TECHNOLOGY ASSESSMENT REPORT:
The Impact of Pre-Transplant Red Cell Transfusions in Renal Allograft Rejection.
Project ID: RENT0610

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January 19, 2011

Acknowledgement

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this project from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this project to the University of Connecticut/Hartford Hospital Evidence-based Practice Center.

Contract Number: 290-2007-10067-I

Disclosure

None of the investigators has any affiliation or financial involvement that conflicts with the material presented in this presentation.

Background: ESRD and Kidney Transplantation

- 450,000 patients in US have ESRD
  - 14,059 renal transplants in 2009
  - Alternative to renal transplant is chronic dialysis

Gabardi S. Pharmacotherapy Principles and Practice. McGraw-Hill, NY, NY: 2010.

OPTN Network. http://www.optn.org/latestdata/viewdatareports.asp

Autorecognition

- HLA are a set of human MHC derived glycoproteins expressed on cell surfaces
  - Allow discernment of self from non-self
- Two main classes:
  - Class I (HLA-A, HLA-B, HLA-C)
  - Class II (HLA-DP, HLA-DQ, HLA-DR)

Gabardi S. Pharmacotherapy Principles and Practice. McGraw-Hill, NY, NY: 2010.

Allorecognition

- Recognition of antigens displayed on transplanted cells (alloantigens)
- Direct pathway – donor APCs migrate to recipient lymph nodes and present antigens to T-cells
- Indirect pathway – recipient APCs migrate into allograft and phagocytize alloantigens
  - Present antigens to T-cells in lymph nodes
- Need this + costimulatory signal to activate T-cells

Gabardi S. Pharmacotherapy Principles and Practice. McGraw-Hill, NY, NY: 2010.

Allograft Rejection

- Hyperacute rejection: immediate recipient immune response against an allograft
  - Due to preformed recipient antibodies (humoral, B-cell mediated) against donor's HLA
- Acute rejection: generally occurs 5-90 days after a transplant
  - Alloreactive T-cell mediated
    - Initiate immune response, cause apoptosis, kill cells through release of cytotoxic proteins
- Humoral rejection: humoral rejection occurring outside of the hyperacute rejection period
  - Antibodies damage allograft cells and complement activities
- Chronic rejection: immunologic processes of chronic rejection may result from cell-mediated, humoral-mediated, or drug-induced allograft damage

Gabardi S. Pharmacotherapy Principles and Practice. McGraw-Hill, NY, NY: 2010.

Immunosuppressive Therapy

- Three main categories of immunosuppressive therapy: induction, maintenance, and treatment
  - Induction therapy: initiated intra- or immediately postoperatively and continued for several days
  - Often given in those with preformed antibodies, history or previous organ transplant, multiple HLA-mismatches, or transplantation of organs with prolonged cold ischemia times
- Maintenance therapy:
  - Routinely provided to patients to prevent acute and chronic rejection
    - Common classes: calcineurin inhibitors (cyclosporin and tacrolimus), antiproliferatives (azathioprine, mycophenylate derivatives), target of Rapamycin inhibitors (sirolimus), and corticosteroids
      - Two or more medications from different categories used
- Acute rejection therapy

Gabardi S. Pharmacotherapy Principles and Practice. McGraw-Hill, NY, NY: 2010.

Methods

- Literature search strategy
  - Systematic search of Medline and Cochrane CENTRAL (from earliest date through August 2010)
    - Targeted search of EMBASE for foreign language articles over same time period
    - Backward citation tracking with manual search of references

Study Eligibility Criteria

- Title and Abstract Review:
  - Inclusion criteria:
    - Human studies (clinical or observational studies)
    - Patients receive transfusion prior to kidney (with or without pancreas) transplant
    - Report on relationship between the transfusion and renal allograft outcomes
      - Outcomes of interest (KQ1): renal allograft rejection, graft survival, patient survival
      - Outcomes of interest (KQ2): impact or predictability of PRA on renal transplant rejection/survival

Validity Assessment

- Each study rated for quality using the following definitions:
- Good: least bias, results considered valid.
- Fair: susceptible to some bias, not sufficient to invalidate results.
- Poor: substantial flaws that imply biases of various types that may invalidate the results.

