ORIGINAL ARTICLE

Non-simultaneous kidney exchange cycles in resource-restricted countries without non-directed donation – a prospective single-center cohort study

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SUMMARY

Recent reports suggest that bridge–donor reneging is rare (1.5%) in non-simultaneous kidney exchange chains. However, in developing countries, the non-directed donors who would be needed to initiate chains are unavailable, and furthermore, limited surgical space and resources restrain the feasibility of simultaneous kidney exchange cycles. Therefore, the aim of this study was to evaluate the bridge–donor reneging rate during *non-simultaneous kidney exchange cycles* (NSKEC) in a prospective single-center cohort study (n = 67). We describe the protocol used to prepare co-registered donor–recipient pairs for non-simultaneous surgeries, in an effort to minimize the reneging rate. In addition, in order to protect any recipients who might be left vulnerable by this arrangement, we proposed the use of standard criteria deceased-donor kidneys to rectify the injustice in the event of any bridge–donor reneging. We report 17 successful NSKEC resulting in 67 living-donor kidney transplants (LDKT) using 23 bridge–donors without donor renege and no intervening pairs became unavailable. We propose that NSKEC could increase LDKT, especially for difficult-to-match sensitized pairs (25 of our 67 pairs) in countries with limited transplantation resources. Our study confirms that NSKEC can be safely performed with careful patient–donor selection and non-anonymous kidney exchanges.

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Key words
ABO incompatible, donor reneging, donor, recipient pairs, living-donor kidney transplantation, non-simultaneous kidney exchange cycle, sensitization

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Introduction

Over the course of 5 years, in order to increase the number of kidney transplants that can be performed in India, we have experimented 17 times with non-simultaneous *cycles* of transplants, in contrast to the non-simultaneous *chains* that have already been widely accepted elsewhere. Kidney exchange began with simultaneous simple cycles of exchanges that involved only incompatible pairs in two or more exchanges, but evolved to incorporate non-directed donors so that a simultaneous chain was created rather than a cycle [1,2]. (Domino paired kidney donation: a strategy to make best use of live non-directed donation.) The introduction of non-simultaneous extended altruistic donor (NEAD) chains in 2007 challenged the then prevailing view that kidney exchanges must be performed simultaneously to prevent harm to a recipient in the event of a donor renege [3]. In contrast, non-simultaneous kidney exchange cycles were—and still are—considered ethically unacceptable, precisely because the harm caused by a donor reneging in a cycle is significantly worse than in a NEAD chain, due to the harm caused to the at-risk recipient who no longer has a willing, but incompatible donor available to facilitate a future kidney exchange [3]. Though initially meeting resistance within the transplant community, NEAD chains have now become accepted practice in some countries and have led to more than 10 000 additional living-donor kidney transplants around the world [4,5].

Despite this success, non-simultaneous chains remain controversial and several highly regarded national kidney exchange programs still do not allow NEAD chains, let alone non-simultaneous cycles (Fig. 1) [6–8]. Non-simultaneous cycles are not common practice in any country. Rather the US and Canada utilize non-simultaneous chains that start with a non-directed donor and end with a patient without a co-registered incompatible donor, whose only option prior to non-simultaneous chains was a deceased-donor kidney [4,5]. A cycle does not involve non-directed donors or patients without a co-registered incompatible donor. The novelty of non-simultaneous cycles is perhaps made more clear when one considers the use of non-simultaneous kidney exchanges by the national programs of the US, Canada, Australia, United Kingdom and Netherlands. None of these high-income countries utilizes non-simultaneous cycles; and only two of the five routinely use non-simultaneous chains. In the US and Canada, non-simultaneous chains, but not cycles, are utilized [4,5]. In the UK, they allow very short non-simultaneous chains [6]. In the Netherlands and Australia, non-simultaneous kidney exchange is not allowed by either chains or cycles [7,8].

Given the successful application of NEAD chains [9,10], the low bridge–donor renege rate in countries where NEAD chains are routinely performed [11], and the ability to transplant more highly sensitized patients with long NEAD chains than with short simultaneous cycles [12] we propose that the transplant community reconsider the ethics of engaging in non-simultaneous kidney exchange cycles. In particular, we make that case that this approach would provide the greatest value in resource-limited, low-and middle-income countries, and in countries where non-directed donation, and thus kidney exchange chains, are not allowed. To text this concept, we have experimented with trusting bridge–donors within cycles (not chains). In this situation, it would be possible for a recipient to give up his or her co-registered donor without receiving a kidney in return. As a safeguard, permission was obtained to utilize an alternatively allocated deceased-donor kidney to repair any chain that might be broken by a bridge–donor reneging. Fortunately, there were no reneges in this study—but that is not the innovative feature; instead, it is the novel application of nonsimultaneity within kidney exchange cycles, rather than within the more familiar nonsimultaneous chains.

While the authors could have completed many of the reported cycles simultaneously, the resources required for that are not present in many low-to-middle-income countries (LMIC). These non-simultaneous cycles were scheduled to examine if such an approach could be safely utilized by transplant centers in LMIC. Our Institution has a long history of performing kidney exchanges [13–16], and this report documents another way of improving the chances for a recipient to receive an organ if they have a willing-but-incompatible donor. We report our initial experience with non-simultaneous kidney exchange cycles (NSKEC) (see Figs 2 and 3). The aim of this study was to evaluate the bridge–donor reneging rate in NSKEC.

