LIVER ADVISORY GROUP

Items relating to machine perfusion of the liver

Four separate topics relating to machine perfusion have been discussed by a group comprising the clinicians at each liver centre involved in machine perfusion, who in turn have been encouraged to discuss and achieve consensus within their centres.

1 Blood for machine perfusion

Current normothermic perfusion devices require third party blood as an oxygen carrier when used according to their CE license. Increasing use of third-party donor blood has led to increased awareness by transfusion colleagues who have identified the need for protocols to enable tracing of blood products that are used as well as ensuring safe transfusion practice.

1.1 Crossmatching of blood

Blood matched at the donor hospital for the purposes of normothermic regional perfusion (NRP) or normothermic machine perfusion (NMP) starting at the donor hospital can use an existing donor blood sample for typing. The transfusion laboratory has the appropriate information and samples from the donor to undertake this.

Due to the absence of a donor blood sample at the recipient centre, and given that the donor is not on the recipient hospital system, standard laboratory practice cannot be followed. While it is possible to use group O RhD negative blood for perfusions, this is not in abundant supply.

1.2 Rh matching and anti-D

Organs do not express antigens of the Rhesus blood group system. However, if a RhD negative organ is perfused with RhD positive blood, and subsequently transplanted into a Rh negative female of child bearing potential, she runs the risks of developing antibodies as a result of RhD pos passenger red cells within the liver, putting future pregnancies at risk of haemolytic diseases of the foetus/new born.

1.3 Administration

The requirements for pre-transfusion identity checks of the blood product and liver need to be established, given the donor liver does not have an identity band.

1.4 Tracing of blood products

All documentation regarding blood transfusion should be completed as part of the organ donor's records for all organs transplanted. The fate of the units used for perfusion should be documented in the 'Organ Transplant' or 'Unknown' patient record on the hospital transfusion laboratory information management system (LIMS), regardless of whether the organ has been transplanted or not. This will facilitate tracing the fate of products should there be an alert in future. Moving livers from the site of crossmatch to a different recipient centre poses increased challenges.

1.5 Summary

A draft document has been produced, reviewed, and is currently out for further review with the blood service who need to standardise their approach.

2 Outcome measures for machine perfusion

2.1 Background

The UK Transplant Registry records different datasets for different organ types, including information relating to early graft function. The liver dataset is devoid of any data relating to early graft function, in contrast to other datasets.

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The introduction of new technology demands an early indication of safety and efficacy, but the best metrics in the UKT dataset at present are crude graft and patient survival at 3 and 12 months, together with pretransplant metrics predicting donor quality such as donor type (DCD or DBD) and age.

2.2 Possible metrics

There are two widely used measures of early allograft function which provide some correlation to graft outcome in livers subject to static cold storage, together with a third new metric which is more accurate. They are as follows:

2.2.1 Olthoff et al. Early Allograft Dysfunction. Liver Transplantation 2010;16:943

Early allograft dysfunction is defined as the presence of one or more of the following:

- Peak ALT or AST >2000iu/L on days 1 to 7 post transplant
- bilirubin > 171 mmol/L (10mg/dL) on day 7
- INR ≥1.6 on day 7

2.2.2 Pareja et al. Model for Early Allograft Function score (MEAF). Liver Tx 2015;21:38

The MEAF score is a score from 0 to 10, where 10 is the worst, and hence allows for a continuous grading of dysfunction in contrast to the dichotomous Olthoff criteria. Also in contrast to Olthoff et al, it only requires data from the first 3 days

- Peak ALT days 1 to 3
- Peak INR days 1 to 3
- Bilirubin day 3

MEAF = ("score ALT" + "score INR" + "score bilirubin"), where "score ALT" = 3.29/(1 + e−1.9132(ln(ALTmax.3days) -6.1723), "score INR" = 3.29/(1+e−6.8204(ln(INRmax.3days)−0.6658),"score bilirubin"=3.4/(1 + e−1.8005(ln(bilirubinday3)-1.0607)

It has been separately validated on a cohort of livers in Leuven (Transplantation 2017;101:e258) and in DCD livers in Cambridge.

