abdelnour, J Heart Lung Transplantation, 2009;28:480-485

Hormone therapy in potential heart donors

- Controlled, randomized trial of 87 donor
- 4 arms (T3, methylprednisolone, T3 + methylprednisolone, placebo)
- Treatment for 5.9 ± 1.3 hours

- "Tri-iodothyronine and methylprednisolone therapy do not appear to acutely affect cardiovascular function or yield."


Venkateswaran, European Heart J, 2009

Interesting Case Study...

Lung Donation after cardiac of recent heart transplant recipient


- ◉ June 2008, Gift of Life, Michigan
- ◉ Potential donor who was recent heart transplant recipient
- ◉ Family consented to Donation after Cardiac Death
- ◉ Bilateral lungs & left kidney transplanted in two recipients


Angel, Progress in 19/232-234 Transplantation, 2009;



Evidence –Based Practice in Donation and Transplantation *Abdominal Transplantation*

Dianne LaPointe Rudow, ANP-BC DNP, CCTC
Director of Clinical Operations
Clinical Director of Living Donor Liver Transplant Program
Center for Liver Disease and Transplantation
New York Presbyterian Hospital





Five Years of Abdominal Transplantation in 15 Minutes

Kidney Transplant: Expanded Criteria Kidney Donation, Donation after Cardiac Death, Incompatible Transplants, Paired / Unpaired kidney exchange, HIV Transplant Recipients, Immunosuppression Update

Liver Transplant: Hepatitis B, Hepatocellular Carcinoma, Cholangiocarcinoma, NIH A2All study, HIV Transplant, Donor Risk Index, Donation after Cardiac Death, Machine perfusion

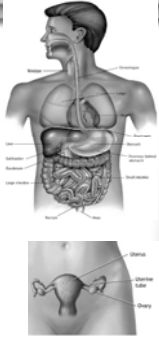
Pancreas transplant:

Multivisceral transplant:

Ovarian transplant: July 1, 2009 -- French doctors report that a woman who banked her ovarian tissue before sickle cell anemia treatment had a baby girl after getting her ovarian tissue transplanted back into her.

Uterine transplant

X-vivo Transplant: Removal of diseased organs dissection of tumors and reimplantation of native organs as cancer therapy



Kidney Transplant

Defining Expanded-Criteria Donor (ECD)

- **Definition:** Kidneys that have donor characteristics which are associated with a 70% increased risk of graft failure compared to reference group
- All donors >60 years
- All donors ages 50-59 with 2 of 3 factors:
 - CVA
 - HTN
 - Terminal Cr > 1.5 mg/dl



Deceased-donor characteristics and the survival benefit of kidney transplantation.

Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, Ojo AO, Port FK.

JAMA. 2005 Dec 7;294(21):2726-33.

- Retrospective cohort using registry data
- Survival benefit seen at 3.5 years when compared with standard criteria donor recipients, due to early ECD mortality
- DSAs with median wait times >1350 days, ECD recipients had 27% lower risk of death than those on dialysis
- DSAs with shorter wait times, ECD donors showed survival advantage in diabetics

NewYork-Presbyterian
The University Hospitals of Columbia and Cornell



Long-term outcome of renal transplantation from older donors

Remuzzi G, Cravedi P, Perna A, Dimitrov BD, Turturro M, Locatelli G, Rigotti P, Baldan N, Beatini M, Valente U, Scalamogna M, Ruggenenti P; Dual Kidney Transplant Group.
N Engl J Med. 2006 Jan 26;354(4):411-3.

METHODS

- > Prospective cohort study of 62 recipients with donor biopsy
- > Donors over 60 years old
- > Compared to 2 groups above and below donor age 60, without biopsy

RESULTS

- > 3 year graft survival in cohort similar to positive-reference group (93%), but superior to negative-reference group (72%)
- > 2 Predictive factors, age of donor and performance of histologic evaluation

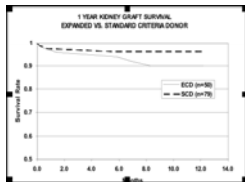
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INCREASED UTILIZATION OF EXPANDED-CRITERIA DECEASED RENAL ALLOGRAFTS: THE IMPACT, EXPERIENCE, AND LESSONS LEARNED

Michael J. Goldstein MD¹, Melissa Coleman BA¹, Pooja Sodha¹, Marina Balina², Maria Goris PA¹, Meredith Aull PharmD³, Darshana M Dadhania MD², David Serur MD², Sandip Kapur MD¹

- Retrospectively studied 139 deceased donor transplants (51 from ECDs and 88 from SCDs) conducted between January 2002-December 2005
- Thymoglobulin induction (7.5mg/kg total dose)
- Mycophenolate mofetil and tacrolimus
- Initial exclusion criteria for the protocol included chronic corticosteroid use and panel reactive antibody (PRA) >50%.