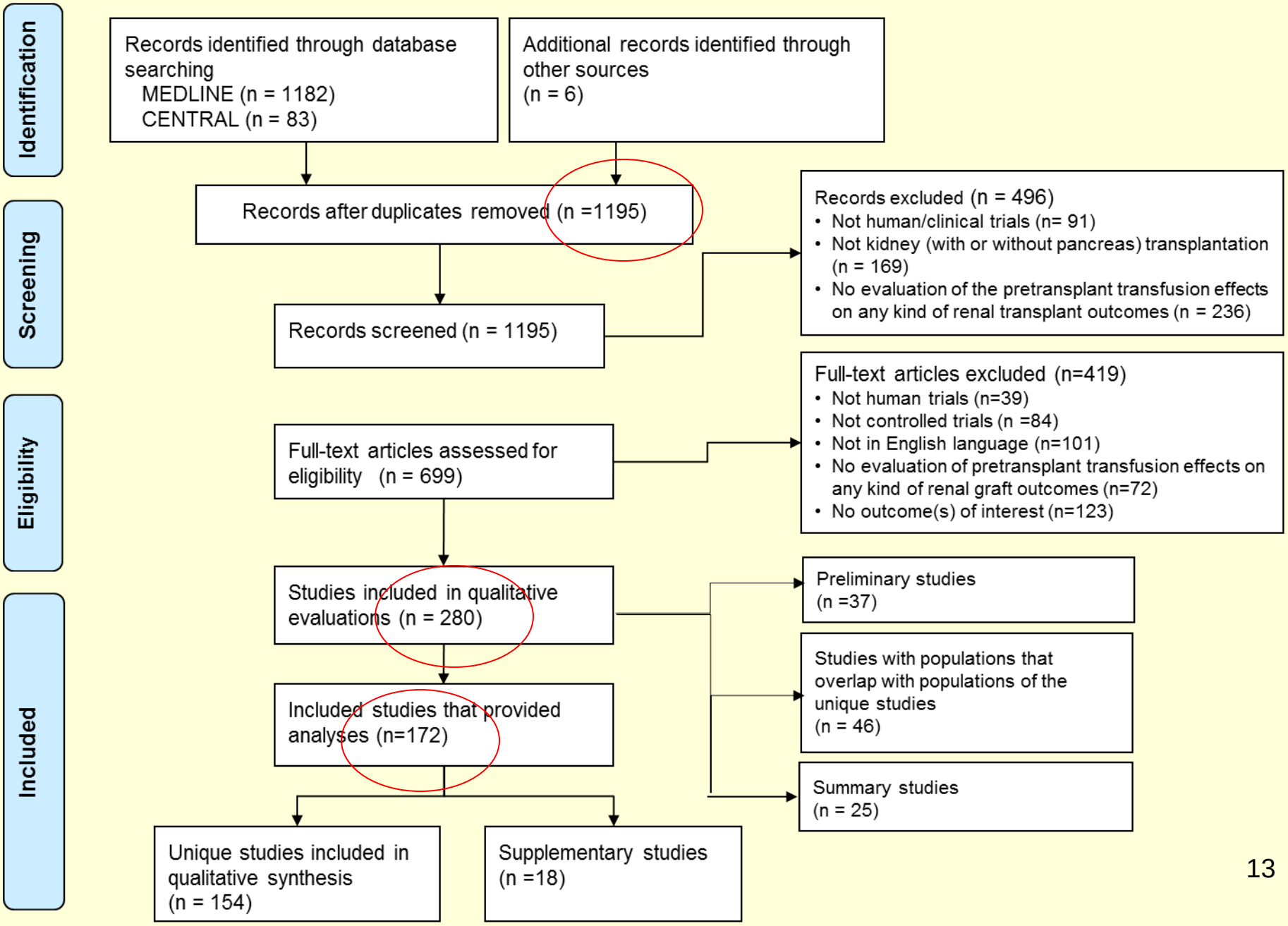
Data Synthesis

- Given severe clinical and methodological heterogeneity, the retrospective nature of virtually all studies, and the inherently poor quality of individual studies upon validity assessment, we did not pool results
  - Different definitions of endpoints, different subpopulations, etiologies of renal failure, role of HLA-matching, living versus cadaver donor, use of perioperative transfusion, previous transplant and pregnancy, history of previous random transfusion with DST trials, different time periods, ABO compatibilities

Grading the Strength of Evidence

- The body of evidence for each key question was rated as follows:
  - High confidence that future studies will not change results
  - Moderate confidence that future studies will not change results
  - Low confidence that future studies will not change results
  - Insufficient evidence
- Risk of bias, consistency, directness, and precision evaluated to derive strength of evidence

PRISMA Diagram for Study Identification and Selection



Insight into Body of Literature: All Included Unique Studies

Trial Types (CCT, ROBS, POBS)	Control Groups (concurrent, historical)	Accounted for Confounding	Demographic data in both groups*	Conducted entirely from 1984 to present
CCT 8.4% POBS 8.4% **ROBS 83.2%**	**Concurrent 84.4%** Historical 7.1% Not reported 8.5%	Yes 20.1% **No 79.9%**	Yes 26.0% **No 74.0%**	Yes 16.2% **No 83.8%**

