ORIGINAL ARTICLE

Organ transplantation from "increased infectious risk donors": the experience of the Nord Italia Transplant program — A retrospective study

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SUMMARY

The purpose of this study was to assess the safety and the clinical outcome associated with organ transplantation from increased infectious risk donors (IRD). We retrospectively identified all adult deceased IRD referred to the Nord Italia Transplant program coordinating center from November 2006 to November 2011. All potential donors were screened for social risk factors that may increase the risk of donor-derived infection with human immunodeficiency (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). All recipients were followed monthly for the first 6 months post-transplant. A total of 86 potential IRD were identified during the study period. Three hundred and seventy-nine organs from IRD were offered to the transplant centers, but only 185 (48.8%) were used for transplantation. Organs from IRD were transplanted into 174 recipients. The complete follow-up data were available for 152 of 174 (87.3%) recipients. During a mean follow-up of 11.7 months (median 12; range 2.4–12), no transmission of HIV, HBV, or syphilis was documented by serology and nucleic acid testing (NAT) testing. Two patients transplanted with organs from HCV-RNA-positive donors, as expected, developed post-transplant HCV infection. In conclusion, the use of organs from IRD was associated with a safe increase in the transplant procedures in our country.

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Key words
expanded donor pool, hepatitis C, increased infectious risk donors, infection, organ transplantation

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Introduction

Advances in surgical techniques, immunosuppression, and antimicrobial prophylaxis have resulted in significantly reduced morbidity and mortality following organ transplantation. As a result, transplantation is currently considered the definitive therapy for individuals with an end-organ failure. Many of the problems that we face today are the result of this revolution, particularly the imbalance between the availability of organs and the increasing number of patients who would benefit from them. The United Network for Organ Sharing (UNOS) currently reports that 121422 patients are listed for all organs [1]. A total of over 56000 patients were active candidates on December 31st, 2015, in the European Union (EU), and it is estimated that 3874 patients died while officially placed on these waiting lists in 2015 across the 28 Member States of the EU [2]. The

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shortage of donors has stimulated the development of strategies that might allow organ procurement from deceased donors. One way to expand the donor pool is to use organs from donors with an increased risk of transmission of infection with human immunodeficiency (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) to transplant recipients [3–7]. The purpose of this study was to assess the safety and the clinical outcome associated with organ transplantation from IRD.

Materials and methods

We retrospectively identified all adult deceased "increased infectious risk donors" (IRD) referred to the Nord Italia Transplant program (NITp) coordinating center from November 2006 to November 2011. According to the Italian Guidelines on quality and safety of organs for transplantation, deceased donors with a recent (≤2 weeks) risk behavior for acquisition of HIV, HBV, or HCV (active illicit drug abuse, promiscuous sexual behaviors, missing medical history, and recent or current incarceration) are classified as IRD [8]. All potential IRD were screened for HIV, HBV, and HCV infection by both serology and nucleic acid testing (NAT). Organs from IRD were offered only to the recipients who were informed about the potential specific risk of transmission and who signed a specific informed consent at the time of listing and again before organ acceptance and transplantation.

Organs from donors positive for HCV antibodies were used only in emergencies or in HCV-RNA-positive infected recipients. HBsAg-positive organs were considered for use in HBsAg-positive recipients or with protective immunity to HBV as a result of immunization (HBsAb titer ≥10 UI/ml) or natural infection. All recipients were screened pre-transplant at their transplant center and were followed monthly for the first 6 months post-transplant by serology and NAT testing for HIV, HBV, and HCV.

The Italian National Transplant Centre (CNT) approved this study, and an infectious disease (ID) expert (*second opinion*) was available round the clock to offer advice on doubtful clinical cases [9,10].

The emergency procedure was defined according to the criteria of CNT programs for emergency heart, lung, and liver transplantation that prioritizes organ allocation among patients affected by the most severe degrees of organ failure [11–15]. All follow-up data of the patients transplanted with organs from IRD were collected from the 13 participating transplant centers.

Statistical analysis

The donor variables gathered from the NITp registry included the following: age, behavior risk factors, cause of brain death, serology and NAT for HIV, HBV, and HCV, type and number of organs offered/transplanted for each donor, and reason for the offer refusal by the transplant centers. Recipients' data collected by the individual centers were as follows: age and gender, date of transplant, type of organ transplanted, type of surgery (emergency or elective transplantation), serology, and NAT for HIV, HBV, and HCV at baseline and monthly for the first 6 months post-transplant; patients and graft survival at 6 and 12 months post-transplant.

