

Bone allograft in the UK: perceptions and realities

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Bone allografts are widely used in the UK in joint revision surgery. Despite this widespread usage, there remain concerns among the surgical community regarding the safety of allografts, in terms of the risk of transmission of infection, together with a persistent misconception that allografts are in limited availability. In this paper we discuss the precautions taken to ensure that allografts are safe, and review the residual risks. We also demonstrate that the availability of allograft in the UK, both actual and potential, greatly exceeds the current clinical demand.

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INTRODUCTION

Bone allografts are widely used by orthopaedic surgeons in the UK. The main clinical applications where bone allografts are used are for impaction grafting in joint revision surgery (1), and in spinal fusion surgery (2). For both these indications, the primary source of bone allograft is femoral heads, donated by patients undergoing hip arthroplasty. Bone grafts may also be donated by deceased donors, and for certain specialist procedures requiring massive bone allografts, such as reconstruction following tumour resection (3), grafts must be obtained from this source. However, we will focus for the purposes of this review on femoral head allografts donated by living donors. Following donation, the allografts are banked, either in local hospital based banks, or larger regional or national banks. They may be utilised either as unprocessed grafts or processed to remove donor marrow content (4), either by the providing tissue bank or in theatre immediately prior to use.

Where bone grafting is required, it is established dogma that autograft is the 'gold standard', in terms of clinical performance. Autograft provides the structural properties of bone graft, together with autologous cells that are necessary for graft incorporation. The most com-

mon source of autograft bone is the patient's iliac crest. There are however significant drawbacks to using autograft. Firstly, there is a limited amount of material that can be safely removed, and this may be insufficient to provide the large volume of graft material required. Secondly, the harvest of autograft can cause long term donor site morbidity; for example, the use of iliac crest autograft for spinal fusion has been associated with chronic long term after effects at the donor site in a significant proportion of patients (5). Finally, the harvesting of autograft from a distal site increases the theatre time required to perform a procedure, which has resource implications for hospitals. For these reasons, allograft may be used to either replace or extend autograft where bone grafting is needed. Allograft has been shown to provide excellent clinical performance in different clinical indications (1, 2), in some cases equivalent to that provided by autograft.

NHS Blood and Transplant (NHSBT) is a special health authority within the NHS, with responsibility for blood, organ and the bulk of tissue donation within the UK. In this role, we regularly meet with surgeons from different orthopaedic specialities to determine what they require in terms of allograft provision, and to ensure that these requirements are met. During these discussions, and notwithstanding

the widespread use of allograft in the UK, two concerns are consistently expressed:

- I) Allografts are unsafe; there is a risk of disease transmission from the donor to the recipient, or transmission of infection from the graft;
- II) There are not sufficient allografts available to meet clinical demand.

In this review, we attempt address these concerns, and discuss whether or not they are justified.

ARE ALLOGRAFTS SAFE?

Any bone allograft has the potential to transmit disease to the recipient. This potential arises from either pre-existing diseases carried by the donor, or from contamination of the graft acquired during the donation process, or subsequent processing. The risk of disease transmission is a function principally of donor selection and screening, and of how the bone is processed and prepared, including any sterilisation and disinfection processes applied. While it is not, and will probably never be possible to state absolutely that there is no risk of disease transmission, the risks can be controlled and minimised to an acceptable level. The risk reduction process begins with donor selection. This is intended to screen out any potential donors who may harbour disease causing agents, or whose bone may not be suitable for transplantation for other reasons. For example it may be mechanically weak due to osteoporosis, or unsafe for transplantation due to a history of malignancy in the donor (there is a potential risk that malignant cells could be transferred to recipients by the graft). The UK guidelines for selection of living and deceased donors of bone are set by specialist committees working under the Joint UK Blood Transfusion Services/National Institute for Biological Standards and Control (NIBSC) Professional Advisory Committee (JPAC), and are freely available to view online (6). These committees are composed of clinical and scientific experts in the fields of blood, organ and tissue transplantation. The remit of JPAC and its subsidiary committees are to prepare detailed service guidelines for the UK Blood Transfusion Services (who are responsible for the majority of clinical tissue banking in the UK) and to provide advice to them as required. Other NHS tissue banks are free to adopt these guidelines. Donor selection has two distinct phases. The first is a thorough review of

the donor's medical and behavioural history. The purpose of this is to identify any disease causing agents the donor may have been exposed to and harbour. These are summarised in Table I.

Medical history is taken to identify any specific risks that the donor may harbour transmissible diseases. Behavioural history will address any aspects of the donor's activities that may increase their exposure to disease causing agents. This will include personal activities, such as intra-venous drug abuse, recent tattooing, or travel history to areas where transmissible disease causing agents (e.g. malaria) are endemic. This initial phase of donor screening is very effective; data show that after medical and behavioural history pre-screening, the risk of a donor subsequently testing positive for viral pathogens during the second phase of donor screening is less than 1 in 1,500 (Tab. II).