CCT=clinical controlled trial, POBS=prospective observational study, ROBS=retrospective observational study

*Demographic data in relation to the population of interest for this technology assessment

Insight into Body of Literature: All Key Questions

	Country Conducted	Validity of Individual Analysis
KQ 1a	Multinational 3.9% **USA 37.9%** **Canada 5.2%** Other 53.0%	Good 7.5% Fair 10.7% **Poor 81.8%**
KQ 1b	Multinational 2.4% **USA 42.6%** **Canada 5.5%** Other 49.5%	Good 4.2% Fair 14.3% **Poor 81.5%**
KQ 2b	Multinational 0.0% **USA 61.5%** **Canada 30.8%** Other 7.7%	Good 0.0% Fair 11.8% **Poor 88.2%**

Key Question 1a:

- Do red blood cell transfusions prior to renal transplant impact allograft rejection/survival and what is the magnitude of that effect relative to other factors (e.g. pregnancy, prior transplantation)?
  - The impact of packed RBCs, whole blood, leukocyte depleted blood, matched blood, and donor-specific blood are combined
  - Data were evaluated regardless of the number of transfusions, number of units transfused, and/or the number of donors
  - Data were evaluated regardless of the time period (pre- or post cyclosporine era)
  - Ib has subgroup analyses exploring these different facets separately

KQ 1a: Rejection Outcomes for Any Transfusion vs. No Transfusion

Impact of transfusions on:	Significant Reduction in Rejection	No Significant Effect on Rejection	Significant Increases in Rejection	Decreased Risk of Rejection	No Change in Rejection*	Increased Risk of Rejection
Graft Rejection Any Time Point	**9/25 (36.0%)**	**13/25 (52.0%)**	3/25 (12.0%)	**28/47 (59.6%)**	**8/47 (17.0%)**	11/47 (23.4%)
Conclusion/ Strength of Evidence	Transfusions had a beneficial to neutral significant effect on rejection outcomes Low			Transfusions had a beneficial to neutral effect on rejection outcomes Insufficient – magnitude hard to gauge		

*Either data showing no difference, or notation in text stating no change

§Either data showing a decrease/increase of any magnitude or notation in text stating a decrease/increase

KQ 1a: Survival Outcomes for Any Transfusion vs. No Transfusion

Impact of transfusions on:	Significant Increases in Survival	No Significant Effect on Survival	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1-Year Graft Survival	**29/55 (52.7%)**	**26/55 (47.3%)**	0/55 (0.0%)	**65/132 (49.2%)**	**63/132 (47.7%)**	4/132 (3.1%)
Max Duration Graft Survival	**30/65 (46.2%)**	**35/65 (53.8%)**	0/65 (0.0%)	**76/146 (52.0%)**	**62/146 (42.5%)**	8/146 (5.5%)
Conclusion/ Strength of Evidence	Transfusions had beneficial to neutral significant effect on 1-year and maximum duration graft survival Low			Transfusions had beneficial to neutral effect on 1- year and maximum duration of graft survival Low		
1-Year Patient Survival	0/16 (0.0%)	**16/16 (100%)**	0/16 (0.0%)	**1/35 (2.9%)**	**32/35 (91.4%)**	2/35 (5.7%)
Max Duration Patient Survival	**1/18 (5.6%)**	**17/18 (94.4%)**	0/18 (0.0%)	**8/41 (19.5%)**	**29/41 (70.7%)**	4/41 (9.8%)
Conclusion/ Strength of Evidence	Transfusions had beneficial to neutral significant effect on 1-year and maximum duration patient survival Low			Transfusions had beneficial to neutral effect on 1- year and maximum duration of patient survival Low		

Multivariate Analyses (1a)

Rejection Outcomes

- 6 analyses
  - 3 retransplantation, 2 transfusion, 1 prior pregnancy
- 2/3 (67%) multivariate analyses showed **retransplantation** to be an independent predictor of **increasing** chances of rejection
- 2/2 (100%) multivariate analyses showed **transfusions** to be an independent predictor of **decreasing** rejection
- 1/1 (100%) multivariate analysis showed **prior pregnancy** to be an independent predictor of **decreasing** rejection

Graft Survival Outcomes

- 30 analyses
  - 14 retransplantation, 12 transfusion, 4 prior pregnancy
- 8/14 (57%) multivariate analyses showed **retransplantation** to be an independent predictor of **worsening** graft outcomes
- 6/12 (50%) multivariate analyses showed **transfusions** to be an independent predictor of **benefiting** graft outcomes
- 1/4 (25%) multivariate analyses showed **prior pregnancy** (≥3 pregnancies) to be an independent predictor of **worsening** graft outcomes

Patient Survival Outcomes

- 8 analyses
  - 7 retransplantation, 1 transfusion, 0 prior pregnancy
- 1/7 (14%) multivariate analyses showed **retransplantation** to be an independent predictor of **worsening** patient survival outcomes
- 0/1 (0%) multivariate analysis showed **transfusions** to be an independent predictor of patient survival outcomes

Key Question 1b.