Methods

This is a prospective single-center cohort study of NSKEC in 67 donor–recipient pairs (DRPs) from August 2015 to February 2020. The study has been reviewed by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the Declaration of Helsinki as well as the Declaration of Istanbul. All persons gave

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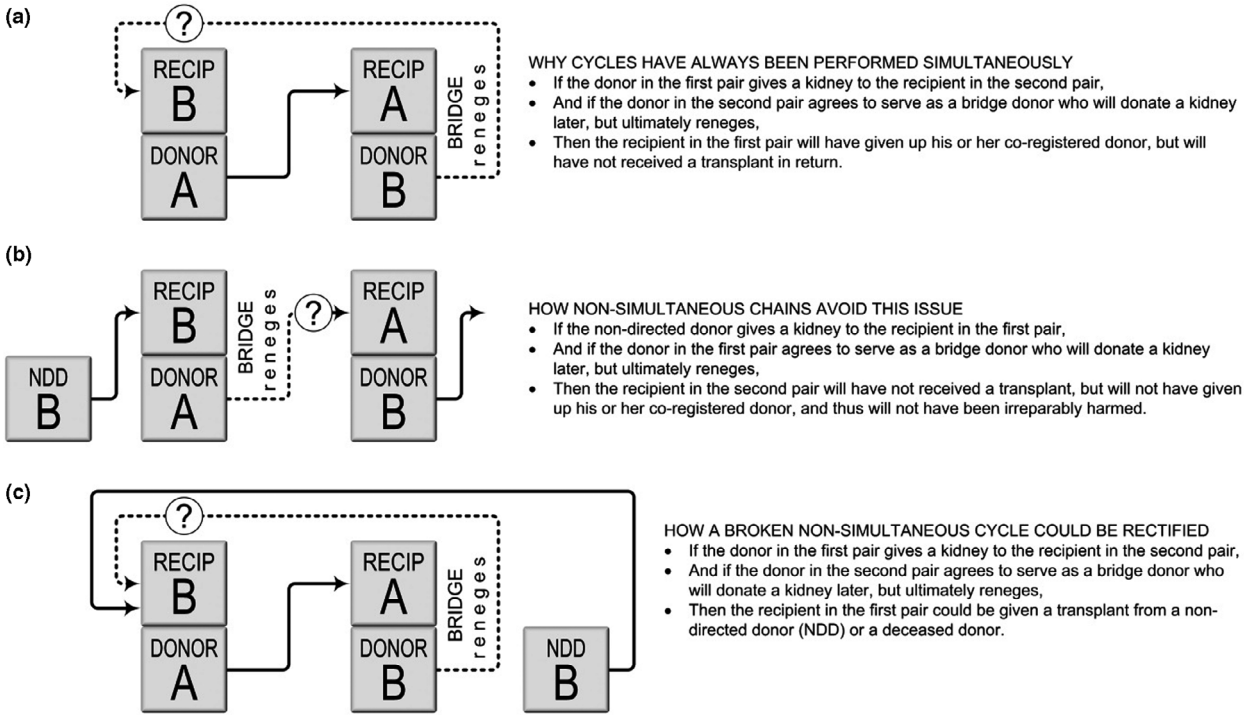

Figure 1 What the outcomes would be if a donor was to renege in a kidney exchange cycle or chain. (a) A 2-way cycle in which donor A has already donated a kidney to recipient A. When donor B does not follow through with a donation to recipient B, recipient B not only fails to receive a kidney, but also loses the opportunity to participate in a future kidney exchange due to no longer having a willing, but incompatible donor who can participate with them in that exchange. Thus, reneging in a conventional 2-way kidney exchange permanently damages recipient B [6]. (b) How a non-directed, altruistic living donor [6] (or deceased donor [14]) initiates a non-simultaneous extended altruistic donor (NEAD) kidney exchange. In this case, reneging by donor A would not cause irreparable harm to recipient A because donor B has not donated their kidney and can participate in an alternative future kidney exchange. (c) How the situation can be rectified if donor A gives a kidney to recipient A, and then donor B reneges on their commitment to provide another organ. In that situation, it would be possible for recipient B to receive a deceased-donor kidney on priority. Thus, reneging in a conventional 2-way kidney exchange cycle may not necessarily cause irreparable harm to recipient B.

their informed consent prior to their inclusion in the study.

The allocation policy of donor–recipient pairs (DRPs) in our center has been reported previously [13–17]. DRPs exchange a kidney for another of similar quality. The Alliance for Paired Kidney Donation software is used to identify the best available exchanges. The prospective donors underwent an extensive psychological evaluation by a psychiatrist, and adequate time was allotted between evaluations and donation to allow donors to carefully consider their decision before the commencement of surgeries in NSKEC. As is the case in the USA and other countries, donors were not required to sign a no-renege contract. However, informed consent was obtained, making sure the patient and donors understood the risks and benefits of NSKEC and of the proposed operations. We trusted each donor's honesty, generosity, and good will to follow through in good faith, as planned. In fact, we found that all recipients were willing to be transplanted last (after all bridge–donors), and all donors were willing to donate a kidney first—perhaps demonstrating their determination to participate without reneging. All participants expressed their willingness to accept whatever surgery schedule would be most likely to improve the outcome of the transplants involving them. In Table 1, which details the precautions taken to prevent unequal outcome in DRPs, we describe the protocol used to prepare donors and recipients for the non-simultaneous surgeries in order to minimize the reneging rate.