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PREEMPTIVE EXPANDED-CRITERIA DECEASED DONOR RENAL TRANSPLANTATION IN PATIENTS OVER 60 YEARS OLD: ANALYSIS OF THE UNOS DATABASE.

Piotr Witkowski, Michael Goldstein, Mark A Hardy, Abbas A Rana, Karim J Halazun, Lloyd Ratner.

Columbia University, Department of Surgery

- Preemptive renal transplantation was performed in 2064 (11%) recipients with non-ECD kidneys and 776 (5%) with ECD kidneys. Patient survival after ECD preemptive renal transplantation did not differ statistically from survival after non-ECD kidney transplantation in patients on dialysis >60 years (p=0.4), whereas as in younger recipients, survival after preemptive ECD transplantation was significantly worse than non-ECD transplants (1,5,10 year survivals of 0.95, 0.82, 0.66 vs. 0.95, 0.86, 0.70, p <0.05).
- ECD preemptive renal transplantation offers the same life expectancy as non-ECD transplantation in patients > 60 on dialysis. In addition such preemptive procedures allow patients to avoid the morbidity and mortality associated with waiting for on dialysis for a suitable graft.



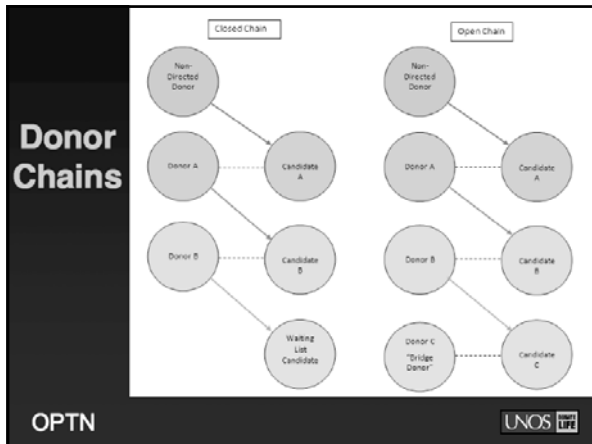
Outcomes of kidneys from donors after cardiac death (DCD): implications for allocation and preservation

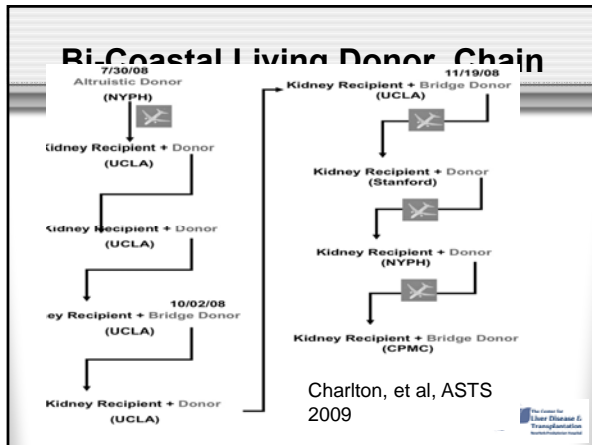
Locke JE, Segev DL, Warren DS, Dominici F, Simpkins CE, Montgomery RA. Am J Transplant. 2007 Jul;7(7):1797-807. 2007 May 25.