TABLE I - POTENTIAL DONOR DERIVED DISEASE CAUSING AGENTS

Class of agent	Specific risk	Screening methodology
Viruses	Transmission of specific viral diseases	Medical and behavioural history, serology screening, NAT ^a
Bacteria and fungi	Transmission of sepsis, contamination of grafts with microbial toxins	Medical history (e.g. recent, active infection)
Prions	Transmission of diseases caused by prion agents (e.g. TSEs ^b)	Medical history (e.g. unexplained dementia, or history of blood transfusion)
Malignant cells	Transmission of malignancies	Medical history (history of or active malignancy)

^aNucleic acid testing

^bTransmissible Spongiform Encephalopathies.

TABLE II - LIVING BONE DONORS TESTED FOR TRANSMISSIBLE VIRAL INFECTIONS, 2001-2010 (NHSBT/HEALTH PROTECTION AGENCY SURVEILLANCE DATA (8))

Total No. of donors tested:	34,750
Hepatitis C positive	13
Hepatitis B positive	10
HIV positive	0
HTLV positive	0*

* HTLV testing commenced in 2004.

The second phase of donor screening is the testing of a blood sample collected at the time of donation for transmissible diseases. The first Technical Directive of the European Cell and Tissue Directive (2006/17/EC) defines the minimum screening requirements for all EU member states. They are predominantly viral markers, and comprise HIV 1 and 2, Hepatitis B and C, and syphilis. Individual member states, or tissue banking organisations within member states, can and do set more stringent criteria over and above EU directive requirements; for example in the UK, HTLV testing is also performed for all donors of tissue to blood service tissue banks. Blood can be tested by two basic techniques; serological screening, which detects antibodies or antigens, and Nucleic Acid Testing (NAT), which detects microbial DNA sequences. The advantage of serological screening for antibodies is that it can provide evidence of a past infection, even if the disease is no longer present - this may indicate a behavioural risk. The serology testing does however rely on the host response to infection, and in the very early stages of infection a potential donor may not have generated sufficient antibodies to be detected. The time between the onset of infection and the time when detection of infection is possible is termed the 'window period'. During this window period, a donor is capable of transmitting an infection but may not test positive. Nucleic acid testing, which directly detects miniscule quantities of microbial DNA, is much more sensitive than serological testing, and reduces this window period. However, as it can only directly detect microorganisms, it will not indicate a cleared past infection. Therefore, the combination of the two techniques both greatly reduces the possibility of a false negative test result and provides an indication of any behavioural risk.

With novel and emerging infections, as was the case with HIV and Hepatitis C, there will be a period where the pathogen is present in the donor population but not known about, and a subsequent period after the pathogen is identified but before a validated test is available. However, pathogen inactivation steps, such as processing and sterilisation help reduce the risk of transmission of both known and unknown pathogens.

There are two core reasons why bone grafts are processed:

I) To make them more clinically effective. There is evidence that the lipid components of donor marrow interfere with the revascularisation and incorporation of bone allografts, and that removing donor marrow can improve their osteoconductivity (9);

II) To make them safer. Much of the potential infectivity of an allograft resides in its blood and bone marrow content. Removing this can reduce much of any potential infectivity (4). This is especially important for prions, for which there is no blood test available, and which are resistant to any sterilisation process we can use for bone allografts.

The principle reason for processing a bone graft is to remove the bone marrow and cell content, leaving a minimally immunogenic bone matrix which is highly osteoconductive. This functions as a supportive scaffold, providing immediate biomechanical support, and which can be colonised by the recipient's cells, over time being remodelled and replaced by host bone. Donor bone marrow is not believed to contribute to this process, and may even retard it (7). Bone may be processed by the tissue bank providing the graft, or by the surgeon immediately prior to use. Marrow depletion protocols used by tissue banks comprise combinations of solvent and/or detergent cleaning, combined with the use of elevated temperatures and positive or negative pressure, whilst those used by surgeons in theatre are necessarily less complex, generally being restricted to the use of pressurised water jets and washing the bone in warm saline or water. Processing methodologies may also be antimicrobial, either via the removal of material that may be harbouring infectious agents, or through the direct antimicrobial effects of processing reagents or elevated temperatures. Currently in the UK, femoral head grafts from living donors are seldom if at all processed by the providing tissue bank due to cost and practicality. They are provided as unprocessed bone, but may undergo cutting, morsellisation and marrow depletion in theatre prior to implantation. In our experience, approximately 90% of femoral head grafts are morsellised prior to implantation, with the remainder being used as structural grafts. For surgeons wishing to use pre-processed bone, shaped or morsellised grafts from deceased tissue donors are available.