In addition to the factors noted in Table 1, another important feature of our program is the utilization of non-anonymous allocation [14]. In this report, at least one donor in each kidney exchange cycle was being asked to risk giving their kidney without their co-registered recipient receiving a kidney—at least a living-donor kidney—if another bridge–donor reneged. Because the recipient needs to trust that they will receive a kidney from the bridge–donor as planned and

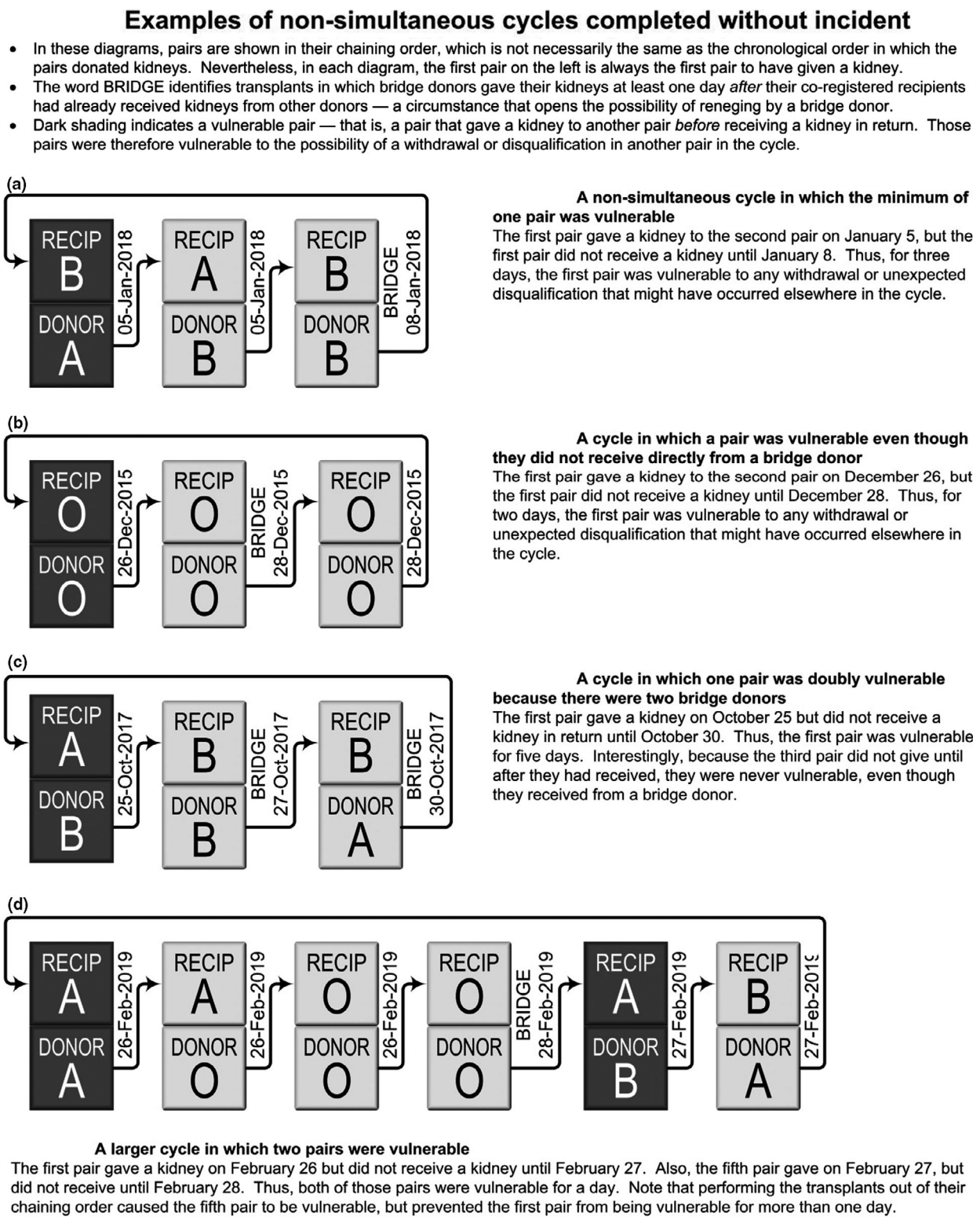

Figure 2 Schematic representations of the 17 non-simultaneous kidney exchange cycles performed. The number of the pair in this figure corresponds to the number in Table 2, so the reader can see the details of each exchange and reference both the figure and the table.

promised, we allowed DRPs to meet each other before and after kidney transplantation—hence the term "non-anonymous allocation." We believe that the bridge–donors in NSKEC are less likely to withdraw their participation if they have personal experience with their proposed recipient.

In this diagram, dark squares indicate the vulnerable pairs. A "vulnerable pair" is one in which the donor is asked to give up a kidney *before* the recipient obtains one. Thus, vulnerable pairs are exposed to the possibility of having given up a kidney without ever having obtained one in return. In a non-simultaneous cycle, at least one pair would have to be vulnerable at some point. Note that this vulnerability is bought about by giving a kidney before obtaining one — and not necessarily as a result of being positioned to receive from a bridge donor. In some cases, it would be possible for a vulnerable pair to be victimized by a reneging bridge donor, but victimization could also be the result of the withdrawal of a non-bridge donor. In the current study, no vulnerable pairs were victimized.

