Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

ABO-incompatible liver transplantation for critically ill adult patients

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Keywords
ABO incompatible, liver failure, liver transplantation, urgent.

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Received: 5 February 2007
Revision requested: 26 February 2007
Accepted: 5 April 2007

doi:10.1111/j.1432-2277.2007.00492.x

Summary

ABO incompatible (ABO-In) liver transplant remains a controversial solution to acute liver failure in adults. Adult liver recipients with acute liver failure or severely decompensated end-stage disease, intubated and/or in the intensive care unit, were grouped as ABO-In ($n = 14$), ABO-compatible ($n = 29$, ABO-C) and ABO-identical ($n = 65$, ABO-Id). ABO-In received quadruple immunosuppression with antibody-depleting induction agents (except two), calcineurin inhibitors, antimetabolites and steroids. No significant difference of patient and graft survivals was observed among ABO-In, ABO-C and ABO-Id: graft survivals were 64%, 62% and 67%, respectively, in 1 year and 56%, 54% and 60%, respectively, in 5 years; patient survivals 86%, 69% and 67%, respectively, in 1 year and 77%, 61% and 62%, respectively, in 5 years. Three ABO-In grafts were lost (one hyper-acute rejection and two hepatic artery thrombosis). Surgical and infectious complications were similarly distributed between groups, except the hepatic artery thrombosis, more frequent in ABO-In (2, 14%) than ABO-I (1, 1.5%, $P < 0.05$). In contrast to previous studies, no significant difference of patient and graft survivals could be observed among all ABO-compatibility settings. Our results suggest that ABO-incompatible transplants should be viewed as an important therapeutic option in adult patients with acute liver failure awaiting an emergency procedure.

Liver transplantation across the ABO barrier remains a controversial issue. Early results were poor, with 5-year graft survivals often as low as 20%. ABO-incompatible (ABO-In) transplants were associated with a high risk of antibody-mediated rejection, severe cell-mediated rejection, vascular thrombosis and ischaemic bile duct complications [1–4]. However, more recent experiences indicate improving results, with up to 60% 5-year graft survival reported [5–7]. Such progress presumably reflects peri-transplant management and improving potency of immunosuppression. Protocols appear to have evolved from triple- [1,2] to quadruple-drug immunosuppression with frequent addition of plasmapheresis, splenectomy or intra-vascular infusion of methylprednisolone or prostaglandin E1 [6,8,9].

ABO-incompatible liver transplants have been most frequently utilized for two indications: emergency transplants for acute liver failure or in cases of living-related donor transplants, when no ABO-compatible (ABO-C) donor is available. The risk of rejection in a critically ill patient with acute liver failure, often with concomitant renal dysfunction, is probably lower than in a stable recipient undergoing elective ABO-In living donor transplant. One can thus ponder whether the trend towards more aggressive immunosuppression, especially when including splenectomy or intravascular infusion, should be similarly applied to both ABO-In transplant indications.

This study specifically addressed the problem of emergency liver transplant in high status adult patients experi-

encing acute liver failure or having severely decompensated end-stage liver disease, intubated in the intensive care unit (ICU). Recipient and graft outcomes and surgical or infectious complications were compared according to the ABO-compatibility status.

Patients and methods

Patient selection

All adult patients (>16 years old) transplanted for emergency indications between August 1991 and August 2005 at the University of Alberta Hospital, Edmonton, Canada were included in the study. The inclusion was extended to August 2006 for the ABO-In transplants. There were no exclusions. All had at least 1-year follow-up, except the last ABO-In patient (6 months). In Canada, priorities for emergency liver transplants are as follow: patients with severe decompensated end-stage liver failure, intubated in ICU (status 4), patients with acute liver failure, intubated in ICU (status 4F) and patients with acute liver failure in ICU but not intubated (status 3F). Status 4F patients include those with fulminant liver failure and those with acute liver failure from graft failure, such as hepatic artery thrombosis or primary nonfunction. Status 4F, 4 and 3F patients have national priority access to all livers available countrywide and, in general, are transplanted with the next available organ. Of note, both paediatric (including those between 16 and 18 years old) and adult (over 18 years old) patients share the same waiting list in Canada.

For the purpose of the study, transplants were grouped according to the ABO-compatibility in ABO-In, ABO-C and ABO-identical (ABO-Id).