- Outcomes of 2562 DCD, 62,800 standard criteria donor (SCD) and 12,812 expanded criteria donor (ECD) transplants reported between 1993 and 2005
- Donor age was the only criterion used in the definition of ECD kidneys that independently predicted graft loss among DCD kidneys
- Kidneys from DCD donors <50 had similar long-term graft survival to those from SCD (RR 1.1, p = NS)

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NIH Sponsored Multi-Center Trial :HIV Positive Kidney Transplantation

- Key points
 - Renal transplantation is both safe and effective in patients with HIV
 - Rejection rates in patients with HIV are increased, although these rejections respond to therapy
 - Several interactions between highly active antiretroviral therapy drugs and immunosuppressants exist, and they should be taken into careful consideration when devising immunosuppression regimens
 - Management of co-infection with hepatitis C virus and HIV is challenging, as progression rate of liver disease is increased in affected patients
 - Treatment and patient oversight by a team of specialists is critically important to the management of renal transplant recipients with HIV
- Frassetto L, Tan-Tam C Stock P, Renal Transplantation with HIV; Nature 10/2009

The Center for Liver Disease & Transplantation www.transplantcenter.org

Despite the introduction of powerful new drugs, graft survival at 3 years shows **NO** improvement

Burdened with medical complications of hypertension, new onset diabetes after transplantation and dyslipidemia



Belatacept (LEA29Y)

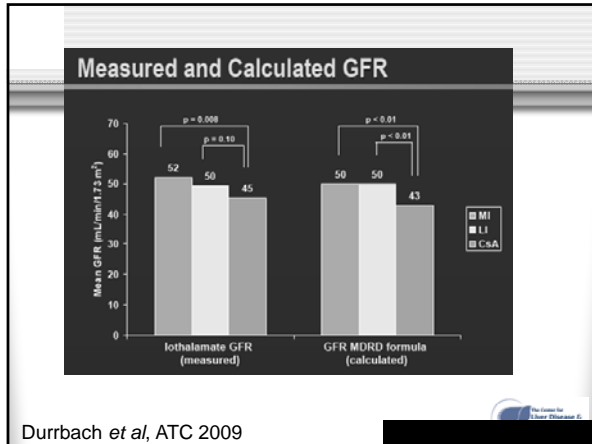
- Selective co-stimulation inhibitor under development by Bristol-Myers Squibb Co.
- Blocks T cell activation and promotes cell death
- Route of administration is IV infusion over 30 minutes



BENEFIT Trials

- IM103-008 (BENEFIT)
 - ♦ Living or deceased donor
 - ♦ First-time recipient: PRA < 50%
 - ♦ Retransplant: PRA < 30%
 - ♦ N = 660
- IM103-027 (BENEFIT-EXT)
 - ♦ Deceased donor meeting EXTended criteria donor (ECD)
 - ♦ First-time kidney transplants
 - ♦ PRA < 30%
 - ♦ N = 540





Summary: BENEFIT-EXT (ECD)

Belatacept compared to CsA demonstrated:

Efficacy

- Similar patient/graft survival
- Better renal function
- Better Cardiovascular/metabolic profile
- Similar rates of acute rejection

Safety and Tolerability

- Similar rates of infection and malignancy
 - Higher number of PTLD: most occurred in recipients with known risk factors
 - Well tolerated as a monthly infusion

Durrbach *et al*, ATC 2009

Liver Transplant

Hepatitis B

- Recurrence of HBV post liver transplant occur <10% long term
 - ♦ Advances in pre transplant antiviral treatment
 - ♦ Improvement in post liver transplant prevention protocols
 - H-BIG plus antiviral mono or combination therapy
 - Protocols include tapering, adjusting mode of administration or cessation of H-BIG over time



Hepatocellular Carcinoma: Beyond Milan Criteria

Table 1. Proposed expanded criteria based on tumor size and number in deceased donor liver transplantation.

Author (year), institution (reference)	Proposed expanded criteria	Radiology/pathology	5-year patient survival (number of patients)
Yoo (2001), UCSF SB	1 nodule < 6.5 cm, or 2-3 nodules < 4.5 cm and total tumor diameter < 8 cm	Pathology	Milan in = 493, 72% EC in = 148, 73%
Yoo (2007), UCSF SB	Same as above	Radiology	Milan in = 150, 80% EC in = 268, 80%
Herrero (2001), Pamplona, Spain SB	1 nodule < 6 cm, or 2-3 nodules each < 4 cm	Radiology	Milan in = 493, NA EC in = 150, NA
Royola (2002), Mt. Sinai, NY SB	1 or more nodules 5 to 7 cm	Radiology	Entire group, 79% Milan, NA
Kretzner (2004), Edmonton, Canada SB	1 nodule < 7.5 cm, any number < 5 cm	Radiology	EC in = 211, 60%
Chen (2007), International Tumor Registry (7)	1 nodule < 6 cm 2-4 nodules each < 5 cm	Pathology	Milan in = 108, 87% (4-year) Milan in = 1038, 82% ¹ EC in = 1148, 64.3% ¹

UCSF = University of California, San Francisco; EC = expanded criteria; NA = not available.
The number of patients in the expanded criteria (EC) group represents only patients beyond the Milan criteria but within expanded criteria.
¹ Recurrence-free survival.

