Hepatitis transmission risk IN kidney Transplantation (the HINT study); a cross-sectional survey of transplant clinicians in Australian and New Zealand

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ABBREVIATIONS PAGE

BBV, blood borne virus

CI, confidence interval

DAA, direct acting antiviral

HBcAb, hepatitis B core antibody

HBsAb, hepatitis B surface antibody

HBsAg, hepatitis B surface antigen

HBV, hepatitis B

HCV, hepatitis C

HCV-Ab, hepatitis C antibody

NAT, nucleic acid testing

OR, odds ratio

TSANZ, Transplantation Society of Australia and New Zealand

ABSTRACT

Background: Interpreting hepatitis serology and virus transmission risk in transplantation can be challenging. Decisions must balance opportunity to transplant against potential infection transmission. We aimed to survey understanding among the Australian and New Zealand medical transplant workforce of hepatitis risk in kidney donors and recipients.

Methods: An anonymous, self-completed, cross-sectional survey was distributed via electronic mailing lists to Australian and New Zealand clinicians involved in kidney transplantation (2014-2015). We compared interpretation of clinical scenarios with paired donor and recipient hepatitis B and C (HBV, HBC) serology to recommendations in clinical practice guidelines. We used logistic regression modelling to investigate characteristics associated with decisions on transplant suitability in scenarios with poor (<50%) guideline concordance (odds ratios, OR).

Results: 110 respondents had representative workforce demographics: most were male (63%) nephrologists (74%) aged 40-49. While donor and recipient hepatitis status was largely well understood, transplant suitability responses varied among respondents. For an HBV surface antigen positive donor and vaccinated recipient, 44% suggested this was unsuitable for transplant (guideline concordant) but 35% suggested this was suitable with prophylaxis (guideline divergent). In four scenarios with transplant suitability guideline concordance <50%, acute transplant care involvement predicted guideline concordant responses (OR 1.69, p=0.04). Guideline concordant responses were chosen less by hepatologists, intensive care doctors (OR 0.23, 0.35 respectively, p=0.01), and New Zealanders (guideline concordant responses OR 0.17, p<0.01; alternative responses OR 4.31, p<0.01).

Conclusions: Despite broadly consistent interpretations of hepatitis serology, transplant suitability decisions varied, and often diverged from guidelines. Improved decision support may reduce clinician variability.

Introduction:

International strategies to expand the donor pool have included closer scrutiny of donors at increased risk for blood borne virus (BBV) transmission.

Transmission of blood borne viruses via solid organ transplantation can have a devastating impact on recipients.[1,2] Risk of donor-derived infection transmission depends upon baseline disease prevalence, which varies worldwide, donor risk assessment, via routine screening assessment of potential donors via clinical history, examination and blood tests, as well as factors including recipient immune status, organ transplanted and availability of prophylaxis.[3] Under-estimation of risk could lead to infection transmission to the organ recipient, but over-estimation of risk may lead to missed opportunities for transplantation.

Although international guidelines typically demonstrate consensus regarding avoiding the highest risk cases, such as hepatitis B and C (HBV, HBC) NAT (nucleic acid test) positive donors,[4-6] variable recommendations exist in cases where risks are lower, as with hepatitis B core antibody (HBcAb) positive donors for non-liver solid organs. Use of HBcAb positive donors varies internationally (3.9% USA, 15% Italy, >50% Asian countries), related to baseline disease prevalence.[7,8] Complicating decision-making are advances in testing and treatment. NAT can safely expand the donor pool,[9,10] however, in low prevalence populations, false positives may lead to organs being falsely rejected.[11] HBV transmission risk can be mitigated by vaccination or post-transplant prophylaxis, but even after transmission a single agent can effectively control viral replication. For HCV, direct acting antiviral (DAA) regimes

are now available which can eradicate virus in under 24 weeks in >95% of individuals with treatment, even post transplantation.[12,13]

Decisions under risk lead to biased decision-making, with variable individual risk thresholds.[14] In the complex transplantation context, this may tend to risk aversion, although this is not well studied.[15] There is variable treatment of increased risk donors within countries as seen in recent work from Canada.[16]

In the current context, the best transplant decisions are not always clear for clinicians, whilst understanding of hepatitis status is increasingly important. This study aimed to survey clinicians' understanding of abnormal hepatitis B and C serology in a kidney transplant setting. Specifically, we aimed to identify specific clinical scenarios where there were gaps in understanding of hepatitis risk of potential donors or recipients, or variability in transplant suitability responses either from current regional guidelines or among clinicians.