A computerized Statistical Package for the Social Science system (version 19; SPSS Inc., Chicago, IL, USA) was used for data collection and analysis. Categorical variables were expressed as absolute numbers and their relative frequencies; quantitative variables were presented as mean, median, and range. The independent samples *t*-test was used to compare two population means and Pearson chi-square and Fischer exact test to compare categorical variables. A P-value <0.05 was considered to be significant.

Results

A total of 86 potential IRD [71 male (82.6%), 15 female (17.4%), mean age 37.8 ± 12.5 years (range 15–67)] were identified during the study period. The donors were classified as IRD because of active illicit drug abuse (55.8%), promiscuous sexual behaviors (19.8%), missing medical history (9.3%), recent or current incarceration (7.0%), or any combinations of these factors (8.1%). Stroke, head trauma, or anoxia was the cause of brain death in 95.3% of the 86 IRD, and the most common cause of death was head trauma (40/86, 46.5%). All IRD were HIV serology and NAT negative; a greater proportion of IRD (66/86, 76.7%) were negative for HBsAg, HCV-Ab, and syphilis; 16 of 86 (18.6%) were HCV positive (75.0% of them HCV-RNA positive), 1 of 86 (1.2%) HBsAg with HBV-DNA positive, and 1 of 86 (1.2%) anti-HCV/HCV-RNA indeterminate and HBsAg+; 2 of 86 (2.3%) IRD had a serology suggestive of latent syphilis. The ID expert was consulted for advice in 93% of the IRD identified and recommended, according to the Italian guidelines, the use of all suitable organs of all donors to recipients who had already signed a specific consent form.

Three hundred and seventy-nine organs from IRD were offered to the transplant centers, but only 185

(48.8%) were used for transplantation. The reason for refusal was related to the IRD status for 97 of 194 (50%) organs (i.e., lack of recipient's informed consent or reluctance of the transplant team to accept organs form IRD donors), poor organ quality in 88/194 (45.4%) (i.e., traumatic injuries, organ diseases diagnosed after biopsy or other complementary test during donor evaluation, and deterioration of donor organ function for haemodynamic instability), and other factors (i.e., logistical reasons) in nine cases (4.6%). The frequency of reasons for refusal according to the type of organ is reported in Table 1. A significantly greater proportion of kidneys were refused based on IRD-related reasons compared to other organs [78.7% vs. 38.9% of lungs, 12.5% of livers ($P < 0.0001$), and 37.9% of hearts ($P = 0.0003$)]. The organs from HCV+ donors were statistically more frequently refused compared to organs from HBsAg/HCV/syphilis-negative donors [51/64 (79.7%) vs. 135/300 (45%), $P < 0.0001$]. Subgroup analysis showed no statistical difference of organ refusal rate by the year of offer [$P = 0.32$], donor age (<40 vs. ≥40 years) [$P = 0.31$], and high-risk behavior [$P = 0.31$].

Organs from IRD were transplanted into 174 recipients [126 male (72.4%), 48 female (27.6%), mean age 49.3 ± 11.3 years (range 9–71)] (84 kidney, 43 liver, 35 heart, seven double lung, two pancreas–kidney, one heart–kidney, one pancreas, and one double kidney). The 6-month and 1-year patient survival rates were 94.1% and 92.3%, respectively. One-year graft survival rate was 92% (98% kidney, 94% heart, 85% liver, and 71% double lung). At baseline pre-transplant screening, 37 (21.3%) recipients were HCV positive (89.2% of them HCV-RNA positive) and 32 (18.4%) were HIV positive. The most common type of surgery was an elective transplant surgery (77%). An emergency procedure was performed especially in thoracic organ transplantation: 27/35 (77.1%) heart and 4/7 (57.1%) double lung, 8/43 (18.6%) liver, and one heart–kidney. A flow diagram of the features of the donors, organs offered, refused, or accepted, and recipients transplanted is reported in Fig. 1.

The complete follow-up data were available for 152 of 174 (87.3%) recipients, as detailed in Table 2; a total of 17 patients were found to have not been tested according to the protocol, and five patients died within 2 months post-transplant for causes unrelated to the IRD category. During a mean follow-up of 11.7 months (median 12; range 2.4–12), no transmission of HIV, HBV, or syphilis was documented by serology and NAT testing.