Immunosuppression and infection prophylaxis

All ABO-In recipients were treated with a quadruple-drug immunosuppression regimen, including antilymphocyte antibody preparations, calcineurin-inhibitor, steroids and antiproliferatives [azathioprine, mycophenolate mofetil (MMF) or sirolimus]. Two extremely sick patients received an anti-IL-2 inhibitor rather than antilymphocyte antibodies. ABO-C and ABO-Id recipients were put on the then current programme standard protocol which included calcineurin-inhibitor, azathioprine or MMF and induction with steroids or with anti-IL2 receptor antibodies in more recent years.

Postoperative prophylaxis included 1 g i.v. cefatoxime three times a day for 48 h, Nystatin 500 000 U/day until discharge and trimethoprim/sulfamethoxazol 400 mg/800 mg daily for the first 6 months. Since 1999, in cases of cytomegalovirus (CMV) mismatch (donor +/ recipient −), prophylaxis was instituted with ganciclovir 1 g p.o. t.i.d. (adjusted for renal function) or p.o. valgancyclovir 450 mg b.i.d. for a total of 14 weeks. Patients with hepatitis B virus (HBV) received post-transplant prophylaxis with lamivudine ± hepatitis B immunoglobulin. No additional prophylaxis was administrated on HCV patients.

Follow-up, side-effects definition and statistical analysis

Graft and patient survival were recorded over a median follow-up of 7.5 years (range: 1–16.5). Side-effects were assessed for the first post-transplant year only. Data were prospectively collected in an electronic database (OTTR, Hickman-Kenyon Systems, Omaha, NE, USA) and retrospectively analysed, as approved by the institutional ethics review board.

The date of listing was defined as the first day patients were listed for an emergency transplant (status 3, 3F or 4F, as defined earlier).

Survivals were analysed by the Kaplan–Meier method and differences between the groups were further tested by the log-rank test. Analysis was also performed by chi-squared or Student's *t*-tests, when applicable. All tests were conducted by using the standard alpha level of 0.05 to indicate statistical significance. Calculations used STATISTICA (Statsoft, Berikon, Switzerland) software.

Results

Patients and transplant characteristics

Over the 14-year study period, 635 liver transplants were performed in 601 patients. Among them, 106 were emergency cases performed in 104 adult patients (>16 years old). They included 14 ABO-In, 29 ABO-C and 65 ABO-Id transplants. None of these were live donor liver transplants.

Recipient characteristics were similar among the three ABO combinations (Table 1). They included half males and half females. The median age was 46 years (16–66). Eighty-seven (81%) were Caucasians, 11 (10%) Asians, seven (6%) North American first nations peoples, two (2%) Hispanics and one (1%) African-American.

Blood group incompatible mis-matches included 10 A donors to O recipients, two A to B, one B to O and one AB to O. In total, 12 of the 14 ABO incompatible (ABO-In) recipients were of blood group O.

The indications for transplant were similar between groups (Table 1). They included 26 (24%) non-A, non-B hepatitis, 18 (17%) hepatitis C virus (HCV)-induced cirrhosis, 17 (16%) re-transplantations, 14 (12%) drug-induced liver failures, six (6%) HBV-induced cirrhosis, four (4%) alcohol-induced cirrhosis, four (4%) Wilson's diseases and 19 (17%) other indications. Overall, 64 (59%) emergent transplants were performed for acute

Table 1. Patient characteristics.

ABO status	Incompatible	Compatible	Identical	*P*
Number	14	29	65	
Median age	42 (17–61)	47 (16–62)	47 (17–66)	NS
Gender	7f/7m	14f/15m	31f/34m	NS
Cause of liver disease				
Non-A, non-B fulminant hepatitis	3	8	15	NS
Drug induced liver failure	4	4	6	NS
HCV [± alcohol, ± hepatitis B virus (HBV)]	2	3	13	NS
Re-transplantation	2	3	12	NS
HBV	2	2	2	NS
Alcohol	0	3	1	NS
Wilson	0	2	2	NS
Cryptogenic	0	1	3	NS
Primary sclerosing cholangitis	0	1	2	NS
Autoimmune	0	1	1	NS
Primary biliary cirrhosis	0	0	2	NS
Other	1	1	6	NS
Transplant status*				
4	4	13	27	NS
4F	9	15	30	NS
3F	1	1	8	NS

*3: patient in intensive care unit (ICU), not intubated; 4: patient intubated in ICU; F: fulminant liver failure.

liver failure and 44 (41%) for severely decompensated end-stage chronic liver failure, in patients in ICU. Seventy-one per cent (10/12) of ABO-In grafts were used in the setting of acute liver failure. Median MELD scores were 36, 33 and 35.5 in the ABO-In, -C and -Id groups (ABO-In vs. -C p: 0.9; ABO-In vs. -Id p: 0.9).