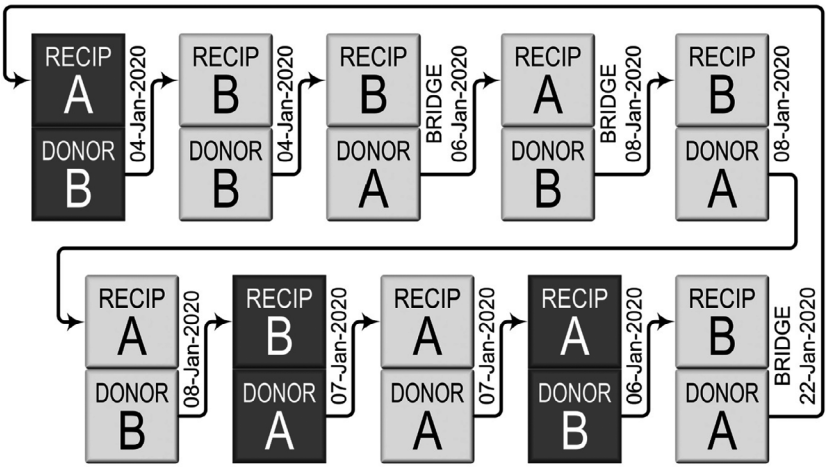

Figure 3 A 10-way cycle utilizing 3 bridge–donors.

Table 1. Protocol to prepare donors and recipients for the asynchronous surgeries in order to minimize the reneging rate.

Recipient-related factors	Measures to prevent [1,9,12,14]
Unequal outcome in DRPs	(a) Careful pre-transplant screening for occult infections and heart disease (b) Robust immunological evaluation with lymphocyte, flow cross match, and donor-specific antibody (c) Experienced transplant team minimizes unequal outcome in perioperative period (d) Counseling that unequal outcome is possible due to acute rejection in 10% patients even with all preventive measures
Recipient becomes unfit for transplant (temporary or long-term)	(a) Careful selection of pairs by multidisciplinary team (b) Daily medical monitoring to prevent medical complications
Death of recipient	(a) Recipient dependent on a bridge–donor is not significantly sensitized (b) Recipient with comorbid conditions, highly sensitized should receive transplant first before his/her donor donates kidney as morbidity /mortality on dialysis is high in developing country (c) Avoid patients with comorbid conditions
Non-medical causes of donor renege	(a) Counseling before surgery (b) Prevent poor transplant outcome in their intended recipients (c) Fitness and commitment of DRPs were reconfirmed before starting non-simultaneous chain
Donor becomes unfit for donation due to medical causes or donor death	(a) Minimize donor wait time (b) Careful selection of pairs by multidisciplinary team

In addition to considering the suitability of the donor, we took measures to prevent donor reneging due to recipient-related factors (see Table 1). The medical fitness of all the DRPs was confirmed by the transplant team before NSKEC were initiated. All potential recipients were hospitalized the evening before their transplants and remained in the hospital until each chain was completed. We ensured that bridge–donors did not wait very long to donate, and all recipients were carefully monitored before transplantation to avoid any

morbidity or mortality on dialysis that could have forced a recipient to withdraw, thereby provoking their co-registered donor to renege for that reason. Recipients whose co-registered donors started cycles involving two bridge–donors were informed that they were bearing more risk than there would be in trusting only one bridge–donor.

None of the recipients dependent on bridge–donors was significantly sensitized, except one DRP in a 6-way exchange [16]. We made a policy of not allowing sensitized recipients (PRA ≥ 20%) to be placed in the position of waiting for a bridge–donor if the possible wait for a substitute deceased-donor kidney might be unacceptably long in the event of a renege. Even though the possibility of a donor reneging was only a hypothetical concern, we made plans to counteract it with a standard criteria deceased-donor kidney through prioritized allocation that would have required special permission from the Gujarat State Government. The ability to provide a kidney transplant for a recipient who is "cheated" in a NSKEC would depend on the recipient's sensitization, blood type, and willingness to accept a deceased-donor kidney.

Results

Our single-center kidney exchange registry is the largest in India and has completed 440 kidney exchange transplants from 2000 to 2020. From 2000 to August 2015, all kidney exchanges (n = 234) were performed simultaneously to eliminate the possibility of any donor reneging. Now, however, we report 17 successful NSKEC, involving 67 living-donor kidney transplants (LDKT). There were two 2-way exchanges (n = 4), eight 3-way exchanges (n = 24), three 4-way exchanges (n = 12), one 5-way exchange (n = 5), two 6-way exchanges (n = 12), and one 10-way exchange (n = 10; see Figs 2 and 3 and Tables 2 and 3).

These 17 NSKEC required 23 bridge–donors who were trusted to donate their kidney after their co-registered recipient had already received a kidney (see Fig. 2). In the course of this study, 22 donors gave kidneys to other pairs before their own co-registered recipients acquired kidneys and 22 donors gave kidneys simultaneous to their own co-registered recipient's transplant. All of the recipients were, however, at risk because either member of any intervening pair could have gotten sick, died, or otherwise withdrawn before the cycle was completed. For example, in Fig. 2a, one recipient was vulnerable to the possibility of reneging by one bridge–donor, but Fig. 2b–d show candidates who were placed at risk by downstream events other than reneging by bridge–donors.

An additional risk that NSKEC entail is that the time between sequential transplants allows donors to know the immediate outcome of their co-registered recipients' transplantation. It is reasonable to expect that a poor outcome for their co-registered recipient would increase the likelihood of donors choosing not to fulfill their commitment. Figure 2b illustrates that an at-risk recipient was vulnerable to two circumstances: possible reneging by a bridge–donor, and the possibility that the recipient in the third pair would have not remained healthy for three days. In Fig. 2c, the vulnerable recipient was at-risk for four events, while in Fig. 2d, there were two at-risk recipients, each of whom was vulnerable to three potential adverse events. Fortunately, as with most LDKT, all 67 kidneys in this study had immediate graft function, and no kidneys failed in the first month.