Methods:

We performed a cross sectional survey of practicing clinicians involved in kidney donation and transplantation in Australia and New Zealand. This included primarily nephrologists, but also transplant hepatologists, intensive care doctors and transplant surgeons. This approach mirrors clinical practice in Australia and New Zealand, where all these groups impact suitability decisions at the time of donor referral and transplant acceptance.

The survey was hosted via the University of Sydney server, as an open web-based survey, accessible via public link. Functionality included ability to review previous answers, and to save responses and return to the survey. Eligibility was assessed by self-reporting. Responses were anonymous and voluntary with no incentives.

We invited participation via email lists of the Transplantation Society of Australia and New Zealand (TSANZ), Australia and New Zealand Society of Nephrologists, Australia and New Zealand Intensive Care Society, regional and national transplant advisory committees as well as emails to more informal groups including transplant surgeons and transplant hepatologists. Targeted appeals from individual clinicians and repeat emails from learned societies helped to increase response numbers. The survey was open for 4 months from December 2014 to April 2015.

Survey format and content

The survey was a scenario-based, electronic survey, comprising 8 clinical scenarios with hepatitis B or C serology results for a potential kidney deceased donor and recipient pair. The scenarios were devised to reflect clinically relevant and realistic higher-risk situations that were likely to pose a challenge to respondents. As an internal validity check, one scenario was designed with more common, benign serology, for which all respondents were expected to demonstrate good understanding. Respondents were presented with scenarios in random order (to reduce the impact of learning during the survey). For each scenario, respondents answered 3 mandatory multiple-choice questions to identify (i) donor hepatitis status, (ii) recipient hepatitis status and (iii) transplant suitability of the donor-recipient pair. Wording was designed to reflect options presented in the regional guidelines.[17] An

option of “unsure” was provided for each multiple-choice question. The survey was piloted internally before distribution to test usability. The survey was amended in response to pilot participant feedback to produce the final questionnaire (SDC, Appendix 1).

Ethics was obtained from Sydney University Human Research Ethics Committee; project number 2014/1016, on 28/11/2014. All survey respondents had access to a Participant Information Statement and a summary of this was provided both in the approved contact email and on the first page of the survey. Consent was implied by participation beyond this point.

Outcomes and Analysis

Outcomes were guideline-concordant[17] interpretation of (i) donor infection status, (ii) recipient infection status and (iii) each pair’s suitability for transplantation.

In those scenarios with poor (<50%) guideline concordance for transplant suitability, univariable and multivariable logistic regression models were fitted to (i) the guideline-concordant answer, and (ii) the most common alternative answer, to identify any factors associated with these outcomes. Potential factors considered were: role (nephrologists; intensive care and other; transplant surgeons; hepatologists); gender; age (<40; 40-50; 50-60; 60+); transplant practice patient burden (<20; 20+ per month); involvement in acute phase of transplant care; awareness of guidelines (strongly agree or agree; strongly disagree, disagree or neutral); and location (Queensland; New South Wales; Victoria; New Zealand; other). A random effect for participant was included in all models, as participants

answered multiple scenarios. Scenario was included as a categorical variable in the model to account for scenario difficulty. All factors were initially entered into the multivariable models and removed using stepwise backwards elimination, with factors remaining in the final model if statistically significant ($p<0.05$); with the exception of role, which remained in all multivariable models, regardless of its p-value.