A total of 13 organs (four hearts, four livers, three kidneys, and one heart–kidney) from 11 anti-HCV-positive [9/11 (81.8%) HCV-RNA positive] donors were transplanted to 12 recipients, eight anti-HCV/HCV-RNA positive, and four anti-HCV negative (two hearts, one heart–kidney, and one kidney) at pretransplant screening. Among the four anti-HCV-negative recipients with anti-HCV/HCV-RNA-positive donor, the complete follow-up results for HCV-Ab and HCV-RNA were only available for three patients because the heart–kidney recipient transplanted with an emergency procedure died 5 days post-transplantation. The kidney recipient remained HCV negative during the post-transplant follow-up without treatment for HCV infection, while the two patients who underwent emergency heart transplantation developed HCV infection: a patient was treated unsuccessfully with peg-interferon plus ribavirin and unfortunately both recipients died due to liver cirrhosis at 5 and 6 years post-transplant, respectively. Two recipients (one double lung and one heart) were transplanted with organs (four offered, three accepted, and one kidney refused due to IRD-related reasons) from a donor with a serology compatible with latent syphilis without infectious complications in the immediate post-transplant period. None of the eight offered organs from two HBsAg-positive donors (one with HCV co-infection) was accepted due to the lack of compatible recipients.

Table 1. Organs offered and refusal reasons according to the type of organ

Type of organ offered	Number of organs offered	Number of organs accepted	Number of organs refused	Refusal reasons		
				IRD-related reasons	Poor quality of organs	Other factors
Kidney	150	89 (59.3%)	61 (40.7%)	48 (78.7%)	11 (18%)	2 (3.3%)
Lung	86	14 (16.3%)	72 (83.7%)	28 (38.9%)	40 (55.6%)	4 (5.6%)
Heart	65	36 (55.4%)	29 (44.6%)	11 (37.9%)	18 (62.1%)	–
Liver	59	43 (72.9%)	16 (27.1%)	2 (12.5%)	13 (81.3%)	1 (6.3%)
Pancreas	18	3 (16.7%)	15 (83.3%)	7 (46.7%)	6 (40%)	2 (13.3%)
Pancreatic islets	1	–	1 (100%)	1 (100%)	–	–
Total	379	185 (48.8%)	194 (51.2%)	97 (50%)	88 (45.4%)	9 (4.6%)

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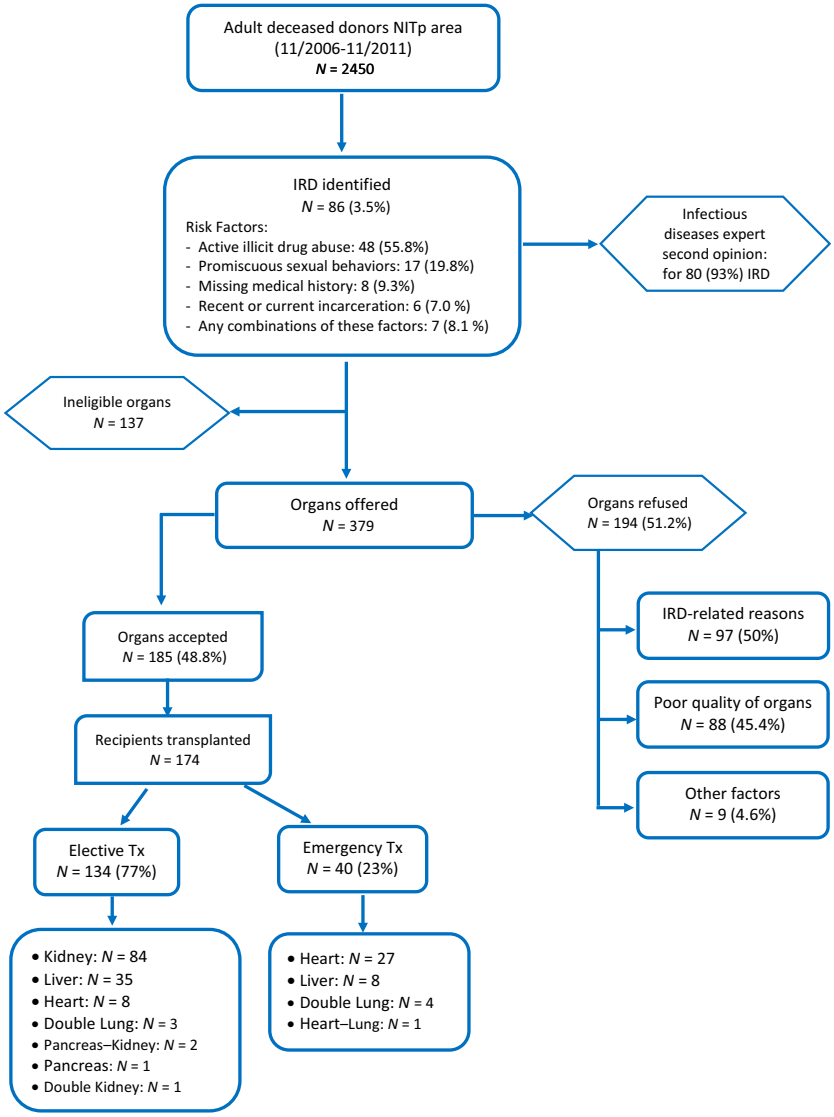

Figure 1 Flow diagram of the features of the donors, organs, and recipients.