These risks to vulnerable candidates become even more complicated as the size of the cycle increases or as timing leads to multiple vulnerable candidates within a single cycle. Figure 3 shows how the candidate in the ninth pair became vulnerable despite the fact that no bridge–donor was involved in creating this vulnerability. Overall, Fig. 3 illustrates a 10-way non-simultaneous cycle that required three bridge–donors.

Despite the possibility of numerous adverse outcomes, our experience with these first 17 NSKEC demonstrated that all were performed without any pair being harmed (see Table 2). Thus, the donor renege rate was 0%, and we never needed to use a deceased-donor kidney to repair a broken cycle. The median bridge–donor waiting time was 2 days (mean 3.2 ± 4.8, range 1–21). That mean is exaggerated, however, by two outliers of 21 and 17 days. In both of those cases, transplants had to be postponed due to recipients contracting respiratory infections after the cycles had been initiated. In all other cases, the bridge–donor waiting times were 1–3 days (median 1). All DRPs were discharged with normal kidney function and without surgical complications or delayed graft function.

Reasons for participating in the kidney exchange were ABO incompatibility (n = 35), sensitization (n = 25, including 17 recipients having panel reactive antibody percentages of 80% or more), and a desire by compatible pairs to obtain better HLA- and age-matching (n = 7). The seven compatible pairs ultimately benefitted by at least a 50% better HLA matching at the A, B and DR loci. Sixteen of the 17 highly sensitized recipients (PRA ≥ 80%) received their kidney either while or before their co-registered donors donated their kidney.

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Table 2. Demographics of donor–recipient pairs and transplant outcomes.

Number	ABO group		Donor–recipient as actually matched	Recipient		Donor		Donor–recipient relation	Transplant date	N-way cycle number	Serum creatinine (mg/dl)	Reason for incompatibility	PRA (%)
	Recipient	Donor		Age (years)	Sex	Age (years)	Sex						
1	AB	A	D5 → R1	45	M	40	F	Wife	17-Aug-15	6	1.1	Sensitized	20
2	A	A	D1 → R2	17	M	46	M	Father	17-Aug-15		0.9	Sensitized	80
3	B	B	D6 → R3	25	M	45	F	Mother	18-Aug-15		Graft loss	Sensitized	30
4	AB	B	D3 → R4	40	M	38	F	Wife	18-Aug-15		3.2	Sensitized	90
5	B	B	***D4*** → **R5**	38	M	38	F	Wife	21-Aug-15		1.3	Sensitized	80
6	A	B	***D2*** → **R6**	45	M	35	F	Wife	07-Sep-15		1.6	ABOi	
7	B	B	D9 → R7	35	M	50	M	Father	16-Nov-15	3	2.1	Sensitized	80
8	AB	A	***D7*** → R8	50	M	45	F	Wife	18-Nov-15		1	Compatible	
9	A	B	***D8*** → **R9**	30	M	53	F	Mother	20-Nov-15		1.5	ABOi	
10	O	O	D12 → R10	35	M	60	M	Father	26-Dec-15	3	Graft loss	Sensitized	90
11	O	O	***D10*** → R11	32	F	56	F	Mother	28-Dec-15		1	Sensitized	80
12	O	O	D11 → **R12**	42	M	40	F	Wife	28-Dec-15		1.4	Compatible	
13	B	A	D16 → R13	43	M	50	F	Wife	07-Apr-17	4	1	ABOi	
14	B	A	D15 → R14	33	M	40	F	Wife	07-Apr-17		0.9	ABOi	
15	A	B	***D13*** → **R15**	40	F	40	M	Husband	10-Apr-17		0.9	ABOi	
16	AB	B	***D14*** → **R16**	25	F	30	F	Mother	10-Apr-17		0.9	Sensitized	20
17	A	B	D18 → R17	45	M	45	F	Wife	09-Jun-17	2	1.1	ABOi	
18	B	A	***D17*** → **R18**	44	F	47	M	Husband	12-Jun-17		2.5	ABOi	
19	A	B	D20 → R19	54	F	55	M	Husband	26-Jul-17	2	0.8	ABOi	
20	B	A	***D19*** → **R20**	58	M	54	F	Wife	27-Jul-17		0.7	ABOi	
21	B	B	D23 → R21	45	M	38	F	Wife	25-Oct-17	3	0.8	Sensitized	20
22	B	A	***D21*** → **R22**	33	M	27	F	Wife	27-Oct-17		0.9	ABOi	
23	A	B	***D22*** → R23	39	M	37	F	Wife	30-Oct-17		0.8	ABOi	
24	A	B	D26 → R25	28	M	31	F	Sister	05-Jan-18	3	0.9	ABOi	
25	B	B	D25 → R24	37	M	30	F	Wife	05-Jan-18		0.8	Sensitized	30
26	B	A	***D24*** → **R26**	52	M	48	F	Wife	08-Jan-18		0.9	ABOi	
27	B	O	D30 → R27	22	M	45	F	Mother	24-Jul-18	4	0.7	Sensitized	80
28	O	O	D27 → R28	46	F	50	M	Husband	24-Jul-18		0.9	Sensitized	90
29	O	A	***D28*** → R29	25	M	50	F	Mother	25-Jul-18		1.1	ABOi	
30	A	B	D29 → **R30**	53	M	48	F	Wife	25-Jul-18		1	ABOi	
31	A	B	D33 → R31	33	F	52	F	Mother	17-Sep-18	3	0.8	ABOi	
32	B	O	***D31*** → R32	42	M	38	F	Wife	18-Sep-18		1.3	Compatible	
33	B	A	D32 → **R33**	31	F	35	M	Husband	18-Sep-18		1	ABOi	
34	B	A	D38 → R34	60	M	50	F	Wife	22-Nov-18	5	0.8	ABOi	
35	A	B	D34 → R35	42	M	40	F	Wife	22-Nov-18		1.2	ABOi	
36	AB	B	***D35*** → R36	42	M	40	F	Wife	23-Nov-18		1	Compatible	
37	B	A	D36 → R37	35	M	32	F	Wife	23-Nov-18		1	ABOi	
38	A	B	D37 → **R38**	28	M	47	F	Mother	23-Nov-18		1.2	ABOi	

Table 2. Continued.