The median time between listing and transplant was similar in the ABO-In (1 day) and the ABO-C groups (1 day, p: 0.9). It tended to be shorter compared to ABO-Id (2 days, p: 0.07). The median cold ischaemia time was similar among all groups [505 min (154–985), 520 min (256–975) and 550 min (148–987) in the ABO-In, -C and -Id ($P > 0.05$)].

Immunosuppression in ABO-In recipients

All ABO-In patients received quadruple immunosuppression. All, except two, received lymphocyte-depleting antibodies (Table 2). Nine received similar maintenance therapy, including cyclosporin, azathioprine and steroids, with four receiving tacrolimus, MMF and steroids. Plasmapheresis was used as adjuvant treatment for rejections only in the first 12 patient and as prophylaxis for high or rising isoagglutinin titres in the subsequent two. Splenectomy was not performed in any of the patients.

Graft and patient survivals and rejection

Overall patient and graft survivals were 69% and 64% in 1 year and 63% and 58%, respectively, in 5 years. Both were similar among the three ABO-compatibility groups (Fig. 1, $P > 0.05$). Patient survivals were 86%, 69% and 67% in 1 year and 77%, 61% and 62% in 5 years for ABO-In, ABO-C and ABO-Id graft recipients, respectively. Graft survivals were 64%, 62% and 67% in 1 year and 56%, 54% and 60% in 5 years for incompatible, compatible and identical grafts, respectively.

Graft losses were similarly distributed between groups ($P > 0.05$). Three appeared in ABO-In, two in ABO-C and four in ABO-Id patients. Two of the three grafts lost in the ABO-In group were in patients with re-transplants (patients 9 and 11, see Table 2) and were due to hyperacute rejection and hepatic artery thrombosis (one of each). The last graft loss (patient 14) was also linked to hepatic artery thrombosis, but appeared after a first transplant. All patients were alive after a new ABO-Id transplant or re-transplant.

Forty-one patients died, and were similarly distributed between groups (Table 3, $P > 0.05$). Of note, deaths because of sepsis occurred in one ABO-In patient (8%), in six ABO-C (20%) and in 10 ABO-Id (15%).

Rejections were similarly distributed among groups (Table 4), except steroid resistant episodes, which were more frequent in the ABO-In than in the ABO-I group ($P < 0.05$). ABO-In patients experienced one hyperacute rejection, five acute cellular rejections sensitive to steroids and three acute cellular rejections resistant to steroids. The hyperacute rejection was treated unsuccessfully with ATGAM and plasmapheresis; the patient required a new transplant (as previously described). Two steroid-resistant

Table 2. Induction and maintenance immunosuppression combinations in the ABO-incompatible recipients.

	D	R	Lymphocyte depleting AB	DAC	CNI	AZA	MMF	SRL	PLASMA	STER	Rejection	Pre-transplant IgG*	Pre-transplant IgM*	Peak IgG*	Peak IgM*	Days from Tx to peak IgG	Days from Tx to peak IgM
1	A	O	+		CICLO	+				+	ACR-S	A: 64	A: 32	A: 1024	A: 1024	9	15
2	A2	O	+		CICLO	+				+	ACR-R	NA	NA	A: 512	A: 4096	15	8
3	A1	O	+		CICLO	+				+		NA	NA	NA	NA		
4	A	O	+		CICLO	+				+	ACR-R	NA	NA	A: 32,768	A: 2048	9	9
5	AB	O	+		CICLO	+				+	ACR-S	A: 256	A: 64	A: 256	A: 64	1	1
												B: 64	B: 64	B: 64	B: 64	1	1
6	A1	O	+		CICLO	+				+	ACR-S	A: 256	A: 16	A: 256	A: 16	1	1
7	A2	O	+		CICLO	+				+		A: 64	A: 32	A: 64	A: 32	1	1
8	A2	O	+		CICLO	+				+		NA	NA	A: 128	A: 256	2	2
9	A	O	+		CICLO	+				+	HAR	A: 2048	A: 128	A: 2048	A: 256	6	6
10	A1	O	+		TAC			+		+		–	A: 64	–	A: 4		6
11	B	O		+	TAC		+			+	ACR-S	–	B: 128	–	B: 4		9
12	A	B	+		TAC		+			+	ACR-S	–	A: 16	–	A: 32		9
13	A	O	+		TAC		+		+	+	ACR-R	–	A: 32	–	A: 256		8
14	A	B		+	TAC		+		+	+		–	A: 4	–	A: 64		11