- Is any such impact of red blood cell transfusions on renal transplant outcomes altered by variables such as:
  i. Planned DST vs. therapeutic transfusions
  ii. # of transfusions, # units of blood, and/or # of donors (units of blood data similar to number of transfusions data, no data for number of donors)
  iii. Use of leukocyte depleted blood (scant data, not reported)
  iv. Changes in immunosuppressant regimens
  v. Other changes in management

KQ 1b (i): Graft Rejection for DST vs. Non-DST Transfusion

	Significant Decreases in Rejection	No Significant Effect on Rejection	Significant Increases in Rejection	Decreased Risk of Rejection §	No Change in Rejection *	Increased Risk of Rejection §
Graft Rejection Any Time Point	**2/3 (66.7%)**	**1/3 (33.3%)**	0/3 (0.0%)	**3/7 (42.9%)**	**3/7 (42.9%)**	1/7 (14.2%)
Conclusion/ Strength of Evidence	DST versus non-DST had a beneficial to neutral significant effect on rejection outcomes Low			DST versus non-DST had a beneficial to neutral impact on rejection outcomes Insufficient – magnitude hard to gauge		

*Either data showing no difference, or notation in text stating no change

§Either data showing a decrease/increase of any magnitude or notation in text stating a decrease/increase

KQ 1b (i): Survival Outcomes for DST vs. Non-DST Transfusion

Impact of DST on:	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1-Year Graft Survival	**2/4 (50.0%)**	**2/4 (50.0%)**	0/4 (0.0%)	**3/16 (18.8%)**	**13/16 (81.2%)**	0/16 (0.0%)
Max Duration Graft Survival	**2/5 (40.0%)**	**3/5 (60.0%)**	0/5 (0.0%)	**6/17 (35.3%)**	**11/17 (64.7%)**	0/17 (0.0%)
Conclusion/ Strength of Evidence	DST versus non-DST had a beneficial to neutral significant effect on 1-year and maximum duration of graft survival Low			DST versus non-DST had a beneficial to neutral effect on 1-year and maximum duration of graft survival Low		
1-Year Patient Survival	0/2 (0%)	**2/2 (100%)**	0/2 (0%)	0/4 (0%)	**4/4 (100%)**	0/4 (0%)
Max Duration Patient Survival	0/2 (0%)	**2/2 (100%)**	0/2 (0%)	0/4 (0%)	**4/4 (100%)**	0/4 (0%)
Conclusion/ Strength of Evidence	DST versus non-DST had a non-significant effect on 1-year or maximum duration patient survival Insufficient			DST versus non-DST had a neutral effect on 1-year or maximum duration patient survival Low		

Multivariate Analyses (1bi)

- Rejection Outcomes
  - 1 analysis assessed DST
  - Found to be an independent predictor of decreasing rejection
- Graft Survival Outcomes
  - 4 analyses assessed DST
  - 1 analysis found DST to be an independent predictor in benefiting graft survival
- Patient Survival Outcomes
  - No available analyses

KQ 1b (ii): Graft Rejection Based on Number of Transfusions, Units of Blood, and Number of Donors

	Significant Decreases in Rejection	No Significant Effect on Rejection	Significant Increases in Rejection	Decrease in Rejection	No Change in Rejection	Increase in Rejection
Number of Transfusions (Any number of transfusion versus Any other number of transfusion)						
Graft Rejection	**2/5 (40.0%)**	**3/5 (60.0%)**	0/5 (0.0%)	**6/18 (33.3%)**	**10/18 (55.6%)**	2/18 (11.1%)
Conclusion/ Strength of Evidence	The use of any number of transfusions had a beneficial to neutral significant effect on rejection outcomes. Low			The use of any number of transfusions had a beneficial to neutral effect on rejection outcomes. Insufficient – magnitude hard to gauge		
Units of Blood (Any number of units transfused versus Any other number of units transfused)						
Graft Rejection	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)
Conclusion/ Strength of Evidence	The use of any number of units of blood had no significant effect on rejection outcomes. Insufficient			The use of any units of blood had neutral effect on rejection outcomes. Insufficient – magnitude hard to gauge		

KQ 1b (ii): Graft Survival Based on Number of Transfusions: Intensity of Transfusion vs. No Transfusion