2.2.3 Agopian et al. L-GrAFT score. JAMA Surgery 2018;153:436

More complex, using data from the first 10 days, although a 7 day version exists. Developed from 2021 patients at Dumont-UCLA as a predictor of 3 month graft failure.
Data requirements are daily values of the following variables up to and including day 7

- AST
- Platelets
- Bilirubin
- INR – maximum in first 10 (7) days

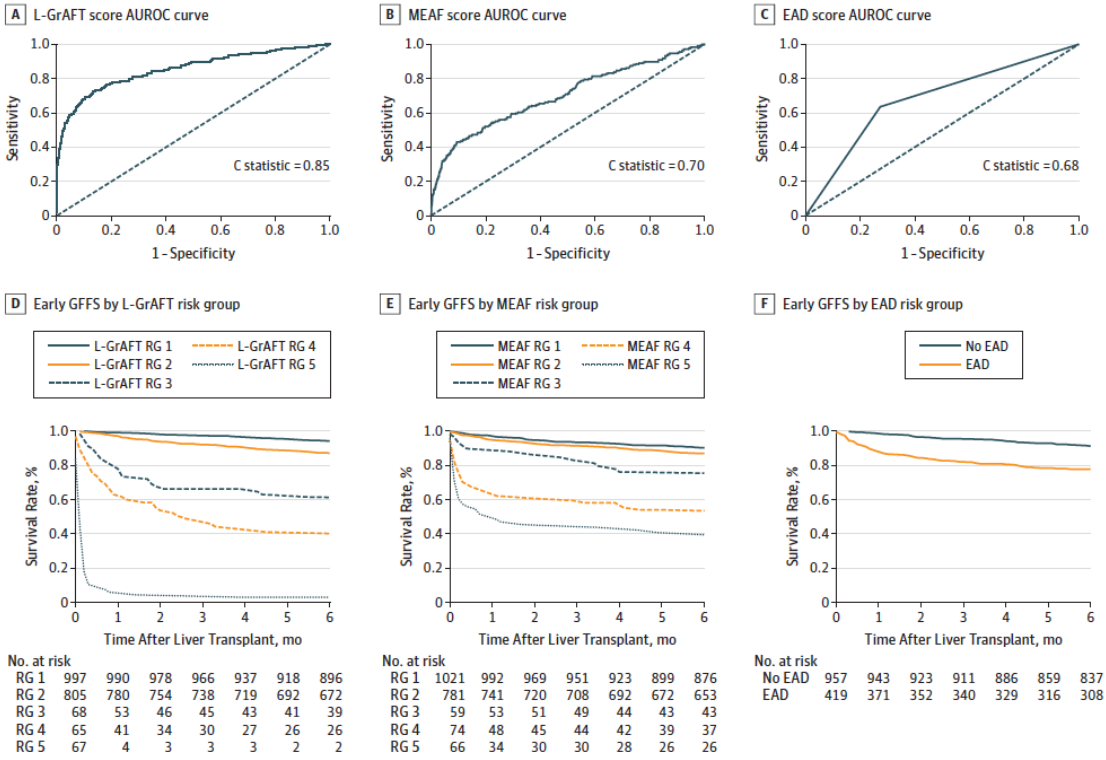
Equation: risk score = 11.27 – 0.429 x (AUClogAST) + 0.005 x (AUClogAST2) + 4.607 x (early slope log AST) + 4.413 x (early slope log AST2) + 0.890 x (log max INR − 0.049 x (AUC log TBIL) + 0.004 x (AUC log TBIL2) + 5.336 x (slope log TBIL) − 0.046 x (AUC log PLT) − 5.249 x (slope log PLT) + 13.086 x (slope log PLT2), where TBIL stands for total bilirubin and PLT stands for platelets

2.3 Comparisons of scores

Agopian's paper compares the c-statistic of each score for predicting 3 month graft survival:

L-GrAFT 10-day equation: c-statistic 0.84
L-GrAFT 7-day equation: 0.83
Pareja MEAF: 0.7
Olthoff EAD: 0.68
BAR score for 3-month patient survival: 0.7
SOFT score for 3-month patient survival: 0.7

Figure 2. Comparison of Model Accuracies as Measured by the Area Under the Receiver Operating Characteristic (AUROC) Curve Among 3 Models of Early Allograft Dysfunction