Bone grafts, whether processed or not, may also be terminally sterilised before being implanted. For banked bone, is advisable that terminal sterilisation be performed if any processing has been done, as the bone will have been exposed to the risk of environmental contamination during processing. The most common methodology for terminally sterilising bone allografts is gamma irradiation, which has the advantage of being able to be applied after the bone has been processed and sealed in its final packaging. While irradiation can be relied upon to inactivate micro-organisms

such as viruses, bacteria and fungi, it is not effective at inactivating prions. There is currently no sterilisation process that can be applied to bone grafts to inactivate prions that will not also destroy the graft. Irradiation also weakens the structural matrix of bone grafts, and leads to a dose dependent reduction in their biomechanical properties. This reduction may or may not be clinically significant; there is some evidence that unprocessed femoral head allografts irradiated at high (50kGy) dose of irradiation do not perform as well clinically as un-irradiated grafts (9), while those irradiated at a lower (25kGy) dose perform equivalently to un-irradiated grafts (10).

The efficacy of these precautions can be inferred by the fact that there has never been a case of donor to recipient disease transmission from a bone graft in the UK. Moreover, evidence suggests that the risk of deep seated infection (a rare but serious complication that affects primary and revision joint arthroplasty) is no higher for procedures utilising bone grafts than those that do not (12).

CAN SUFFICIENT ALLOGRAFT BE PROVIDED TO MEET CLINICAL DEMAND?

This is a concern that is often expressed by surgeons, and it is a common perception that insufficient bone allograft is available in the UK, or that there is a waiting list. To investigate this concern, it is first necessary to understand what the clinical demand for bone allograft is. It is well established that in the UK, the major use of bone allograft by bulk is in impaction grafting during joint (principally hip) revision. When using bone graft for this purpose, most surgeons prefer to utilise femoral head allografts from living donors, as this is a readily available graft, is easy to work with, and has good results in the orthopaedic literature (1). The essential question to ask therefore is how many joint revision procedures are performed using bone allograft, and how many primary hip replacements are performed over the same period? This analysis also needs to consider that hip revision procedures often require more than one femoral head; in our experience, the average number of femoral heads used per revision is 2.43. Additionally, not all femoral heads removed during hip replacement will be available for transplantation; not all patients will consent or be medically suitable to donate their bone, and not all hospitals where hip replacement is performed will have donation programmes in place to

enable femoral heads to be donated to a local, regional or national bank.

In performing this analysis, the National Joint Registry (NJR) for England and Wales is a valuable tool. The NJR was established in 2002 to collect information on joint surgery and monitor the performance of joint replacement implants. It collects data on all hip, knee, ankle, elbow and shoulder replacement and revision surgery performed within the NHS and independent hospitals. Of particular interest to our analysis, the NJR dataset for revision arthroplasty includes a question whether or not bone graft was used during the procedure. It should be noted that the definition of 'bone graft' in this context could include allograft, autograft or artificial bone substitute; estimates of the proportion of these cases that utilise allograft range from the vast majority to approximately 50%.

To facilitate the analysis, a custom dataset extract was kindly provided by the NJR, summarising the number of primary hip replacements and hip revisions performed during the calendar year 2010 (Tab. III). This revealed that in 2010, 6,727 revision hip arthroplasties were performed in England and Wales, 1,871 (29.8%) of which used bone graft. There was considerable variation between the percentage of revision arthroplasties using bone graft amongst individual hospitals (Tab. II), ranging from 1.1% to 47.4% amongst those hospital trusts performing the most hip revision procedures. If, to take the highest demand scenario, we assume that the potential demand for bone allograft is equal to that hospital trust utilising the highest percentage of bone graft in hip revision, and that every revision arthroplasty utilises allograft rather than autograft or synthetic bone substitute, we can estimate the total demand for bone graft, in hip revision, to be 7,749 femoral heads per annum. We also know from the NJR data that over this same period, 70,669 primary hip replacements were performed. In our experience, a proportion of these femoral heads will not be suitable or available for donation, principally due to the donors not meeting our medical acceptance criteria for bone donation: we find that approximately 35% of potential donors fall into this category. However, this still leaves a donor pool of up to 45,934 grafts per annum, six times our 'worst case' clinical demand assumption.