Impact of number of transfusions on:	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
Number of Transfusions (1-5 vs. 0)						
1-Year Graft Survival	**1/5 (20.0%)**	**4/5 (80.0%)**	0/5 (0.0%)	**10/19 (52.6%)**	**9/19 (47.4%)**	0/19 (0.0%)
Max Duration Graft Survival	**2/3 (66.7%)**	**1/3 (33.3%)**	0/3 (0.0%)	**9/19 (47.4%)**	**10/19 (52.6%)**	0/19 (0.0%)
Number of Transfusions (5-10 vs. 0)						
1-Year Graft Survival	**2/4 (50.0%)**	**2/4 (50.0%)**	0/4 (0.0%)	**11/20 (55.0%)**	**7/20 (35.0%)**	2/20 (10.0%)
Max Duration Graft Survival	**2/3 (66.7%)**	**1/3 (33.3%)**	0/3 (0.0%)	**10/20 (50.0%)**	**8/20 (40.0%)**	2/20 (10.0%)
Number of Transfusions (≥10 vs. 0)						
1-Year Graft Survival	**1/3 (33.3%)**	**2/3 (66.7%)**	0/3 (0.0%)	**9/12 (75.0%)**	**3/12 (25.0%)**	0/12 (0.0%)
Max Duration Graft Survival	**1/1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)	**9/12 (75.0%)**	**3/12 (25.0%)**	0/12 (0.0%)
Conclusion/ Strength of Evidence	The use of 1-5, 5-10, or >10 transfusions versus no transfusion had a beneficial to no significant effect on graft survival. Low			The use of 1-5, 5-10, or >10 transfusions versus no transfusion had a beneficial to neutral effect on graft survival. Low		

KQ 1b (ii): Graft Survival Based on Number of Transfusions: Higher vs. Lower Intensity Transfusions

Impact of number of transfusions on:	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
Number of Transfusions (≥5 vs. 1-5)						
1-Year Graft Survival	**4/7 (57.1%)**	**3/7 (42.9%)**	0/7 (0.0%)	**9/21 (42.9%)**	**12/21 (57.1%)**	0/21 (0.0%)
Max Duration Graft Survival	**6/9 (66.7%)**	**3/9 (33.3%)**	0/9 (0.0%)	**11/26 (42.3%)**	**11/26 (42.3%)**	4/26 (15.4%)
Number of Transfusions (≥10 vs. 1-5)						
1-Year Graft Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	**4/10 (40.0%)**	**6/10 (60.0%)**	0/10 (0.0%)
Max Duration Graft Survival	No data	No data	No data	**3/9 (33.3%)**	**6/9 (66.7%)**	0/9 (0.0%)
Number of Transfusions (≥10 vs. 5-10)						
1-Year Graft Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	**2/12 (16.7%)**	**10/12 (83.3%)**	0/12 (0.0%)
Max Duration Graft Survival	No data	No data	No data	**1/11 (9.1%)**	**10/11 (90.9%)**	0/11 (0.0%)
Conclusion/ Strength of Evidence	The use of higher number of transfusions versus lower number of transfusions had a beneficial to no significant effect on graft survival. Low (Insufficient for ≥10 transfusions on Max Graft Survival Analyses)			The use of higher number of transfusion versus lower number of transfusions had a beneficial to neutral effect on graft survival. Low		

KQ 1b (ii): Patient Survival Based on Number of Transfusions: Intensity of Transfusion vs. No Transfusion

Impact of number of transfusions on:	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
Number of Transfusions (1-5 vs. 0)						
1-Year Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)
Max Duration Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)
Number of Transfusions (5-10 vs. 0)						
1-Year Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	**1/3 (33.3%)**	**2/3 (66.7%)**	0/3 (0.0%)
Max Duration Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	**1/3 (33.3%)**	**2/3 (66.7%)**	0/3 (0.0%)
Number of Transfusions (≥10 vs. 0)						
1-Year Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	**1/2 (50.0%)**	**1/2 (50.0%)**	0/2 (0.0%)
Max Duration Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)
Conclusion/ Strength of Evidence	The use of any number of transfusions had no significant effect on 1-year and maximum duration patient survival. Low			The use of any number of transfusions had beneficial to neutral effect on 1-year and maximum duration patient survival. Low		

KQ 1b (ii): Patient Survival Based on Number of Transfusions: Higher vs. Lower Intensity Transfusions