Only complete questionnaires were used for analysis. Demographic characteristics of incomplete responses were compared to eligible responses using univariable logistic regression. Demographic characteristics of the respondent population were compared to workforce estimates.[18]

Results:

We included 110 respondents accrued over four months, with 61 respondents excluded as shown in Figure 1. Reasons for exclusion were incomplete survey responses, ineligible respondents, and one case of technical error. When compared to workforce characteristics, demographics were broadly consistent.[18] Among eligible respondents of complete versus incomplete survey responses demonstrated no significant difference in gender ($p = 0.37$) or clinical roles ($p=0.06$), but did find significant differences in age ($p=0.04$) and in location ($p=0.03$), with respondents aged over 60 and from New Zealand both under-represented in the final analysis set.

Characteristics of eligible respondents are shown in Table 1. Most respondents (50%) reported caring for an average 1-20 transplant patients per month, and were aware of clinical practice guidelines (51% agree, 9% strongly agree). The majority

(70%) worked in full time clinical practice, and 24% respondents were engaged in research. Sixty-one% provided acute transplant care at a transplanting centre.

Figures 2 and 3 present the responses to each question for HBV and HCV respectively. High levels of concordance within the internal validity check scenario suggested the survey, of novel design, is a valid instrument.

Interpretation of donor and recipient risk status

Both donor and recipient hepatitis status were generally well identified across the scenarios (Table 2), with >90% appropriate risk attribution in the majority of scenarios. In one HBV scenario, 62% respondents identified a HBcAb positive and hepatitis B surface antibody (HBsAb) positive donor as a low risk for hepatitis transmission, in concordance with current guidelines, but 30% suggested this donor posed no hepatitis transmission risk. In two scenarios with hepatitis B surface antigen (HBsAg) positive donors, an average 11% respondents incorrectly suggested this as low risk rather than high. For an isolated HBcAb positive recipient, 18% respondents had incorrect answers evenly split among 3 alternative responses to the correct “exposed, no active virus”.

In two scenarios with a HCV-Ab (hepatitis C antibody) positive HCV NAT negative donor, this was identified as a hepatitis transmission risk by an average 35% respondents, in concordance with guidelines. However the majority of respondents (average 60%), including all responding hepatologists, suggested this donor posed no hepatitis C transmission risk.

Concordance of transplant suitability decisions

Transplant suitability decisions showed widespread variability in responses among clinicians and discordance from guidelines. Excluding the validity check scenario, the highest rate of guideline concordance was 81%, which fell rapidly in other scenarios. In four scenarios (2 HBV, 2 HCV), guideline concordance was <50%. In two scenarios, the most popular alternative was selected more than guideline concordant responses. With donor and recipient both HCV-Ab positive HCV NAT negative, only 7% selected the guideline concordant “unsuitable” response, where 63% selected an alternative “suitable with consent” response. For an HBV exposed, low risk donor (HBcAB positive, HbsAb positive) and naïve recipient, 48% selected “suitable with prophylaxis” (guideline divergent) while only 20% selected the guideline concordant “suitable with informed consent”. Two scenarios had a more even split between guideline concordant and most popular alternative response: HCV-Ab positive HCV NAT negative donor and HCV naïve recipient (47% unsuitable, guideline concordant; 35% suitable with consent, guideline divergent), and active donor infection (HBcAb positive, HBsAg positive, HBsAb negative) and immunized recipient (isolated HBsAb positive) where 44% selected the guideline concordant response “unsuitable” and 35% selected the most common alternative response “suitable with consent and prophylaxis”.

Suitability responses at times showed a wide spread of attitudes among respondents. For example, in a HBV scenario with an exposed donor (HBcAb positive, HBsAg negative, HBsAb positive) and a naïve recipient, 15% deemed the transplant as suitable without any special measures, and 13% deemed the transplant unsuitable.

Across the seven higher-risk scenarios an average 6% respondents self-identified as “unsure”. Variability in suitability responses persisted even where hepatitis status of both donor and recipient were nearly universally recognized.