Table 2. Baseline characteristic of the 152 recipients with a complete follow-up.

	HIV−					HIV+				
Transplanted organ	HBsAg− HCV−	HBsAg− HCV+	HBsAg+ HCV−	HBsAg+ HCV+	Syphilis+	HBsAg− HCV−	HBsAg− HCV+	HBsAg+ HCV+	Syphilis+	Total
Kidney	58	2				13	5		3	81
Double lung	5	–			1					6
Heart	24	1			1					26
Liver	10	12	3	1			7	3		36
Pancreas	1	0								1
Pancreas kidney	1	–				1				2
Total	99	15	3	1	2	14	12	3	3	152

Discussion

Among the 120 organ transplant recipients with a negative HIV serology at the time of transplantation, with a regular post-transplant follow-up, no cases of HIV transmission have been documented. In addition, no transmission has been recorded in 97 of 99 (98%) recipients who were seronegative at the time of

transplant for HIV, HCV, HBV, and syphilis. These results are consistent with other single-transplant center reports [16–19] and confirm that donor-derived disease transmission remains a rare complication [20,21]. In our study, out of three HCV-RNA-negative recipients of organs from HCV-RNA-positive donors, only two heart recipients transplanted with an emergency procedure with anti-HCV/HCV-RNA-positive donors developed a serious HCV-related liver disease in the absence of an effective and safe HCV therapy. However, there was no other documented HCV transmission in the cohort. The recent approval of direct-acting agents, well tolerated, safe and highly effective, to treat HCV infections may modify the post-transplant outcome of the recipients who received organs from anti-HCV/HCV-RNA-positive donors and policies regarding the use of organs from HCV donors should be reconsidered [7,22,23].

In terms of donor characteristics, IRD were significantly younger than deceased donors reported in NITp area during the study period 2006–2011 (mean age 37.8 $\pm$ 12.5 vs. 56.2 $\pm$ 18.9 years, $P < 0.0001$) and were mostly male (82.5 vs. 54.8%, $P < 0.0001$) [24]. Active illicit drug abuse was the most common increased-risk behavior, without variation by year; only 25.5% of them were HCV-Ab positive.

In our experience, the availability of a 24/7 *second opinion* ID expert was nevertheless crucial to increase the number of offered organs; the ID expert has recommended the use of suitable organs of all donors for whom his support was requested from the donor procurement organization.

However, we observed a high percentage of organs recovered but not transplanted (51.2%), despite the young age of the donors. The refusal was independent from the ID opinion and was related to poor quality of organs or to the fear of the transplant team. More than one-third of thoracic organs (38.9% of lungs, 37.9% of hearts) were rejected for IRD-related reasons, despite the high number of patients on the waiting list and the shortage of these organs. This may be related to the lack of confidence of transplant teams to accept organs from IRD. Our study did not investigate how many recipients on the waiting list were informed about the possibility to accept or decline organs from IRD. However, our data showed that in half of the cases the organ refusal was based on IRD-related reasons; particularly a specific informed consent at the time of listing was available only for a few recipients before transplantation, even for candidates for life-saving transplants. Probably, the reluctance to use organs from IRD is caused by the stigma associated with social risk factors, widespread in Italian public opinion. In our clinical experience, patients often perceive that organs from donors with social risk factors, especially active illicit drug abuse or promiscuous sexual behaviors, have a considerable risk of HIV transmission; similar patient attitudes toward IRD organ offers were described by Ros *et al.* [25]. In the present study, none of the recipients of organs from IRD with at least a NAT testing post-transplant developed a donor-derived HIV infection. Our study did not find any significant difference in 1-year graft and patient survival compared to recipients transplanted in NITp area during the study period [kidney 98% vs. 93% ($P = 0.1$), heart 94% vs. 85% ($P = 0.2$), and liver 85% vs. 82% ($P = 0.8$)]. This finding is similar to that found by other reports suggesting no difference in post-transplant survival between recipients who received organs from IRD and those who received organs from standard-risk donors [19,26–29].