Impact of number of transfusions on:	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
Number of Transfusions (≥5 vs. 1-5)						
1-Year Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)
Max Duration Patient Survival	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)
Number of Transfusions (≥10 vs. 1-5)						
1-Year Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)
Max Duration Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)
Number of Transfusions (≥10 vs. 5-10)						
1-Year Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)
Max Duration Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)
Conclusion/ Strength of Evidence	The use of higher number of transfusions versus lower number of transfusions had no significant effect on 1-year and maximum duration patient survival. Low			The use of higher number of transfusions versus lower number of transfusions had small impact on 1-year and maximum duration patient survival. Low		

Multivariate Analyses (1bii)

Rejection Outcomes

- 7 analyses evaluated number of transfusions or number of units transfused
- 3/5 (60.0%) multivariate analyses showed number of transfusions to be an independent predictor of fewer rejection outcomes
  - Data set included patients who may have received zero pretransplant transfusions
- 2 analyses examined higher intensity (> 5 transfusions) versus lower intensity of transfusions (1-5 transfusions)
  - 1/2 (50.0%) analyses found that greater than 5 transfusions was an independent predictor of increasing risk of rejection (with regard to living donors, not cadaver donors)
  - Both analyses were from same study

Multivariate Analyses (1bii)

Graft Survival Outcomes

- 18 analyses evaluated number of transfusions or number of units transfused
- 11/18 (61.1%) analyses did not find transfusions (ranging from 1 to greater than 10) to be an independent predictor of graft survival in either direction
- 6/18 (33.3%) multivariate analyses showed transfusions of different intensities to be an independent predictor of worsening graft survival
- 1/18 (5.6%) analyses found one or more transfusions to be an independent predictor of benefiting graft survival
- 2/2 (100.0%) analyses found transfusions of higher intensity (> 5 transfusions) to be an independent predictor of worsening graft survival for both living and cadaver allografts versus lower intensity (1-5 transfusions)

Multivariate Analyses (1bii)

Patient Survival Outcomes

- 7 analyses evaluated the number of transfusions or number of units transfused
- 4/7 (57.1%) analyses did not find the number of transfusions or number of units transfused to be an independent predictor of patient survival in either direction
  - 3/4 (75.0%) of these studies were limited to 5 transfusions or fewer
- 3/7 (42.9%) multivariate analyses showed number of transfusions to be an independent predictor of worsening patient survival outcomes
  - 2 analyses were from the same study and examined 6-10 transfusions vs. zero and > 10 transfusions vs. zero
  - 1 study examined transfusions greater than 40 units

KQ 1b (iv-v): Rejection Outcomes for Any Transfusion Versus No Transfusion in Studies Conducted From Different Time Periods

Impact of transfusions on graft rejection	Significant Decreases in Rejection	No Significant Effect on Rejection	Significant Increases in Rejection	Decrease Risk of Rejection	No Change in Rejection	Increase Risk of Rejection
Before 1984	**5/7 (71.4%)**	0/7 (0.0%)	2/7 (28.6%)	**15/19 (78.9%)**	1/19 (5.3%)	3/19 (15.8%)
Initiated 1984 to 1991	**2/2 (100.0%)**	0/2 (0.0%)	0/2 (0.0%)	**5/7 (71.4%)**	1/7 (14.3%)	1/7 (14.3%)
1992 – Present	**1/2 (50.0%)**	0/2 (0.0%)	**1/2 (50.0%)**	**3/9 (33.3%)**	**2/9 (22.2%)**	**4/9 (44.5%)**
Conclusion/ Strength of Evidence	Up to Year 1992, transfusions may have a significant beneficial to neutral effect on rejection. Thereafter, transfusions may or may not provide this effect. Low			Up to Year 1992, transfusions may have a beneficial to neutral effect on rejection. Thereafter, transfusions may or may not provide this effect. Insufficient – magnitude hard to gauge		

KQ 1b (iv-v): Graft Survival Outcomes for Any Transfusion Versus No Transfusion in Studies Conducted From Different Time Periods

Impact of transfusions on	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1 Year Graft Survival						
Before 1984	**24/40 (60.0%)**	**16/40 (40.0%)**	0/40 (0.0%)	**60/93 (64.5%)**	**30/93 (32.3%)**	3/93 (3.2%)
Initiated 1984 to 1991	0/4 (0.0%)	**4/4 (100.0%)**	0/4 (0.0%)	**1/6 (16.7%)**	**5/6 (83.3%)**	0/6 (0.0%)
1992 – Present	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	**1/9 (11.1%)**	**8/9 (88.9%)**	0/9 (0.0%)
Max Time Graft Survival						
Before 1984	**23/49 (46.9%)**	**26/49 (53.1%)**	0/49 (0.0%)	**65/102 (63.7%)**	**33/102 (32.4%)**	4/102 (3.9%)
Initiated 1984 to 1991	**2/6 (33.3%)**	**4/6 (66.7%)**	0/6 (0.0%)	**3/8 (37.5%)**	**5/8 (62.5%)**	0/8 (0.0%)
1992 – Present	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	**2/9 (22.2%)**	**7/9 (77.7%)**	0/9 (0.0%)
Conclusion/ Strength of Evidence	Regardless of the time period, transfusions have a beneficial to neutral effect on graft survival Low			Regardless of the time period, transfusions have a beneficial to neutral effect on graft survival Low		