The results of the univariable and multivariable models for transplant suitability outcomes in the four HBV and HCV scenarios where guideline concordance was less than 50% are presented in Figure 4 (full results SDC, Appendix 2). Location was a strong factor influencing responses, with New Zealanders less likely to respond in concordance with guidelines (OR 0.17, 95% CI 0.06 – 0.46, p<0.01), and more likely select the most common alternative response (OR 4.31, 95% CI 1.99 – 9.35, p<0.01). Role was a significant factor for differences in guideline concordance (p=0.01) with hepatologists (OR 0.23, 95% CI 0.06 – 0.92) and intensive care specialists (OR 0.35, 95% CI 0.18 – 0.82) less guideline concordant in these scenarios. Care of transplant patients in the acute setting at a transplanting centre was associated with more guideline concordant responses (OR 1.69, 95% CI 1.01 – 2.80, p = 0.04). Awareness of guidelines, transplant patient burden, gender, and age were not predictive of guideline concordant or most popular alternative responses.

Discussion:

This survey of transplant clinicians showed good understanding of hepatitis serology of donors and recipients. Despite this, translation to consistent transplant suitability decisions was highly variable.

What is the reason for variable transplant decisions when donor serology is correctly interpreted? Awareness of guidelines does not appear to be the primary issue, as only 22% self-identified as unaware of where to find current guidelines. Further, awareness of guidelines did not impact on transplant suitability responses (i.e. those aware of guideline recommendations were not more or less likely to answer in concordance with them). This suggests either a lack of understanding of current guidelines, or more likely that clinical evidence has out-paced guidelines. Australian and New Zealand guidelines, last published in 2011, were updated during this study.[19] Notable changes include support for consideration of higher risk serology scenarios, including hepatitis C positive donors, and consideration of prophylaxis for HBcAb positive donors, although other recommendations remain conservative.

Are regional or personal preferences driving practice? To identify any shift in contemporary practice, we examined factors influencing suitability responses in scenarios where <50% respondents answered according to guidelines. Hepatologists were perhaps more progressive in attitude, being less guideline concordant, and tending to select the most common alternative response ($p = 0.07$). In the TSANZ network, transplant hepatologists can provide guidance on hepatitis infections to other transplant clinicians, hence these responses may suggest guidelines are too risk averse. Respondents involved in acute transplant care at a transplanting centre, who are likely to be making more frequent suitability decisions than other respondents, selected more guideline concordant responses, however. New Zealand clinicians were less likely to select guideline concordant responses and more likely to respond with the most common alternative response, which supports the hypothesis of emerging differences in practice. If out-dated guidelines were the

sole problem, we would expect less inter-clinician variability than was demonstrated. This study was unable to discern variations in practice between individual centres or groups, as data were not captured at this level.

Does the wider literature and international guidelines provide support for alternative suitability responses and explain variability? With HBV, once natively infected, the potential for re-activation always remains despite being HBV NAT negative as there is an ongoing reservoir for the virus in the liver. HBV can incorporate in the genome and is maintained in covalently closed circular deoxyribonucleic acid form, which cannot be eliminated and has potential for future reactivation. This is in distinct contrast to HCV. Recent literature on HBcAb positive kidney donors demonstrated no clinical impact on recipients, and low rates of HBsAg seroconversion.[20] Despite this, international clinical practice guidelines vary suggesting such donors are unsuitable,[6] require routine prophylaxis,[21] prophylaxis depending on recipient HBsAb titre[4] or donor HBV NAT positivity,[22] or treatment of recipient only after seroconversion.[20] The most recent Australasian guidelines emphasise prophylaxis for recipients.[19] This is consistent with the most common guideline-divergent response (48%), suggesting those respondents may have been more pragmatic than previous guidelines.

Where donors are HBsAg positive, the risk of transmission is low in certain circumstances (such as with non-liver solid organs, if donor HBV NAT is negative, to an immunized recipient and with prophylaxis), and a recent study suggests there was no difference in outcomes for recipients receiving HBsAg positive donor organs.[23] Indeed, some literature suggest using these donors for recipients in kidney

transplantation, with appropriate treatment post-transplant depending upon recipient vaccination status.[24] However, concerns remain given at least one recently publicized case of fulminant hepatic failure in a kidney recipient of such an organ.[2] International guidelines hence typically advise against use of these donors except in life-threatening cases. It may be that informed respondents were being less conservative than guidelines, but the wide variation in responses remains notable.