Number	ABO group		Donor–recipient as actually matched	Recipient		Donor		Donor–recipient relation	Transplant date	N-way cycle number	Serum creatinine (mg/dl)	Reason for incompatibility	PRA (%)
	Recipient	Donor		Age (years)	Sex	Age (years)	Sex						
39	A	O	D43 → R39	35	M	32	F	Wife	26-Feb-19	6	1.3	Sensitized	80
40	O	O	D39 → R40	34	F	58	F	Mother	26-Feb-19		0.8	Sensitized	80
41	O	O	D40 → R41	42	M	57	F	Sister	26-Feb-19		1	Sensitized	80
42	B	A	D44 → R42	53	M	50	F	Wife	27-Feb-19		0.6	ABOi	
43	A	A	D42 → **R43**	43	M	40	F	Wife	27-Feb-19		0.8	Sensitized	30
44	A	B	***D41*** → **R44**	55	M	40	F	Wife	28-Feb-19		1.2	ABOi	
45	O	O	D47 → R45	32	F	36	M	Husband	22-May-19	3	0.6	Sensitized	90
47	O	B	***D45*** → R46	42	M	36	F	Wife	23-May-19		1	ABOi	
46	B	O	D46 → **R47**	32	M	31	F	Wife	23-May-19		1	Compatible	
49	A	B	D51 → R48	34	M	30	F	Wife	29-May-19	4	1	ABOi	
48	AB	A	D48 → R49	42	M	35	F	Wife	29-May-19		1	Compatible	
50	A	B	***D49*** → R50	48	M	45	F	Wife	30-May-19		1	ABOi	
51	B	A	D50 → **R51**	45	M	34	F	Wife	30-May-19		1	ABOi	
52	B	B	D54 → R52	45	F	50	M	Husband	15-Jul-19	3	0.9	Sensitized	80
53	B	B	D52 → R53	39	M	24	F	Wife	15-Jul-19		1	Sensitized	80
54	B	B	***D53*** → **R54**	35	M	33	F	Wife	16-Jul-19		1	Sensitized	20
55	B	B	D64 → R55	42	F	50	M	Brother	04-Jan-20	10	0.8	Sensitized	80
56	B	A	D55 → R56	42	M	40	F	Wife	04-Jan-20		0.9	ABOi	
58	A	B	***D56*** → R57	25	F	50	M	father	05-Jan-20		0.8	ABOi	
57	B	A	D60 → R58	24	M	47	F	Mother	05-Jan-20		1	ABOi	
59	A	A	D62 → R59	39	M	40	F	wife	06-Jan-20		0.7	Sensitized	80
60	B	A	D59 → R60	43	M	43	F	wife	06-Jan-20		0.8	ABOi	
61	A	B	***D57*** → R61	47	M	43	F	wife	07-Jan-20		1	ABOi	
62	B	A	D63 → R62	28	M	26	F	Wife	07-Jan-20		1.2	ABOi	
63	A	B	D61 → R63	47	M	43	F	wife	07-Jan-20		0.9	ABOi	
64	A	B	***D58*** → **R64**	31	M	60	F	Mother	22-Jan-20		1	ABOi	
65	A	O	D67 → R65	35	M	32	F	Wife	30-Jan-20	3	0.9	Sensitized	80
66	B	O	D65 → R66	23	M	43	F	Mother	30-Jan-20		0.9	Sensitized	20
67	A	O	***D66*** → **R67**	35	M	40	F	Wife	31-Jan-20		1	Compatible	

ABO, ABO incompatible pair; Compatible, compatible pairs; ***D***, bridge–donor; F, female; M, male; PRA, panel reactive antibody; **R**, recipient at risk of renege.

In this table, the pairs are identified as the presenting incompatible, co-registered pairs, and they are ordered from top to bottom by the date of the transplant for the recipient in each pair. In the fourth column, the actual donor and recipient combinations that took part in kidney exchanges are shown. Each of the cycles is identified by the shaded background of the rows of the table. The bridge–donors are identified in a bold, italicized font. The recipients at risk of reneging are underlined, or if they are at risk of reneging from two preceding bridge–donors, then they are double-underlined. The number of the pair in this table corresponds to the number in Fig. 2, so the reader can see the details of each exchange and reference the figure.

Table 3. Number of events and time at risk for vulnerable recipients.

Figure	Time vulnerable (day)	Number of events exposing vulnerable recipients to uncertainty
2a	3	1 event (bridge)
2b	2	2 events (bridge, recipient 3's health)
2c	5	4 events (bridge, recipient 3's health, recipient 3 success, 2nd bridge)
2d-pair 1	1	3 events (donor 5's choice, recipient's health 5, recipient's health 6)
2d-pair 5	1	3 events (bridge, recipient 4 success, recipient's health 5)
3-pair 1	18	14 events (recipient 3 success, bridge 3, recipient 4 success, bridge 4, recipient's health 4, 5, 6, 7, 8, 9, 10, donor 7's choice, donor's choice, recipient 10 success)
3-pair 7	1	6 events (recipient 4 success, bridge 4, recipient's health 4, 5, 6, 7)
3-pair 9	1	8 events (recipient 4 success, bridge 4, recipient's health 4, 5, 6, 7, 8, donor 7)

In the first 6-way kidney exchange, five recipients were sensitized, including three highly sensitized patients. We initially planned for simultaneous surgeries in this first 6-way non-simultaneous cycle. However, the cycle was hindered twice due to infections in two different recipients each time. The gap between the first and last transplant was 21 days. The PRA of the first recipient who was put at risk of bridge–donor reneging was 20%. It was the success of this first non-simultaneous cycle that served as the impetus for us to expand the practice.