KQ 1b (iv-v): Patient Survival Outcomes for Any Transfusion Versus No Transfusion in Studies Conducted From Different Time Periods

Impact of transfusions on	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1 Year Patient Survival						
Before 1984	0/9 (0.0%)	**9/9 (100.0%)**	0/9 (0.0%)	1/19 (5.3%)	**16/19 (84.2%)**	2/19 (10.5%)
Initiated 1984 to 1991	0/5 (0.0%)	**5/5 (100.0%)**	0/5 (0.0%)	0/5 (0.0%)	**5/5 (100.0%)**	0/5 (0.0%)
1992 – Present	0/3 (0.0%)	**3/3 (100.0%)**	0/3 (0.0%)	0/6 (0.0%)	**6/6 (100.0%)**	0/6 (0.0%)
Max Time Patient Survival						
Before 1984	**1/12 (8.3%)**	**11/12 (91.7%)**	0/12 (0.0%)	**6/23 (26.1%)**	**14/23 (60.9%)**	3/23 (13.0%)
Initiated 1984 to 1991	0/5 (0.0%)	**5/5 (100.0%)**	0/5 (0.0%)	**2/8 (25.0%)**	**5/8 (62.5%)**	1/8 (12.5%)
1992 – Present	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)	0/6 (0.0%)	**6/6 (100.0%)**	0/6 (0.0%)
Conclusion/ Strength of Evidence	Regardless of the time period, transfusions have a significant beneficial to neutral effect on patient survival Low			Regardless of the time period, transfusions have a beneficial to neutral effect on patient survival Low		

Key Question 2a.

- How have panel reactive antibody (PRA) assays changed over time? Do all PRA assays measure the same things? What things contribute to intra-assay variability? How correlative or independent of one another are these measures?
- This was a background question answered in a narrative fashion, not subject to systematic review

PRA Testing

- Panel Reactive Antibody (PRA) testing: seeks to evaluate who is most at risk of antibody rejection
  - Patients with preformed antibodies against HLA antigens are at risk of hyperacute/humoral rejection
  - PRA 80%: Means that a patient is incompatible with 80% of donors
    - PRA >10% are considered sensitized
    - PRA ≥80% are considered highly sensitized
  - PRA system used since 1960s

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Determining PRA

- Complement Dependent Cytotoxicity (CDC): Oldest test for PRA
  - Patient serum tested against donor B and T cells
    - If serum contains antibodies against HLA antigens, antibodies will bind to the lymphocytes. When complement is added to serum, lymphocytes are killed and detected by stain
  - Problems with CDC
    - Only detects complement fixing (Class I IgG and IgM) antibodies
    - Detects non-HLA antigens
    - Depends on lymphocyte and complement quality
    - Limited by cell panel used
  - Cannot be used as only test of sensitization

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Determining PRA

- Enzyme-Linked Immunoabsorbant Assay (ELISA): Solid phase assay which is more sensitive than CDC
  - Different kits
    - Quickscreen and QuickID
      - Only detects HLA Class I antibodies
    - B-screen, LATM, PRA-STAT
      - Detects HLA Class I and II antibodies

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Determining PRA

- Flow Cytometry:
  - House method: uses whole lymphocytes
  - Microbead method: purified HLA antigen coated microbeads
    - Identifies Class I and II antibodies
    - Specifies which HLA mismatches occur
  - Flow PRA and Luminex are commercial kits
- CDC < ELISA = microbead flow cytometry

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Problems with PRA

- Different assays
  - Varying sensitivity and specificity
- Different PRAs
  - 44% of centers use peak PRA
  - 56% use current PRA
- Composition of antigen panels
  - Vary depending on kit or locally procured cell panels
  - May differ from potential donor population

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Calculated PRA

- United Network for Organ Sharing (UNOS)
  - October 1, 2009: recommended against PRA system and for a calculated PRA (CPRA) strategy
- CPRA is based on the unacceptable HLA antigens to which patients are sensitized and which, if present in a donor, would represent an unacceptable risk for the candidate
- CPRA computed from HLA antigen frequencies among 12,000 kidney donors in the United States between 2003 and 2005 and represents the percentage of actual organ donors that express one or more unacceptable HLA antigens.
- If an HLA antibody is identified in a patient, a kidney with that antigen would not be offered
- The higher the CPRA, the fewer kidneys would be offered
- By March 2009, only 13 of 256 kidney transplant centers did not enter specific HLA antigen incompatibilities in the UNOS system
- 90% of patients with PRA $\geq$80% also had high CPRA in the same range