This table includes induction and maintenance immunosuppression only, please refer to the text for acute rejection therapy.
*A, B refer to anti-A and anti-B titers; clinical decisions were based on IgM only after patient 9.
D, donor blood group; R, recipient blood group; A, blood group A, sub-group not done; DAC, daclizumab; CNI, calcineurine inhibitors; AZA, azathioprine; MMF, mycophenolate mofetil; SRL, sirolimus; PLASMA, plasmapheresis; STER, steroids; TAC, tacrolimus; CICLO, ciclosporin; NA, not available; ACR-S, acute cell rejection, steroid sensitive; ACR-R, acute cell rejection, steroid resistant; HAR, hyperacute rejection.

rejections were treated with OKT3 alone and with OKT3 and plasmapheresis; one successfully (Table 2, patient 2) and the other not (Table 2, patient 4). The latter patient died while awaiting retransplant. The last steroid-resistant rejection (Table 2, patient 13), which demonstrated C4d deposition on biopsy, was successfully treated with rituximab.

Of note, both agglutinin IgG and IgM titres were used till patient 9, and clinical decision was thereafter based on IgM only. In most of the patients, peak agglutinin titres appeared within 2 days after transplant or remained within low levels (Table 2). On the contrary, in five cases, levels were high (≥256), with later peaks (≥6 days after transplant). Such events appeared in one patient with hyperacute rejection, one with steroid sensitive acute cell rejection and three with steroid-resistant acute cell rejection. One of the three A2 to 0 recipients experienced a late increase in the titres, which was linked to a steroid-resistant acute cell rejection.

Complications

Thirty-nine (36%) patients had a biliary complication, nine (8%) an hepatic artery stenosis, four (4%) an hepatic artery thrombosis and five (5%) a portal vein thrombosis. They were similarly distributed among the three groups (Table 4), except the hepatic artery thrombosis, more frequent in ABO-In (2, 14%) than ABO-I (1, 1.5%, $P < 0.05$). The most frequent infectious complications were several varieties of pneumonia, bacteremia, urinary tract infection, intra-abdominal infection and pseudomembranous colitis (Table 4). The rate of cancer was similar among all the three groups.

Discussion

In contrast to earlier published studies, showing decreased graft survivals, this report demonstrated similar graft and patient survivals with ABO-In, compatible and identical emergency adult liver transplants. This was achieved with the application of a protocol of quadruple-drug immunosuppression, including lymphocyte-depleting antibodies and steroids in all patients, except two.

This study was focussed on the investigation of ABO-In emergency transplants in adults only, as this group of patients bears very specific issues. Adult ABO-In recipients have been reported to do worse than children, with respect to patient and graft survival [7]. Issues linked to emergency transplants are also different from those linked to living-related transplants, the other common indication for ABO-In transplant. The latter involves a small-for-size liver, with less reserve and which as a result is more sensitive to early injuries. More potent immunosuppression may well be obligatory to minimize the possible early