Of the 67 patients transplanted, one died three months post-transplantation due to an infection following antirejection therapy, but that patient's graft was still functioning at the time of death. A second patient lost their graft to rejection at the three-month point. In the second-year post-transplantation, a third patient lost their graft due to hemolytic uremic syndrome and then died due to uremia after graft loss. Thus, the overall graft survival was 95% (64/67) and the overall patient survival was 96% (65/67) with a median follow-up of 2 ± 1.3 years (range: 0.0–4.3). Mean serum creatinine at last follow-up was 1 ± 0.4 mg/dl (range: 0.6–3.2). The biopsy-proven acute rejection rate was 7.4% (n = 5).

Mean warm ischemia time, cold ischemia time, anastomosis time, and intra-operative urine output were 127 ± 50 s (range: 25–220), 98 ± 42 min (range: 50–180), 31 ± 10 min (range: 14–60), and 900 ± 400 ml (range: 200–2100), respectively. All donors underwent retroperitoneal laparoscopic donor nephrectomy [14]. Donor survival was 100%. None of the donors was excluded after a psychological evaluation. All donations were non-anonymous; as such, the patients and donors shared a special bond and continue to keep in touch regularly as friends. All donors stated that they felt a great sense of satisfaction after helping persons outside of their family, and that they will recommend NSKEC to others.

Discussion

This study assesses the bridge–donor reneging rate during NSKEC in a developing country where non-directed living donation is prohibited. This study responds to the fact that large kidney exchange cycles increase opportunities for hard-to-match patients, but are not possible in India, given the prohibition against non-directed donors and the scarcity of surgical capacity in many transplant centers [18]. In order to overcome this obstacle, we performed NSKEC and this is the first report of NSKEC (n = 67) to overcome these logistical constraints.

We used short cycles to decrease bridge–donor waiting times, and we reconfirmed the medical fitness of all pairs before starting the non-simultaneous surgeries. We utilized short bridge–donor waiting times (mean 2 days; range 1–21 days), given the work of Cowan *et al.* [11], who found that the risk of bridge–donor reneging is higher when the bridge–donor wait time is longer. Limiting the number of bridge–donors in each non-simultaneous cycle and minimizing bridge–donor waiting times should be priorities. This serves not only to simplify logistics, but also to minimize the impact on the bridge–donors' lives. Butt *et al.* [19] reported the first modified sequence asynchronous transplant chain (MATCH) in the United States in which a donor gave their kidney before their co-registered recipient received a kidney from an altruistic donor. In case of donor reneging, the plan in the MATCH study was to provide an alternative kidney from a different altruistic donor or from a deceased donor. In this report, we present non-simultaneous cycles, rather than chains, and our experience is considerably larger compared to the prior report utilizing a non-simultaneous, out of sequence chain [19].

Utilizing deceased-donor kidneys to repair NSKEC broken by a renege might disadvantage patients on the waiting list given that non-directed living kidney donation and kidney exchange cycles are not allowed, thus

not providing a mechanism to return living-donor kidneys to patients on the waiting list. Nevertheless, we believe that the additional transplants produced would reduce the overall pressure on the waiting list by removing more patients from the waiting list than the number of deceased-donor kidneys required to repair broken cycles. To date, this has been the case.

Thus, our study from a developing-world country confirms that donor reneging is rare in a carefully selected DRP cohort, and our study supports further exploration of the concept of NSKEC to expand access to LDKT through kidney exchange, particularly when a lack of resources and access to non-directed donors would prevent the utilization of NEAD chains. This approach may significantly expand kidney exchange in developing-world countries such as India.

We believe the current study demonstrates that NSKEC can allow resource-challenged transplant programs to complete large kidney exchange cycles, which have been shown to improve access for hard-to-match patients [1,10]. Given our access to a significant number of deceased-donor kidneys and given our similar favorable long-term outcomes with standard criteria deceased-donor kidneys, we believe our plan for repairing broken chains with a deceased-donor kidney is acceptable.

Consecutive and non-simultaneous exchanges

This report of NSKEC describes cycles that include at least one kidney donation taking place at least 24 h after the donor's co-registered recipient received their kidney. However, the concept of non-simultaneous exchange could also apply to consecutive exchanges on the same day, where bridge–donor reneging would still be possible. Our experience with NSKEC in which bridge–donors were successfully trusted for more than 24 h has also made us comfortable with consecutive, rather than simultaneous exchanges, on the same day. While not reported here, we have completed more than 35 consecutive kidney exchanges without any donor reneging, and we suggest this as a first step for centers considering this approach.

