Joint UKBTS / HPA Professional Advisory Committee (¹)
Summary Sheet

1.	**Paper for the JPAC meeting on:**	10 November 2011
2.	**Date submitted:**	04 November 2011
3.	**Title (including version no.):**	Risk assessment for immunosuppression and corneal donation
4.	**Author(s):**	Philip Yates on behalf of SAC-TCTP

5.	**Brief summary:**	Proposal to allow potential deceased tissue donors with a history of either
		
		    1. malignancy on chemotherapy, or
		
		    2. autoimmune disease on immunosuppressive therapy
		
		to donate corneal tissue provided that all serological tests are negative and that NAT testing is performed for HIV, HCV and HBV and shown to be negative.

6.	**Action required by the JPAC:** (What do you want JPAC to do in response to this paper?) e.g. • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy	To endorse the recommendation
7.	**Any other relevant information:**	Paper attached

(¹) **Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee**

Risk assessment for immunosuppression and corneal donation

Proposal

To allow potential deceased tissue donors who may be immunosuppressed due to a history of either
1. malignancy on chemotherapy, or
2. autoimmune disease on immunosuppressive therapy

to donate corneal tissue provided that all serological tests are negative and that NAT testing is performed for HIV, HCV and HBV and shown to be negative.

Background

Unlike for other tissues, corneal donation is permitted from donors with a history of many types of malignancy – intraocular malignancy and haematological malignancy are obligatory exclusions. This is because the cornea is avascular and therefore not likely to be involved in distant metastasis. In the UK donors with a history of malignancy currently account for 20-25% of all corneal donations and are thus a valuable source of this tissue. Many of these patients will have either been on chemotherapy at the time of death or in the months preceding their death. In addition to this 14% of potential donors were deferred due to a history of being on either steroids or chemotherapy and a further 5% of potential donors were deferred due to a history of either malignancy or autoimmune disease.

The current tissue donor guidelines do not permit a donor who is immunosuppressed from donating due to the theoretical possibility of this interfering with the serological assays used by UKBTS for viral antibody screening. The questions of what steroid dosage, or which type of chemotherapy protocols, can cause enough immunosuppression to affect virology screening and how soon after the treatment has stopped will the effect have disappeared have been raised on many occasions and with a variety of experts. Unfortunately no one has been able to provide a satisfactory response to these questions. An enquiry to Scott A. Brubaker, the Chief Policy Officer of the American Association of Tissue Banks, regarding this topic revealed that in the USA "*consideration of treatment related to the malignancy is left up to evaluation by the individual tissue bank medical director and the tissue bank's written policy…….*
The evaluation shall include: the type of malignancy, clinical course, and treatment prior to acceptance of a donor. The evaluation and reasons for acceptance shall be documented in the donor's record…..
When possible, we try not to be overly prescriptive, especially where medical director discretion is involved. …. They don't want to be shackled. I can understand why since there can be various levels of immunosuppressive therapies encountered so each is a case-by-case scenario."

Current UKBTS position

The relevant UKBTS deceased tissue donor selection guidelines state:

Immunodeficiency
    See   Immunosuppression

Immunosuppression
    Obligatory   **Must not donate if:**
                      a) Immunosuppressed.
                      b) Donors with recovered immunodeficiency:
                      Refer to a Designated Medical Officer.
    See if Relevant   Autoimmune Disease
                      Immunoglobulin Therapy
                      Steroid Therapy

Steroid Therapy
    Obligatory   **Discuss with a Designated Medical Officer if:**
                      Has been regularly taking steroid tablets, injections or enemas, or applying creams over large areas.
    Discretionary   **1.** a) If occasional use of creams over small areas of skin for minor skin complaints, accept.
                      b) If using steroid inhalers for prophylaxis, accept.
                      2. Eyes:

See if there is an entry for the underlying condition. If acceptable and not on an immunosuppressive dose, accept.