- Predictors of outcome:
 - ♦ Pathology: poorly differentiated grade of microvascular invasion (negative)
 - ♦ Down staging successfully with local regional therapy (positive prognostic marker)
 - ♦ High AFP >1000 (negative)
 - ♦ LDLT (no difference)
 - ♦ Oral Agents: Randomized phase III trial comparing sorafenib vs placebo for previous untreated HCC: Sorafenib HCC Assessment Randomized Protocol (SHARP) (positive > 3mos)

Yao, AJG 2008, 8:1982-1989



Cholangiocarcinoma is no longer an absolute contraindication to transplant

- Becker et al.* Outcome analysis of for 280 patients with cholangiocarcinoma treated with liver transplant over an 18 year period (UNOS DATA)
 - ♦ 1 and 5 year survival (74% and 38%), 3 year survival after 2000 is 68%
 - ♦ assume neoadjuvantive therapy (chemoradiation and or resection)
- UNOS Proposal 2006:**
 - ♦ Hilar CCA <3cm
 - ♦ Appearance of malignant appearing stricture confirmed by biopsy or cytology
 - ♦ Abnormal ca19-9 (>100U/ml)
 - ♦ Evidence of aneuploidy
 - ♦ Unresectable
 - ♦ Absence of lymph node and peritoneal involvement
- MELD exception for CCA: region 5 and 7

J Gastrointest surg 2008;12:17.*; Gores GJ, et al, Liver Transplantation 2006;12(s3).

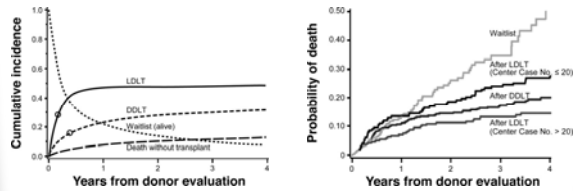


A2ALL

- Consortium of 9 transplant centers, data coordinating center, and NIH/NIDDK project scientist
- Funded by NIH/NIDDK cooperative agreement (U01)
- Supplemental funding from HRSA and ASTS
- First prospective multi-center study of adult-to-adult living liver transplantation
- Longitudinal observational studies and clinical trials are being simultaneously conducted
- Primary goal: Evaluation of donor and recipient outcomes of LDLT from 1998 - 2008

A2ALL

A2ALL shows LDLT Improved Outcomes



Survival benefit in 249 patients who underwent LDLT compared to 389 who waited for DDLT

Berg et al. A2ALL STUDY GROUP. Gastro. 2007.



Risk of Living Donor Graft Failure A2ALL data

TABLE 6. Factors Associated With Graft Failure/Death Based on Cox Regression

Variable	Hazard Ratio	95% Confidence Interval	P Value
Recipient age at transplant (per 10 y)	1.41	(1.15-1.73)	0.0008
Donor age at transplant (per 10 y)	1.13	(0.91-1.41)	0.2766
Donor biologically related	0.67	(0.43-1.03)	0.0699
Cold ischemia time (per h)	1.19	(1.06-1.33)	0.0024
Center case number ≤20	1.83	(1.20-2.80)	0.0049

Annals of surgery 242, 2005



A2ALL Recipient and Donor Morbidity

- ***Recipient:** (N=384/216)
 - ♦ Overall complication rate of LD is similar to DD recipients
 - ♦ Increased incidence of bile leaks (32% verses 10%)
 - ♦ Increased incidence of unplanned re-exploration (26% vs 17%)
 - ♦ HAT (6.5% vs 2.3%)
 - ♦ Retransplant (15% vs 9%)
- ****Donor:** N=393
 - ♦ No complications 62%
 - ♦ One complication 21%
 - ♦ Two or more 17%
 - ♦ Most were minor (clavien 1)
 - ♦ Life threatening 2%
 - ♦ Complications leading to death 0.8%