A new observation from this experience with non-simultaneous cycles is that when donors relinquish a kidney before their co-registered candidates receive a kidney, there are risks beyond just the possibility of a bridge–donor reneging. Non-simultaneous cycles can fail if *any* intervening pair withdraws their participation for any reason. An additional risk that non-simultaneous cycles entail is that the time between sequential transplants allows donors to know the immediate outcomes of their co-registered recipients' transplants, and this knowledge, if the immediate outcome was poor, may increase the risk of a bridge–donor choosing not to proceed with donation. The risks to vulnerable candidates become more complicated as the number of pairs involved in the cycle grows or as timing leads to multiple vulnerable candidates within a single cycle, as evidenced by the three vulnerable pairs in the 10-way exchange who are at risk for multiple potential adverse events. Thus, compared to NEAD chains, non-simultaneous cycles require additional measures to protect vulnerable participating pairs, and we propose that our non-anonymous allocation approach is a successful example of one such measure.

Non-anonymous allocation

The standard practice in the developed world is *anonymous* allocation for kidney exchange [20–30]. However, we practice *non-anonymous* allocation to increase trust and transparency among the hospital team and the DRPs [13,14]. All DRPs in each proposed NSKEC met prior to allocation, before transplants were scheduled, and even after transplants. We believe that the bridge–donors in NSKEC are less likely to withdraw if they have personal experience with their proposed recipient. It is also clear from recent reports that when prospective donors appreciate the risks of continued dialysis and the benefits of kidney transplantation for their assigned recipients, the chances of donors reneging are diminished [11]. Our policy of non-anonymous allocation allows the sharing of a special bond before transplantation, and we believe this aspect of our program has played an important role in our 0% reneging rate. However, this practice is associated with risks of additional psychological consequences, especially in the event of immunological or non-immunological complications, graft loss, or death [29].

Kidney exchange, deceased donation, and the element of time

Rees *et al.* [1], Melcher *et al.* [31], and Furian *et al.* [32] have proposed the use of non-directed and deceased-donor kidneys to initiate non-simultaneous kidney exchange chains. In contrast, our study proposes that deceased-donor kidneys (or altruistic living-donor kidneys in countries that allow this) can be used to remediate any bridge–donor reneging in non-simultaneous cycles—in a sense creating a non-simultaneous chain that ends with the deceased or altruistic donor, rather than beginning with such a donor. Non-simultaneous cycles should be carried out only when there is a clear path for repairing broken chains with non-directed

living-donor kidneys or deceased-donor kidneys, and only when the vulnerable candidate is not significantly sensitized so that it will be relatively easy to find an acceptable replacement donor if necessary.

This proposal is a continuation of a series of innovations that have separated the acts of donating and receiving a kidney. This progression began with list exchanges in 2004 [33–35]. List exchanges demonstrated that one could trust the deceased-donor pool to "pay back" the co-registered recipient of a living donor who gave first [35]. Similarly, NEAD chains have proven that one can trust bridge–donors whose co-registered recipients receive a kidney before the bridge–donor donates [9,16]. The MATCH kidney exchange concept suggests that living donors can donate first, and either trust another living donor to donate to their co-registered recipient afterward, or have their broken NEAD chains repaired with an alternative bridge–donor or an altruistic non-directed donor [19]. Furthermore, it has been suggested that NEAD chains can be initiated with deceased-donor kidneys, rather than with non-directed living-donor kidneys [31].

The proposal presented here extends these concepts by bringing together risks and benefits that have already been shown to be acceptable for ESRD patients and their willing, but incompatible living donors. With the NSKEC approach, living donors and recipients can, for example, take less risk than with a list exchange. In NSKEC, all of the co-registered pairs have a reasonable expectation of receiving a living-donor kidney transplant through completion of a successful cycle, although they accept the risk that they might receive a deceased-donor kidney instead. In contrast, in a list exchange, the recipient is compelled to accept a deceased-donor kidney with no opportunity to receive a LDKT. Thus, our proposal to repair broken cycles with deceased-donor kidneys exposes recipients to a risk that is less than that of list exchange recipients who must agree to accept a deceased-donor kidney at the outset. The only recipients for whom this approach may not be appropriate are those who are hard to match due to high levels of sensitization. But even for highly sensitized persons, the small risk of not receiving a transplant because of a donor reneging may well be preferable to the certainty of not receiving a transplant because of not being included in any kidney exchange at all.

A possible limitation of our study is that our cohort of 67 pairs included an overwhelming preponderance of spousal donors (48/67) with a wife being the co-registered donor for her husband in about 61% of all of our pairs. That rate is similar to what we have observed among our center's living-related-donor transplants, and it could be a significant factor in the high rate of compliance that we have observed. A larger cohort with fewer spousal pairs could expose a somewhat higher rate of donor reneging.

The Indian Society of Organ Transplantation clinical practice guideline is designed to provide information and to assist decision-making in relation to kidney exchange vs ABO incompatible kidney transplants (ABOiKT) [17]. The economic constraints and patient death with functioning allograft due to tropical infections are common even in ABO-compatible kidney transplant (ABOcKT) and worse in ABOiKT in India [13]. To date, we have performed 30 ABOiKT with outcome inferior to ABOcKT. This leads to kidney exchange being preferred over ABOiKT.

The other alternatives to NSKEC in the near future would be involvement of other transplant units and shipping of donor kidneys to increase surgical resources and thus facilitate simultaneous KPD transplants (as it is routine in the United States or in some European programs, such as the Czech-Austrian program [36].

Conclusions

This is a single-center study of NSKEC without any donor reneging among 67 DRPs. Our study from a developing-world country confirms that donor reneging is rare in a carefully selected cohort of DRPs, and our experience supports further studies to expand this concept. Our study is relevant for resource-restricted low-to-middle-income countries and also for programs in countries where altruistic donation and NEAD chains are not allowed.

Authorship

All persons listed as authors have contributed substantially to the design, performance, analysis, reporting, and writing of the work.

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