See if Relevant	Autoimmune Disease
	Skin Disease
	Tissue and Organ Recipients
Additional Information	Steroid therapy in high doses causes immunosuppression. This may mask infective and inflammatory conditions that would otherwise prevent donation.

Autoimmune Disease

Obligatory	**See:**	
	Is there an entry for the condition?	
	Must not donate if:	
	The donor has needed treatment to suppress the condition in the last 12 months.	
Discretionary	**Eyes:**	
	If no ocular involvement, accept.	
See if Relevant	**If treated with immunoglobulin or plasma exchange or filtration:**	
	Transfusion	

Additional Information Treatment to suppress the condition may be with steroids, immunosuppressive drugs, antimetabolites, antibodies directed against parts of the immune system as well as other therapies. These will affect the donor's immune system. This may make the donor more susceptible to certain types of infection and also will make some infections more difficult to diagnose.

Autoimmune disease is caused by the body attacking itself. This is with antibodies that are in the fluid part of the blood (plasma), and with immune cells directly attacking target cells in the part/s of the body affected.

Current legislation and guidelines

1. Human Tissue Authority 'Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment' (2010)

Donor selection, evaluation and testing
Selection criteria for donors of tissues and cells
79. Donors must be excluded from donation if any of the criteria in Annex A apply, unless donation is justified on the basis of a documented risk assessment approved by the DI
Annex A - Selection criteria for donors
1.1.3. Presence, or previous history, of malignant disease, except for primary basal cell carcinoma, carcinoma *in situ* of the uterine cervix, and some primary tumours of the central nervous system that have to be evaluated according to scientific evidence. Donors with malignant diseases can be evaluated and considered for cornea donation, except for those with retinoblastoma, haematological neoplasm, and malignant tumours of the anterior segment of the eye.
1.1.8. Indications that test results of donor blood samples will be invalid due to:
   (a) the occurrence of haemodilution, according to the specifications in Annex II, section 2, where a pre-transfusion sample is not available; or
   (b) treatment with immunosuppressive agents.

2. SaBTO Guidance on the microbiological safety of human organs, tissues and cells used in transplantation (2011)

Section 8. Microbiological testing of donors and donations
General principles
8.4 Laboratory screening can take the form of serological testing for antibody, for antigen, and molecular testing for the DNA or RNA sequences of infectious agents. The EC Directive currently requires serological testing of donors irrespective of NAT testing (see Table 3). Whilst antibody detection relies on the host response, antigen and molecular assays directly detect components of the infectious agent.
Changing scene in microbial detection
8.9 Screening tests for detecting infections have improved over recent years with a move from single antibody modality to combination antigen and antibody tests. The co-existence of immunosuppression in a potential donor, either through disease or iatrogenic treatment (e.g.

high steroid dosage) should be borne in mind when using an antibody-only test since immunosuppression may delay and attenuate the host serological response. Assays which directly detect the virus are not affected adversely by immunosuppression and thus antigen testing (HBsAg and HCV Ag) and genomic testing (HBV, HCV and HIV NAT) are appropriate in this situation.

8.13 Some human materials may exhibit an innate inability to transmit infection, either because of the nature of the material, or through partitioning of infection away from the product, or through pathogen inactivation (which may be deliberate), or the result of processing before use. For example, the cornea, being avascular, is considered unlikely to transmit Human T-cell Leukaemia Virus (HTLV) or malaria. Where a material destined for human use has been shown not to transmit an infection, or when its processing has demonstrated removal of infection, or where there is a deliberate and validated pathogen inactivation step, or a combination of more than one of these parameters, a risk analysis may allow modification of the testing requirements at the time of donation. This may be particularly relevant to the generation of stem cell lines where prolonged culture, often with antibiotics, may prevent the transmission of infections (e.g. *T. pallidum*). Where a risk analysis identifies that the risks of transmission have been mitigated as described above, it may be appropriate to consider removing the necessity for donor screening.