* Freise et al AJT-2008 8: 2569-2579
 ** Ghoobrial et al. Gastroenterology 2008 135:468-476



HIV Transplant Recipients

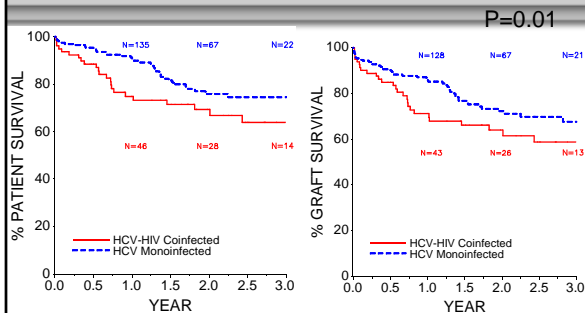
NIH sponsored Trial HIV Positive Transplant Recipients

- HIV-TR is a NIAID-supported multicenter cohort study of 17 U.S. transplant centers evaluating outcomes in HIV infected patients
- All coinfecting LT recipients with HIV viremic control in the multicenter HIVTR cohort were included
- Data suggested that post txp survival did not differ in the HIV positive group who had the following characteristics:
 - Patients tolerating HAART
 - Pre transplant CD4 >200 cells
 - HCV positive patients had worse outcomes



Co-Infected Patient and Graft Survival is Worse

AASLD 2009



NA Terrault, B Barin, T Schiano, F Poordad, M Wong, M de Vera, D Simon, L Rosenthal, D Jayaweera, L Johnson, K Olthoff, T Stosor, K Sherman, B Eghtesad, R Harland, F Regenstein, J Hamilton, T Pruett, M Roland, P Stock



Donor Risk Index (DRI)

Feng S. et al. AJT 2006;6:783-790

Table 3: Donor factors significantly associated with liver allograft failure (1998–2002)*

Donor parameter	RR	95% CI	p-Value
Age			
<40	1.00		
40–49	1.17	1.08–1.26	0.0002
50–59	1.32	1.21–1.43	<0.0001
60–69	1.53	1.39–1.68	<0.0001
>70	1.65	1.46–1.87	<0.0001
African-American race (vs White)	1.19	1.10–1.29	<0.0001
Donor height (per 10 cm decrease)	1.07	1.04–1.09	<0.0001
COD = CVA	1.16	1.08–1.24	<0.0001
COD = Other†	1.20	1.03–1.40	0.018
D/CD	1.51	1.19–1.91	0.0006
Partial/Split	1.52	1.27–1.83	<0.0001

Using SRTR Data, Cox regression model identified 7 characteristics that independently predicted significantly increased risk of graft failure (risk adjusted)



Hypothetical Examples of DRI

Table 5: Specific combinations of donor risk factors and the corresponding donor risk index

Donor factor	Reference donor	Example 1	Example 2	Example 3	Example 4	Example 5
Age	Under 40	64	64	64	25	25
Cause of death	Trauma	Trauma	Stroke	Stroke	Trauma	Trauma
Race	White	White	White	White	White	White
D/CD	No	No	No	No	No	Yes
Partial/Split	No	No	No	No	No	No
Height (cm)	170	170	170	170	170	170
Location	Local	Local	Local	Local	Local	Local
Cold time (h)	8	8	8	14	14	14
Donor risk index*	1.00	1.53	1.77	1.86	1.06	1.60

*Calculation: Donor risk index = $\exp(0.154 \text{ if } 40; \text{ age } < 50) + (0.274 \text{ if } 50; \text{ age } < 60) + (0.424 \text{ if } 60; \text{ age } < 70) + (0.501 \text{ if } 70 \leq \text{ age}) + (0.039 \text{ if COD = stroke}) + (0.145 \text{ if COD = CVA}) + (0.184 \text{ if COD = other}) + (0.176 \text{ if race = African American}) + (0.126 \text{ if race = other}) + (0.411 \text{ if D/CD}) + (0.422 \text{ if partial/split}) + (0.066 \text{ if } 170\text{-height} / 10) + (0.105 \text{ if regional share}) + (0.244 \text{ if national share}) + (0.010 \times \text{coldtime})$.