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Correlation Between Assays

- Overall Analyses
  - ELISA vs. ELISA, ELISA vs. Flow Cytometery
    - Well correlated for Class I and II
  - ELISA vs. CDC
    - Reasonably correlated for Class I in two of three analyses
  - Analysis in patients with graft failure
    - ELISA Assay Class I and II (PRA-Stat) with Flow Cytometry Class I and II (Flowscreen); $r = 0.49$, $p<0.001$
    - CDC Cytotoxicity Assay with Flow Cytometry Class I and II (Flowscreen); $r = 0.28$, $p<0.001$
    - CDC Cytotoxicity Assay with ELISA Assay Class I and II (PRA-Stat); $r = 0.30$, $p<0.001$

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Key Question 2b.

- How useful are PRA assays in predicting sensitization from blood transfusions, donor specific antigen (DSA) sensitization, and renal transplant rejection/survival—especially in the setting of Q2a?

KQ 2b: Rejection Outcomes for Lower vs. High PRA Levels

	Significant Reduction in Rejection	No Significant Effect on Rejection	Significant Increases in Rejection	Decreased Risk of Rejection	No Change in Rejection*	Increased Risk of Rejection
1-Year Graft Rejection	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)	**1/1 (100.0%)**	0/1 (0.0%)	0/1 (0.0%)
Max Duration Graft Rejection	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/2 (0.0%)
Conclusion/ Strength of Evidence	Lower PRA% may not significantly impact rejection Low			Lower PRA% may reduce the risk of rejection Insufficient – magnitude hard to gauge		

*Either data showing no difference, or notation in text stating no change

§Either data showing a decrease/increase of any magnitude or notation in text stating a decrease/increase

KQ 2b : Graft Survival for Lower vs. Higher PRA Levels

	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1-Year Graft Survival	**3/5 (60.0%)**	**2/5 (40.0%)**	0/5 (0.0%)	**3/8 (37.5%)**	**3/8 (37.5%)**	2/8 (25.0%)
Max Duration Graft Survival	**1/9 (11.1%)**	**8/9 (88.9%)**	0/9 (0.0%)	**6/14 (42.9%)**	**6/14 (42.9%)**	2/14 (14.3%)
Conclusion/ Strength of Evidence	Lower PRA% is associated with a significant beneficial to neutral effect on 1-year and max duration graft survival Low			Lower PRA% may or may not impact 1-year and maximum duration graft survival Low		

KQ 2b : Patient Survival for Lower vs. Higher PRA Levels

	Significant Increases in Survival	No Significant Effect	Significant Decreases in Survival	>10% Increase in Survival	10% to -10% Change in Survival	>10% Decrease in Survival
1-Year Patient Survival	No data	No data	No data	No data	No data	No data
Max Duration Patient Survival	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)	0/2 (0.0%)	**2/2 (100.0%)**	0/2 (0.0%)
Conclusion/ Strength of Evidence	Lower PRA% may not significantly impact maximum duration patient survival Low			Lower PRA% may or may not impact maximum duration patient survival Low		

Summary

- The data is generally weak and the strength of evidence is low to insufficient
  - There is a reasonable chance that future research could alter these conclusions
- Transfusions generally have a beneficial to neutral effect on renal allograft outcomes
  - Over differing time periods, there is a shift away from beneficial and towards a neutral effect
  - A potential confounder, in some studies those who developed high PRAs with transfusion did not undergo transplantation
  - Lower PRAs generally has a beneficial to neutral effect on renal allograft outcomes
    - Studies did not assess impact of higher PRAs from transfusion alone versus any cause (prior transplantation, mothers receiving grafts from their children)
    - PRA varies based on assay used, when PRA determined in relation to stimuli, use of modulators (immunosuppressant, statins, plasmapheresis, etc)
    - There is a movement towards CPRA system where specific incompatibilities are determined but the impact of transfusions on CPRA are not well described

Future Research Directions

- Multi-institutional studies are needed
  - Too much variability in practice between institutions to allow good applicability
- Adequate reporting of demographics
- Randomization or adjust for confounders
- Standard definitions of outcomes
- Standard follow-up time (1year)
- Transfusions should not just be counted in the dialysis or transplant center
- CPRA testing so specific HLA antigen sensitivities resulting from transfusions identified
  - The impact of immunosuppression on outcomes in sensitized patients due to transfusion needed