Discussion

The legitimacy of this proposal is based on following two principals:
1. It is permissible under the HTA Directions to accept donors for whom a risk criterion applies provided a documented risk assessment has been approved.
2. Under the SaBTO guidelines where a material destined for human use has been shown not to transmit an infection, a risk analysis may allow modification of the testing requirements at the time of donation

In this risk assessment three specific criteria need to be considered:
1. The effect of immunosuppression on antibody production.
2. Does current UKBTS testing for tissue donors exclude viral infection?
3. Can cornea from infected donors transmit the infection to recipients?

1. The effect of immunosuppression on antibody production.

It has long been recognized that patients on immunosuppressive therapy following organ transplantation may have reactivation of hepatitis B and their response to active immunization is poorer than normal. However patients on chemotherapy for malignancy and patients with HIV infections have also been shown to have detectable antibodies against viral infections. There is a major lack of scientific data showing what level of immunosuppression is brought about by chemotherapy for malignancy or immunotherapy for autoimmune disease and how long this persists for after the treatment is stopped.

Can antibodies develop *de novo* and be detected in a patient who is on immunosuppressive therapy at the time of viral infection or immunization?

Despite immunosuppressive chemotherapy, HIV-1 antibodies appeared between 26 and 54 days after transplantation in the three organ recipients who survived more than 4 weeks after receiving organs from an HIV infected but seronegative organ and tissue donor in 1985.[1] The fourth organ recipient died 24 days after transplantation with no detectable HIV antibodies at the time of death. Anti-rejection therapy consisted of various combinations of steroids, cyclosporine and azathioprine.

Three organ recipients receiving immunosuppressive therapy at the time they were infected with HIV were evaluated for HIV antigen and antibody.[2] Two had received organs from a cadaveric donor subsequently found to be HIV positive whilst the third was infected by a blood transfusion five weeks after a renal transplant. Anti-rejection therapy consisted of steroids, cyclosporine and azathioprine. Antibodies to HIV were first detected at days 27, 36 and 81 (the only previous sample on this patient on Day 30 had been negative).

In 2000-2001 an outbreak of HCV occurred at a haematology/oncology clinic due to cross-contamination of shared saline bags. Blood samples were collected in 2002 as part of the investigation[3] some 16 months after the outbreak and analyzed using a combination of second-generation EIA and NAT testing. Of the 472 patients seen at the clinic 264 agreed to be tested of which 102 patients (39%) had received chemotherapy during the outbreak period. A total of 92 new HCV infections were identified of which 72 had received chemotherapy during this period. All 20 (100%) patients who had not received chemotherapy were EIA positive compared to 56 out of 72 (78%) who had received chemotherapy.

A study designed to evaluate the immunogenicity of HBV vaccine in oncology patients who were currently receiving chemotherapy was reported in 1985[4]. Vaccine was given at 0, 1 and 6 months and samples were tested for antibody at monthly intervals for the first 6 months and then again at months 9 and 12. Of the 26 patients who agreed to join the trial, 2 withdrew after 2 months of follow-up, 8 died as a result of their malignancy after receiving two doses of vaccine and after receiving the third dose of vaccine a further three died and two withdrew. Thus only 11 completed the full twelve month follow-up period. Of the 11 surviving more than one year after primary immunisation 8 (73%) responded, in contrast only one out of the 11 (9%) participants who died responded. Of the entire starting group 11 (42%) were recorded to respond by making anti-HBs on at least one occasion after vaccination. Levels of anti-HBs antibody were relatively low but increased to a peak at nine months at 59 (+/-10) mIU/ml.

Can existing antibodies to viral infections continue to be detected in a patient once they have been commenced on immunosuppressive chemotherapy?

Shortly after diagnosis a patient with lymphoma was bitten by a rabid animal[5]. He was treated with a course of five doses of rabies vaccine and advised to refrain from chemotherapy until the end of the vaccination schedule. Due to low antibody levels (0.2 iu/ml compared to the recommended protective level of 0.5 iu/ml) following the first course of vaccine, a second course was administered using double dose vaccine. After the third double dose his antibody level had risen to 2.73 iu/ml. On completion of the second course of vaccination and eight weeks after the attack he was commenced on chemotherapy consisting of fludarabine, mitoxantrone and dexamethasone. Four months after starting chemotherapy the rabies antibody level was 1.93iu/ml but seven months after starting chemotherapy it had fallen to 0.15 iu/ml. As this was below protective levels, a further course of rabies vaccine was administered and his antibody levels increased again to 3.84 iu/ml.