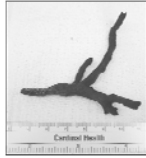
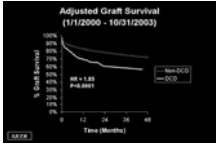


Donor Risk Index

- DRI and MELD:
 - ♦ Bonney et al: Transplantation, 2009; 87(12)
 - Meld at txp and DRI >1.7 associated with poorer graft survival (p=0.03)
 - ♦ Schaubel et al : AJT, 2008 8(2)
 - Meld >20 had survival benefit regardless of DRI
 - Low MELD(6-8) and High DRI= high mortality (p=0.0005)
 - ♦ Goldstein et al, AASLD 2009
 - Survival benefits of early access to transplantation with HDRI transplantation in patients in regions with the longest waiting times



LIVER TRANSPLANT: DCD OUTCOMES



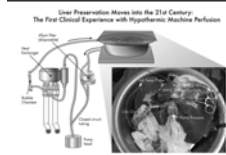
- Biliary Cast Syndrome:
- 9-25% of DCD recipients
- Recurrent cholangitis, resistant bacteria
- Ultimately Re-transplant or Death



Expanding the Donor Pool: Machine Perfusion Outperforms Standard Cold Storage Liver Preservation

Guarrera et al, AJT February 2010

- Phase 1 Trial: Hypothermic Machine Perfusion (HMP) has comparable outcomes to cold storage (CS)
 - ♦ Continuous O₂
 - ♦ Key nutrients
 - ♦ Removes toxins
- 20 CS vs 20HMP
- HMP has >LOS,>complications
- Phase II: Expand to ECD



et al, AJT 2010

Living Donation

- Federal Oversight of Live donors
- Guidance for the Development of Program Specific Living Kidney Donor Medical Evaluation
- Guidance for the Development of Program Specific Living Liver Donor Medical Evaluation
- Consensus Conferences on Donor care
 - ♦ Amsterdam Forum (Delmonico, Transplantation. 2005 Mar 27;79(6 Suppl):S53-66. Review.
 - ♦ Vancouver Forum (Barr et al, Transplantation 81(10)2006)
 - ♦ Guidelines for the unrelated kidney donor (Dew MA, Am J Transplant. 2007 May;7(5):1047-54)



Pancreas Transplant

- Lack of Randomized Controlled Trials
- Goal establish normglycemia
- 5 year graft Survival:
 - ♦ 71% skp
 - ♦ 56%PAK
 - ♦ 53%PTA
- Reduced mortality compared to diabetic kidney transplant and waitlisted patients
- Improvement in diabetic nephropathy and retinopathy
- Improvement in cardiovascular risk profile

Dean et al current opinion in organ transplant 2008 13:85-90



Small Bowel Transplant

- One year graft survival has approached that of other organs
- Better understanding of immunosuppression, donor and recipient selection



Future of abdominal Transplant

EVIDENCE-BASED PRACTICE IN ABDOMINAL TRANSPLANTATION

A Literature Review for
Kidney, Pancreas, Liver and Intestinal Procurement
(2008-2009)

Tracy DeMars RN, CPTC
NATCO Symposium for Advanced Transplant Professionals
(January 2010)

Association between donor-recipient serum sodium differences and orthotopic liver transplant (OLT) graft function.

Determine if the co-existence of recipient hyponatremia and donor hypernatremia negatively impact graft function

- 250 recipients studied
- LFTs and length of hospital stay evaluated
- Confounders considered (Donor and recipient demographics, CIT, MELD and preservation solution)

“Donor hypernatremia and recipient hyponatremia were not found to be associated with immediate post operative allograft function.”

Cywinski, J.B. et al. Liver Transplantation 2008 Jan; 14(1):59-65

Utility of Liver Allograft Biopsy Obtained at Procurement

Compares frozen-section (FS) and permanent-section (PS) to identify histologic characteristics underrepresented by FS.

- 52 ECD liver transplants evaluated by hepatopathologists using both FS and PS

“A high correlation was observed between FS and PS. Underestimation of steatosis by FS was associated with allograft dysfunction. Surgical assessment of cholestasis, congestion, and steatosis was accurate whereas inflammation, necrosis, and fibrosis were underestimated in allografts suffering parenchymal injury. In conclusion, the correlation between FS and PS is high, and significant discrepancies are rare.”