The risk of transmission from HCV-Ab positive HCV NAT negative donors remains to be fully defined;[6] this was one area respondents had difficulty in interpreting serology. Fluctuating viremia is possible and may still pose a transmission risk, despite sparse evidence of transmission in non-liver solid organ transplantation. Thus interpreting this as a no risk scenario (58% responses) was incorrect. Current guidelines recommend against the use of these donors except for HCV NAT positive recipients. However, once an individual is documented to be HCV NAT negative on 2 separate occasions 12 weeks apart, or on a single occasion more than 12 weeks after any at risk exposure, they are deemed clear of the virus. This highlights that HCV has no reservoir of infection and needs ongoing viral replication for maintenance of infection. A range of new DAAs are available that can be used in renal impairment and can achieve HCV eradication with 8-24 weeks of treatment in 95-100% of individuals.[12] There has been increasing acceptance in transplant centres to eradicate HCV both pre and post-transplant,[13] and very recent changes to the local TSANZ guidelines regarding consideration of HCV positive donors for negative recipients, similar to recent international position statements[19,25]. Respondents may have been pre-empting these updates.

A strength of our work is that we gathered a representative sample of the regional nephrology workforce, by age, gender, and location, compared to national workforce surveys.[18] Our survey distribution method was broadly inclusive, as there is no clear denominator of eligible clinicians to approach. The limitation of extending an invite to participate very broadly is that we cannot estimate, a response rate. Certainly low absolute numbers of respondents in some comparator sub-groups, especially transplant hepatologists, limit inferences that can be made and generalisability in these groups. As with any survey, we cannot rule out selection bias from respondent self-selection, but we would expect volunteer responders to be more engaged with this area and perhaps demonstrate more knowledge than the wider pool. Our comparison of incomplete versus complete responses demonstrated some differences in characteristics, which could be due to difficulties encountered by some subgroups accessing the survey due to hospital firewalls and out-dated internet browser software.

Although the results of this study are likely to be generalizable across the wider Australia and New Zealand transplant workforce, whether they are generalizable beyond this is less certain. Previous studies investigating variability in transplant suitability with abnormal hepatitis serology were confined to limited HBV scenarios in liver transplants;[26,27] no similar studies have applied such a broad range of cases, or considered renal transplantation. Our results are consistent with studies showing variations in attitudes to, and transplant practice concerning increased risk donors and screening tests.[16,28,29] Whether clinicians' real-life decision making mirrors their responses to theoretical scenarios is uncertain, noting this survey focused on virological risk alone and did not capture the myriad of other considerations that may

impact on decision making by clinicians including an individual's waiting time, illness severity, and their values and preferences.

To address residual uncertainties, an audit of increased-risk hepatitis donor referrals to understand handling of these cases in real world conditions would be informative. Systematic review of clinical practice guidelines and the evolving evidence base would also provide a strong foundation to build consensus response. Exploring whether similar variability persists in other countries and as guidelines evolve would also be of interest.

Noting the speed at which this field is evolving, and that guidelines by nature cannot always keep up with emerging evidence, real-time decision support or consensus opinion on such controversial areas that is updated by trusted clinicians would be of value. Given the complexity of the area, developing targeted education programs for clinicians making these high-impact decisions in fast-paced environments may also help to build more consistency in approach.

Conclusion:

The application of knowledge of hepatitis risk in scenarios with donors and/or recipients with abnormal hepatitis serology is an area of demonstrable uncertainty among transplant clinicians. This is despite good isolated understanding of donor and recipient hepatitis risk status. The results of this study suggest a complex pattern of factors underpinning variability in clinical approach to abnormal hepatitis serology, where guidelines do not always support most current evidence-based practice.

Given the clinical implications of decision-making in this area at both an individual patient level and a broader public health perspective, this study suggests there is a role for more pragmatic guidance to support consistent treatment of higher-risk hepatitis scenarios and hence improve clinical practice.

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Table 1: Respondent characteristics presented as total numbers for final responses. Answers to questions were exclusive (single-choice only), except for questions denoted with * where respondents were asked to select all applicable responses.