The purpose of our study was to assess the safety and the clinical outcome associated with organ transplantation from IRD, with a recent risk behavior for acquisition of HIV, HBV, or HCV in our country. Italy, with about 60 million of inhabitants (201 inhabitants per square kilometer) and about four thousand new diagnoses of HIV infection annually, contributes significantly to outline the profile of the HIV epidemic in EU. A total of 123000 (115000–145000) individuals aged 15 or more were estimated to be living with HIV/AIDS in Italy at the end of 2012 [30,31]. The estimated HIV prevalence among adults in Italy in 2012 was 0.28 (0.24–0.32) per 100 residents aged 15 or more. These rates are similar to what reported in United States (US) and other Western European countries [32].

In spite of the large diffusion of HCV infection and its strong association with liver disease, the epidemiology of HCV in Italy is still unclear. In November 2012, the Italian Ministry of Health confirmed that prevalence of HCV seropositivity was higher in Southern and Insular areas (about 8.0%) than in Central and Northern regions (about 2.0%). However, the reports on which this statement was based are outdated or were obtained in limited areas [33–38]. In the geographic area of EU, the estimate prevalence of HCV infection varies between 2.4% for Western and Central EU and 2.9% for Eastern EU [39,40]. In the US, a follow-up of National Health and Nutrition Examination Survey study analyzing survey data from 2003 to 2010 estimated a prevalence of 2.7 million persons chronically infected with HCV, corresponding to a population prevalence of chronic hepatitis C of 1.0% [41,42].

The spread of HBV infection has gradually decreased in Italy in the last decades as shown by the steady

reduction in the incidence rates of acute hepatitis B, from 10 per 100 000 inhabitants in 1984 to 0.85 per 100000 in 2012, and by the reduced prevalence of HBsAg chronic carriers in the general population, from nearly 3% in the 1980s to 1% in 2010 [43]. In the US, data from National Notifiable Diseases Surveillance System revealed that from 2010 through 2014 there was an 11.9% decrease in the number of reported cases of acute hepatitis B and the overall incidence rate for 2014 was 0.9 cases per 100000 population [42]. The estimate prevalence of persons living with HBV chronic infection in the US varies between 850 000 and 2.2 million.

Limitations of the study

The present study has limitations. First of all, the relatively small sample size (86 IRD) and the difficulty in collecting data prospectively do not permit to draw definitive conclusions about the actual risk of transmission. Unfortunately, despite the follow-up of all recipients of IRD is mandatory in Italy, five of 18 centers did not transmit the follow-up data to the CNT and did not answer to the multiple request of data for this study. However, as all Italian transplant centers transmit annually to the CNT their data, including mortality and major complications [44], we assume that no HIV, HBV, or HCV transmission occurred in the 22 of 174 recipients of organs from IRD. With the aim to increase the accuracy of the follow-up data of the entire Italian solid organ transplant population, the CNT has recently modified its computerized informative system with the introduction of new mandatory fields, including the serology and NAT results that must be entered annually regardless of the type of organ donor. We hope that in the future this will allow a more accurate evaluation of the actual risk of transmission. The risk of window-period (WP) for HCV and HIV infection ranges from 0.26 to 300.6 per 10 000 donors based on WP for ELISA and 0.027–32.4 based on NAT and from 0.09 to 12.1 per 10 000 donors based on WP for ELISA and 0.04–4.9 based on NAT, respectively [45,46]. However, despite the relatively small number of patients reported in the present study, the lack of any transmission is encouraging and might be helpful for reducing the fear of using organs from these donors. In addition, our study did not consider the possibility to identify those recipients who will benefit most from accepting organs from IRD in accordance to what reported by Chow *et al.* [47] in 2013 who addressed the varying phenotypes of recipients receiving renal transplants and their risk of waitlist mortality.

In conclusion, in our study, the use of organs from IRD was associated with a safe increase in the transplant procedures in our country. However, a careful donor risk assessment, including NAT testing for HIV, HBV, and HCV, and close follow-up of the recipients, including blood samples storage, are highly recommended. Finally, our findings may contribute to an improvement in transplant physicians' awareness of the quality and safety of using organs from IRD; this is crucial for an accurate information given to the transplant candidates in order to increase patients' willingness to consider IRD organ offers.

Authorship

PAG: designed study, critically revised and approved the article. DDG: analyzed data and drafted the article. DL: collected the clinical data. AR: collected the clinical data. GP: collected the clinical data. ANC: critically revised and approved the article.

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Conflict of interest

The authors of this manuscript have no conflict of interests to disclose as described by the Transplant International.

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