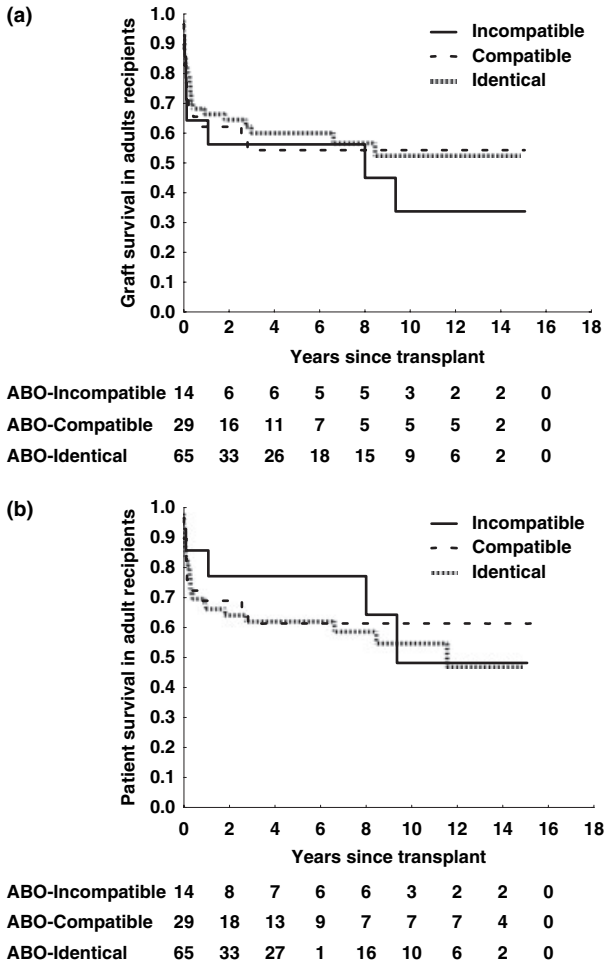

Figure 1 Graft (a) and patient (b) survivals were similar between the three ABO-compatibility groups of adult emergency transplant ($P > 0.05$).

Table 3. Causes of death.

ABO status	Incompatible	Compatible	Identical
Cardio-vascular		4	10
Sepsis	1	6	10
Malignancy	1		3
Recurrence HCV or HBV	2	1	1
Multi-system organ failure		2	2
Rejection/graft failure	1		
Other	1		4

immunological injury in such scenarios where patients are also more likely to mount an aggressive antigraft immune response. In contrast, patients requiring emergency transplants are critically ill, frequently have concomitant renal dysfunction, and are thus more prone to infections and immunosuppresion side-effects, and perhaps less likely to mount an aggressive rejection response, as reflected by low isoagglutinin titres in several studied patients. They usually receive whole liver grafts. In such patients with urgent need, careful selection of an immunosuppressive combination is required to balance the increased morbidity of enhanced immunosuppression against the increased immunological risk of ABO-In transplants. Indeed, the overall low patient and graft survival reported in the present study (63 and 58% at five years) and the overall high rates of complications (higher than in nonemergency transplant, data not shown) reflect the degree of illness of the emergency transplant candidates. Our patient survival results were parallel to those of other recent reports [1–3,10].

Regarding the statistical power and the risk of type II error, ABO-In liver transplantation is a relatively rare condition, but the expected difference of graft survival is big. Published data on emergency transplant demonstrated graft survival close to 63% in 3 years in the ABO-I or -C group compared to 30% in the ABO-In group [10]. Using these data, we would have expected a statistical power of 66%, in our study including 94 ABO-C or identical transplants and 14 ABO-In. As such, the risk of type II error appeared relatively limited, but not excluded, especially in considering the small number of patients, and data have to be discussed accordingly.

Of importance, not only similar patient, but also similar graft survivals were achieved among the various ABO-compatibility groups in the current series. This is in contrast to previous reports where retransplantation was required to achieve acceptable patient survivals after ABO-In transplants, with resulting poor graft survivals [1–3,10]. This observation is more striking, knowing that only adult recipients were included in our series, while most others also involve children, who are known to have better outcomes in similar circumstances. We believe that these improved graft outcomes reflect overall improvement in the outcome of ABO-In transplants, thanks to refined peri-transplant management and better immunosuppressive strategies. The blood group subtype was known in six out of ten A blood group patients donating to blood group 0 recipients. Among them, three were A2. This combination was previously reported to be linked to a better outcome, and as such these transplants may partly explain the observed results [11]. Two of the three A2 to 0 transplants remained rejection-free in the present report. All three were alive with functioning grafts. We believe that the ABO-In transplant should be viewed as an important option in acutely ill patients awaiting an emergency liver transplant, and A2 to 0 transplants should be favoured, when possible.