Characteristic	Respondent Numbers
Total Respondents:	**110**
Clinical Role	
Nephrologist	81
Transplant Surgeon	12
Intensive Care Specialist	10
Transplant Hepatologist	5
Other	2
Gender	
Male	69
Female	41
Age	
<30	1
30-39	29
40-49	47
50-59	26
60-69	6
70+	1
Location	
New South Wales	42
Victoria	22
Queensland	15
New Zealand	14
Western Australia	5
Australian Capital Territory	4
South Australia	4
Northern Territory	2
Tasmania	2
Transplant Patients – number per month	
0	7
1-20	55
21-40	31
>40	17
Transplant Patients – type *	
Patients awaiting kidney transplant	87
Patients acutely receiving a kidney transplant, at a transplanting centre,	67
Long-term patients with past kidney transplant recipients	84
Living kidney donors	70
Deceased kidney donors	43
Other	16

Table 2: Proportions of respondents who answered in concordance with four outcomes for each scenario: identifying donor and recipient risk status in concordance with guidelines, and selecting transplant responses in that were guideline concordant or where guideline concordance was <50%, the most common alternative response.

Scenario				Respondents answering correctly (%)			
						Transplant suitability	
Hepatitis B	**Core antibody**	**Surface antigen**	**Surface antibody (IU/ml)**	**Donor risk status**	**Recipient risk status**	**Guideline concordant**	**Most common alternative response**
Donor	-	-	>100	95 Vaccinated	100 Naïve	96 Suitable	N/A
Recipient	-	-	-				
Donor	+	-	>100	62 Exposed, low risk	99 Naïve	20 Suitable, consent	48 Suitable, prophylaxis
Recipient	-	-	-				
Donor	+	+	-	86 Exposed, high risk	93 Vaccinated	44 Unsuitable	35 Suitable, prophylaxis
Recipient	-	-	12				
Donor	+	+ (NAT +)	-	97 Exposed, high risk	82 Exposed, no virus	61 Unsuitable	N/A
Recipient	+	- (NAT -)	-				
Donor	+	+	-	87 Exposed, high risk	100 Naïve	81 Unsuitable	N/A
Recipient	-	-	-				
Hepatitis C	**Antibody**	**NAT**					
Donor	+	-		36 Exposed, risk	95 Naïve	47 Unsuitable	35 Suitable, consent
Recipient	-	N/A					
Donor	+	+		99 Exposed, risk	93 Exposed, no virus	58 Unsuitable	N/A
Recipient	+	-					
Donor	+	-		34 Exposed, risk	90 Exposed, no virus	7 Unsuitable	63 Suitable, consent
Recipient	+	-					

Figure 1: Assessment of 171 survey responses to identify 110 complete and eligible responses suitable for analysis.

Figure 1.jpg

Figure 2: Matrix of responses for all HBV scenarios, shown as proportions of respondents (y axis; %), Guideline concordant answers are denoted *; most common alternative transplant suitability responses (if guideline concordant answer <50%) are denoted ^. For full survey response options, see SDC, Appendix 1.


Figure2.jpg

Figure 3: Matrix of responses for all HCV scenarios, shown as proportions of respondents (y axis; %), Guideline concordant answers are denoted *; most common alternative transplant suitability responses (if guideline concordant answer <50%) are denoted ^. For full survey response options, see SDC, Appendix 1.


Figure3.jpg

Figure 4: Transplant suitability responses by respondent characteristics for four scenarios (2 HBV, 2 HCV) where guideline concordance was <50%. Odds ratios for guideline concordant responses or most common alternative responses. Significant responses denoted by * $p < 0.05$ ** $p < 0.01$

Figure4.jpg

Supplementary Digital Content:

Appendix 1: Survey in full

SDC Appendix 1.pdf

Appendix 2: Logistic regression models for 4 transplant suitability scenarios where guideline concordance was <50%, for outcomes (i) guideline concordant responses and (ii) most common alternative responses. Significant p-values (<0.05) highlighted in grey.

Appendix 2.docx