The limits of this very basic estimation must be acknowledged; we have only considered one potential use of bone allograft, that of hip revision, and not others such as knee revision, or spinal fusion. However, we can state with confidence that all other uses of femoral head allograft put

TABLE III - UK HOSPITAL TRUSTS PERFORMING MOST HIP REVISIONS, AND PERCENTAGE USING BONE GRAFT (2010 DATA)

Name of trust	No. hip revision procedures	No. using bone graft	% using bone graft
Wrightington Wigan And Leigh NHS Foundation Trust	231	91	39.4
Nuffield Orthopaedic Centre NHS Trust	226	97	42.9
Robert Jones And Agnes Hunt Orthopaedic And District Hospital NHS Trust	205	61	29.8
The Royal Orthopaedic Hospital NHS Foundation Trust	194	40	20.6
North Bristol NHS Trust	185	74	40
Norfolk And Norwich University Hospitals NHS Foundation Trust	135	50	37
Sheffield Teaching Hospitals NHS Foundation Trust	127	31	24.4
East Kent Hospitals University NHS Foundation Trust	125	12	9.6
Nottingham University Hospitals NHS Trust	114	35	30.7
Cardiff and Vale University Local Health Board	112	33	29.5
Abertawe Bro Morgannwg University Local Health Board	102	7	6.9
North Tees And Hartlepool NHS Foundation Trust	99	21	21.4
Taunton And Somerset NHS Foundation Trust	98	13	13.3
Royal Devon And Exeter NHS Foundation Trust	97	10	10.3
Royal National Orthopaedic Hospital NHS Trust	94	1	1.1
Northumbria Healthcare NHS Foundation Trust	81	15	18.5
Aneurin Bevan Local Health Board	78	15	19.2
York Teaching Hospital NHS Foundation Trust	78	37	47.4
Gloucestershire Hospitals NHS Foundation Trust	77	24	31.2
East Sussex Hospitals NHS Trust	75	15	20

together only amount to a small proportion of that used for hip revision. We have also based our estimation of clinical demand on the top end of the usage scale, a hospital trust that uses bone allograft in 47.4% of its hip revision procedures. This is far higher than the average percentage use, 29.8%. However, even accounting for these, there is obviously a large excess potential supply of bone available. Presently, bone may be banked either by the trust themselves, regional banks collecting bone from more than one local hospital, or by NHSBT's national banking service. The total number of femoral heads banked by these three sources is only a fraction of the potential amount available; for example, over the time period in question NHSBT banked 4,083 femoral heads. The number of femoral heads banked elsewhere is not known, but is unlikely to be more than a fraction of that banked by NHSBT. One factor which renders it difficult for individual hospitals to establish a bone banking programme is regulatory requirement imposed by the Human Tissue Authority. There is a financial burden due to the cost of the licence itself, plus human resource commit-

TABLE IV - NUMBER OF FEMORAL HEADS BANKED AND ISSUED ANNUALLY, 2007-2011 (NHSBT)

Year	No. grafts banked	No. grafts issued
2007	3,313	3,038
2008	2,761	2,876
2009	2,806	2,243
2010	4,083	2,697
2011	4,410	2,642

ments required to meet the requirements of the licence and inspections. Participating in NHSBT's banking service has the advantage of NHSBT assuming responsibility for these issues, and providing participating hospitals with satellite site licences and staff training permitting them to collect femoral heads for NHSBT's centralised banking service.

Table IV summarises the collection and provision of femoral head allografts from living donors by NHSBT during the calendar years 2007 to 2011. Between 2007 to 2009,

clinical demand closely approximated the number of grafts available, and may in reality have been restricted by limited availability. It was common during this period for there to be a short waiting list for grafts, and this may have contributed to the perception amongst surgeons that there was limited availability. This was addressed through improving the efficiency of NHSBTs collection services, by concentrating resources in hospitals with the potential to donate large numbers of femoral heads, and improving the efficiency of collection therein, and closing down donation programmes in smaller donation centres. This resulted in a significant increase in the number of grafts banked, and in 2010 and 2011 the number of grafts banked greatly exceeded the number of grafts supplied. This has enabled the implementation of a stock management system to more closely match banking to clinical requirement. However, should clinical requirements increase, the number of collection sites can easily be increased through the provision of satellite licences and training of hospital staff in the correct protocols and procedures for the collection of bone grafts.

DISCUSSION

This purpose of this paper is to address two concerns commonly expressed by surgeons regarding the provision of bone allograft. Firstly, we have discussed the risk of disease transmission via bone allograft, and the precautions in place to prevent this happening. While bone allograft (or any other form of allograft) can never be stated to be 100% safe, the risks of disease transmission are extremely low; indeed, there has never been a recorded case of disease transmission from a bone allograft in the UK. Surgeons will often ask for a precise assessment of risk, even if it is

very low, in terms that they can express to patients. This is of course difficult to provide for an event that has never occurred. However, based on surveillance data from the screening of living bone donors (11), it has been calculated that the residual risk of transmitting Hepatitis B or C through a bone graft after donor selection and screening is less than 1 in 2.3 million; at current rates of bone graft use, this equates to one potential transmission every 500 years. Secondly, we have addressed the perception that bone allograft is limited in supply, and have established not only that there is more than enough allograft currently available to meet clinical requirements, but also there is a large additional supply of allograft that is not currently banked, but could be if clinical requirement were to increase.

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