Several authors have found decreased antibody levels in children after chemotherapy. However, the number whose antibody levels fell below the protective level differed widely and there was no consensus as to which antibody specificities are predominantly lost. The largest study was by Reinhart et al[6] (2003) who investigated the levels of antibodies against measles, mumps, polio, rubella, diphtheria, tetanus and Haemophilus type b in 139 children with malignancies at the time of diagnosis, during chemotherapy, after cessation of intensive treatment and after revaccination. The measles, mumps, diphtheria, tetanus and Hib antibody titres declined in nearly all children during and after treatment.

	Mean antibody level at time of diagnosis		Mean antibody level at cessation of treatment		No. of children with a >50% decrease of initial antibody level	No. of children with antibody level below protective level
Measles	1.91 (+/- 0.3)	U/ml	0.71 (+/- 0.08)	U/ml	43%	6%
Mumps	190 (+/- 13)	U/ml	123 (+/- 11)	U/ml	31%	6%
Diphtheria	0.47 (+/- 0.05)	U/ml	0.34 (+/- 0.05)	U/ml	52%	21%
Tetanus	1.79 (+/- 0.14)	U/ml	1.28 (+/- 0.13)	U/ml	44%	0%
Hib	7.96	U/d	2.87	U/d	n.g.	13%
Polio type 1	n.g.		n.g.		n.g.	18%
Polio type 2	n.g.		n.g.		n.g.	12%
Polio type 3	n.g.		n.g.		n.g.	25%
Rubella	n.g.		n.g.		n.g.	0%

n.g. = not given

Non-detectable levels of antibodies after therapy only occurred in those who already had low antibody levels at the time of diagnosis of the malignant disease.

The type of patients under consideration as tissue donors are either patients with malignancy receiving intermittent short courses of high dose chemotherapy or patients with autoimmune disease receiving long term lower dose chemotherapy. The above studies have shown that patients on these types of treatment can both produce antibodies to new infections and continue to produce antibodies to previous infections or vaccinations. Although the levels of antibodies may be suppressed to a degree, current serological testing should sensitive enough to detect the residual viral specific antibodies.

2. Does current UKBTS testing for tissue donors exclude viral infection?

When Commission Directive 2006/17/EC was drafted the guidelines were based on the premise that testing deceased tissue donors would be by serological testing alone. The UKBTS testing for microbiological infection in deceased tissue donors far exceeds that required by the HTA Directions as the UK has elected to make NAT testing for HIV/HCV/HBV mandatory testing for cadaveric donors. In addition to this it also screens for HIV antigen as part of the combined ELISA antigen / antibody test for HIV and for HBV antigen in the form of the HBsAg test. Neither of these types of tests will be adversely affected by immunosuppression and can therefore be confidently used to exclude a diagnosis of HIV, HCV or HBV in potential donors. Indeed it would be expected that if a patient's antibody response to a viral infection was suppressed then the levels of viral antigen should increase and be more readily detected.

Cornea being avascular can not transmit HTLV so the absence of a molecular test for HTLV antigen would not be a problem and this is permissible by SaBTO.

3. Can cornea from infected donors transmit the infection to recipients?

HIV, HCV, HBV
A review of the literature has shown no documented cases of transmission of HCV or HIV by corneal transplantation but two possible cases of HBV transmission.

There are three reports[7,8,9] covering nine recipients of cornea form HIV positive donors none of whom subsequently seroconverted. This was in contrast to the recipients of organs and unprocessed bone who did seroconvert. These negative reports suggest that transmission of HIV by corneal transplantation may be difficult.