Our experience suggests a point of caution be raised regarding the use of ABO-In grafts in patients requiring

Table 4. Complications.

ABO status	Incompatible	Compatible	Identical	*P*
Patients with hyper-acute rejection	1	0	0	NS
Patients with ACR	8	12	29	NS
Patients with ACR-steroid resistant	3	1	3	<0.05*
Surgical complications				
Biliary complications	6	9	24	NS
Hepatic artery stenosis	2	3	4	NS
Hepatic artery thrombosis	2	1	1	<0.05*
Portal vein thrombosis	2	1	3	NS
Bacterial infections				
Pneumonia	3	7	35	NS
Bacteriemia	4	3	17	NS
Urinary tract infection	3	4	16	NS
Intraabdominal abcess/peritonitis	4	4	16	NS
Pseudomembranous colitis	1	2	10	NS
Other bacterial infections	4	8	21	NS
CMV	5	6	20	NS
VZV	1	0	4	NS
HSV I	0	3	14	NS
HSV II	0	1	0	NS
EBV	0	1	0	NS
Fungal infections	1	8	18	NS
Patients with cancer				
Skin	0	0	3	NS
Nonskin	1	1	2	NS

ACR, acute cell rejection.
*Incompatible vs identical.

re-transplant. Both re-transplant patients have lost their grafts, because of hyper-acute rejection and hepatic artery thrombosis, and had to undergo a new re-transplant. This observation, together with other reports [10], suggests that the use of ABO-In livers for re-transplantation may present an even greater challenge, and should be considered with caution. These cases have, among other challenges, increased the risks of artery complications, linked both to the re-transplant and the ABO-incompatibility status [12]. The higher rate of hepatic artery thrombosis linked to ABO-In was, indeed, confirmed by the present study.

The immunosuppression protocols used in this retrospective study are based on quadruple-drug therapy, with lymphocyte-depleting antibody used in all ABO-In cases except two extremely ill recipients. This combination is a modest increase in the level of immunosuppression compared to the standard protocols of triple therapy used in the ABO-C patients. We believe this choice may be responsible for a rate of infectious complications that was similar to those in the identical and compatible groups despite the high risk of all such emergent patients. Along the same line, no splenectomy was performed to minimize the surgical morbidity. On balance, one patient and one graft were lost early after transplant in the incompatible group because of immunological events. In addition, peak isoagglutinin titres demonstrated higher levels in patients experiencing rejections (Table 2). These observations reinforce the need for close monitoring of isoagglutinin levels, and argue for prophylactic institution of plasmapheresis or antigen-specific immunoadsorption when such levels increase [13,14]. Such a strategy of pre-emptive therapy with plasmapheresis has, indeed, been introduced and used in the management of the last two ABO-In cases. Along the same line, the use rituximab may also be of interest, but requires further investigation in the specific setting of emergency ABO-In transplantation in high-risk patients [15–18].

This retrospective study included various combinations of quadruple immunosuppression and no clear conclusion can be drawn regarding the superiority of one or the other. This heterogeneity is not only due to the duration of the observation period, but also to the fact that drug selection has to be performed according to often numerous complications that critically ill patients have. Because of the risk of enhanced immunological attack, including humoural rejection, we favour broad lymphocyte depleting induction agent in most cases. Two extremely sick patients, included in the study, received an induction with anti-IL2 receptor antibodies. We would also favour a

subsequent combination with a potent calcineurin inhibitor, an antiproliferative agent and steroids. Most recent data report the enhanced activity of MMF [19] and tacrolimus [20], supporting their selection in such cases.

We report maintenance of acceptable patient and graft survivals in all ABO-compatibility settings in a series of 106 adult emergency liver transplants. We believe that these outcomes reflect the overall improvement in the management of ABO-In transplants, including peri-operative management and immunosuppressive strategies. ABO-In liver grafts should be viewed as an important treatment option in select adult patients with acute liver failure in need of an emergency liver transplant.

Acknowledgements

The authors would like to thank Abdul Salam, MSc for the statistical analysis.

Authorship

CT, FA, NK: research design. CT, MA-Q, FA, GM: data collection. CT, DB, JS, VB, NK: data analysis. CT, DB, JS, VB, NK: writing.

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