Lo, J., et al. Liver Transplantation. 2008;14(5) 639-646

Consequenses of Cold-Ischemic Time on Primary Nonfunction and Patient and Graft Survival in Liver Transplantation

The Objective was to describe the functional relationship between cold-ischemia time (CIT) and primary nonfunction (PNF), patient and graft survival in liver transplant.

- Identified relevant articles Medline, EMBASE and the Cochrane database, including the non-English literature identified in these databases, were searched from 1966 to April 2008.
 - 26 studies met criteria
 - Evaluated graft survival at 1 month, 3 months, 6 months and one year

Maximum patient and graft survival occurred with CITs between 7.5–12.5 hrs at each survival interval.

“The results of this work imply that CIT may be the most important pre-transplant information needed in the decision to accept an organ.”

Stahl, E.S., et al. PLoS ONE 3(6): e2468. doi:10.1371/journal.pone.0002468

Patient and Graft Outcomes from Deceased Kidney Donors Age 70 Years and Older: An Analysis of the OPTN/UNOS Database

Impact of donors ≥ 70 years of age and transplant outcomes

- 601 deceased donor transplants 2000-2005
- Groups compared
 - Younger ECD (50-69)
 - Older ECD (≥ 70)
- Follow up until 2007

“Older ECD kidney transplants are associated with a higher risk for graft loss and patient death. However, the risk was highest when older ECD kidneys were transplanted into recipients younger than 60 years of age.”

Chavalitdhamrong D., et al, *Transplantation*. 2008;85:1573-1579

Standard Criteria Donor Pancreas Donation Status is Associated With Improved Kidney Transplant Outcomes

Identify if pancreas donation status could reflect organ quality and be predictive of kidney graft outcomes following Standard Criteria Donor (SCD) kidney transplantation.

- Retrospective analysis of deceased donor kidney alone transplants
 - Group 1 - kidney alone recipients from pancreas donors
 - Group 2 - kidney alone recipients from non-pancreas donors
 - Compared patient and graft survival between groups at 10-yr post-transplant

“Donor pancreas donation status is an independent predictor of improved outcomes of SCD kidney recipients.”

Weiss, A. et al. *ClinicalTransplant*. 2009 Sep;23(5):732-9.

Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

Prospective study to determine if machine perfusion improves kidney allograft outcomes

- 336 consecutive donors deceased donors (SCD and ECD) one kidney placed on machine perfusion the other to cold storage all 672 recipients followed for one year to evaluate:
 - Delayed graft function (requiring dialysis in first week following surgery)
 - Rate of decreasing serum creatinine
 - Acute rejection
 - Length of hospital stay

"Hypothermic machine perfusion was associated with a reduced risk of delayed graft function and improved graft survival in the first year after transplantation"

Moers, C., New England Journal of Medicine. 2009; 360(5):7-19

Predictors Associated with Terminal Renal Function in Deceased Organ Donors in the Intensive Care Unit

Factors determining renal function at organ recovery in deceased kidney donors, as well as, the prevalence and risk factors associated with elevated prerecovery creatinine and calculated GFR.

- 458 deceased donors
- Multivariate analysis:
 - BMI-Higher body mass index was associated with worse renal function
 - Admission GFR and Creatinine - major determinants of respective prerecovery values
 - Glucose - Higher average glucose values and greater variability in glucose (when included) were associated with worse prerecovery renal function

*Administration of desmopressin acetate was highly associated with preserved renal function

"The data identify several important factors that predict renal function at kidney recovery in deceased donors. In particular, tighter control of blood glucose may improve renal function in potential organ donors, but prospective studies are needed to confirm these findings."

Blasi-Ibanez, A. Anesthesiology. 2009 Feb;110(2):833-41

Utilization of Donors Who Have Suffered Cardiopulmonary Arrest and Resuscitation in Intestinal Transplantation

Analyze intestinal grafts from donors who suffered cardiopulmonary arrest and resuscitation and to evaluate the outcome of recipients of organs coming from resuscitated donors when compared with recipients of nonresuscitated donors.

- Retrospective data analysis
 - 12 of 65 donors suffered cardiopulmonary arrest and CPR

"There were no significant differences in outcome parameters such as operative time, blood use, ventilation days, length of stay, time to enteral independence, rejection, enteric bacteremia, and survival."

Matsumoto, C.S. Transplantation. 2008 Oct;86(7):941-6