There are two reports[10,11] where HCV positive multi-organ and tissue donors both transmitted HCV to organ and other tissue recipients but not to cornea recipients. These negative reports suggest that transmission of HCV by corneal transplantation may be difficult.

There has been one report[12] covering two cases of possible HBV transmission in the mid1980s. The recipients developed hepatitis two and four months respectively after corneal transplantation and were found to be positive for HBsAg. Archived frozen blood samples from both donors tested positive for HBsAg and one donor had a history of iv drug use. At that time there were no specific additional testing techniques available to confirm the donor as the source of infection. In one case the recipient of the second cornea did not become infected whilst in the other case there is no mention as to the virological status of the recipient of the second cornea.

HTLV
Cornea being avascular will not transmit HTLV. A review of the literature has shown no documented cases of transmission of HTLV by corneal transplantation.

There are two reports[13,14] both covering the same case where an HTLV positive multi-organ and cornea donor transmitted HTLV to the three organ recipients but not to the two cornea recipients. .This negative report supports the premise that transmission of HTLV by corneal transplantation may not be possible.

Syphilis
There is no evidence in the literature, either experimental or clinical to suggest the transmission of syphilis via cornea grafting, whilst there are a couple of negative animal experimental studies.

To date, after more than 60 years of eye banking, there have been no reported cases of syphilis transmission by corneal transplantation.

In 1952, Randolph[15] reported a series of experiments designed to try to transmit syphilis to rabbits. In the first set of experiments, corneas from 10 rabbits with latent syphilis were transplanted to normal recipient rabbits. After three months the grafts were removed, macerated and injected subconjuctively and intratesticularly, into normal rabbits. After eight months, no rabbit had developed syphilis.
In a second set of experiments, cornea extract from 20 rabbits with active syphilis were injected subconjuctively and intratesticularly into 20 normal rabbits. Again, no transmission of disease was observed.

In 1995 Macsai and Norris[16] performed a study to determine the effects of commonly employed corneal storage conditions on the survival and infectivity of Treponema pallidum. T. pallidum was inoculated into OptiSol storage medium or a T. pallidum survival medium and incubated in cornea viewing chambers for 24 h at 4°C. When inoculated intradermally into rabbits, none of the 10 sites developed lesions from suspensions incubated in OptiSol. T. pallidum incubated in the survival medium yielded lesions at one of 10 sites. In contrast, freshly extracted organisms produced lesions at all 10 sites.
In another set of experiments, the infectivity of corneal tissue from rabbits inoculated intratesticularly with T. pallidum 10 days earlier was determined. Corneas from infected rabbits were excised, extracted, and tested for infectivity either immediately after removal or after 24-h storage in OptiSol. Recipient rabbits developed lesions at five of 50 intradermal sites when the corneas were tested immediately and without rinsing. When the corneas were rinsed to remove blood and aqueous humor before extraction the recipient animals did not yield lesions at any of 200 intradermal sites.
The results of this study indicate that retention of T. pallidum infectivity is poor under typical corneal storage conditions and that rabbit corneal tissue contains few, if any, infectious T. pallidum organisms under the experimental conditions employed.

In view of this work in animals and the absence of any documented human cases in the literature, it seem unlikely that clear corneas from syphilitic donors are responsible for the transmission of this disease

Conclusions

a) Although there is a degree of suppression in antibody production in patients on chemotherapy for malignancy, or immunotherapy for autoimmune disease, this is unlikely to be so severe as to produce false negative results in UKBTS viral antibody screening tests given the sensitivity of the assays currently used.
b) The addition of serological testing and molecular testing for viral antigens for HIV, HBV and HCV ensures that any of these infections would be detected even if a false negative viral antibody screening test was present. Cornea being avascular can not transmit HTLV so the absence of a molecular test for HTLV antigen would not be a problem and is permissible by SaBTO.
c) Even if an infection was present in the donor, all the evidence suggests that transmission of any of these infections from donor to recipient via corneal grafts is very difficult, if indeed at all possible.

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20/10/2011