The Liver Graft Assessment Following Transplantation (L-GrAFT) score (A; C statistic, 0.85) had the highest AUROC statistically significantly superior to both the Model for Early Allograft Function (MEAF) score (B; C statistic, 0.70; $P < .001$) and the early allograft dysfunction (EAD) score (C; C statistic, 0.68; $P < .001$). The L-GrAFT model allowed for greater discrimination of 3-month graft-failure risk (D) compared with the MEAF score (E) and the binary EAD definition (F). Five risk groups (RGs) for 3-month graft failure for both L-GrAFT and MEAF were defined on the basis of risk score distribution, including (1) very low risk (≤50th percentile), (2) low risk (>50th to ≤90th percentile), (3) moderate risk (>90th to ≤93.3 percentile), (4) moderate-to-high risk (>93.3 to ≤96.6 percentile), and (5) high risk (>96.6 percentile). GFFS indicates graft failure–free survival.

2.4 Caveat

One of the caveats in any current predictive score is that none have been validated with livers undergoing MP. The transaminase levels may be artificially lowered during MP (but not NRP) by virtue of a washout phenomenon.

2.5 Proposal

There is a benefit in using a graded measure. The Agopian et al L-GrAFT score seems to be the ideal measure. The centre representatives recommend that NHSBT should start collecting the necessary data to calculate the 7-day L-GrAFT score. Given the large amount of data this involves it has been suggested that this is done for a trial period of 6 months and then data completeness is assessed.

It is possible that NHSBT will be able to refine the equation as UK data are accrued, especially with respect to DCD livers and machine perfused livers.

3 Machine perfusion parameters to be recorded by NHSBT

Given the novelty of machine perfusion, and following the recommendations of NICE for the "*Ex situ* machine perfusion for extracorporeal preservation of livers for transplantation (IPG636)", it is desirable to keep not only a national record of which livers underwent MP by NHSBT (a specific NICE requirement), but also identify selected machine perfusion parameters to enable audit and determination of factors predicting good and poor outcomes.

3.1 Factors thought to predict viability

Current suggestions for factors that predict liver viability during normothermic perfusion from the literature (mainly Birmingham, Cambridge, Groningen and Toronto) include:

a) Parenchymal viability

- Rate of fall of lactate
- Lactate concentration at 3 hours
- Falling glucose
- pH >7.2 or 7.3
- Ability to maintain pH
- Bile production
- ALT at 2 hours
- Appearance of liver

b) Cholangiocyte viability

- Bile pH
- Bile glucose
- Ratio of bile pH to perfusate pH
- Ratio of bile glucose to perfusate glucose

3.2 Minimal dataset

The perfusion group agreed that a minimal dataset which would ideally be stored at NHSBT should include

- Liver weight post benchwork before cannulation
- Lactate fall in first hour (or between 15 & 60 mins)
- Total amount (mmol) of bicarb given in first 4 hours to achieve a pH>7.2
- Perfusate ALT at 2 and 4 hours
- Bile volume in first 4 hours
- Bile and perfusate pH and glucose at 2 and 4 hours

4 Moving livers that are undergoing perfusion from one centre to another

4.1 Background

Current practice is to place a liver on a machine at the receiving centre, and then assess viability. It may become necessary to decline the liver during perfusion due to recipient, logistical or donor liver reasons, with the liver then being fast tracked and accepted by another centre. The question then arises as to how to transport the liver, with several options:

a) The liver is moved on the machine, assuming the machine is portable
b) The liver is removed from the machine and placed on ice for transport

There are problems associated with each of (a) and (b): the liver may be steatotic so cooling would be counterproductive; one centre would lose its machine to another for an undetermined period; transporting a liver on a machine would need an escort (recommendation from OrganOx); and so on.
It is noteworthy that no centre owns its machine; they are all on loan from OrganOx.

4.2 Offering of livers: to fast track or not

Given the liver is on a machine, and thus time is no longer critical, one question that arises is whether the liver on the machine should be fast-tracked, or offered as part of the NLOS. This may depend as to whether it is turned down on account of recipient/logistical reasons or donor reasons. There are arguments in favour of keeping the liver local for allocation to another patient (logistically easier but open to gaming the NLOS).

Suggestion, to be discussed:

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The group recommended the liver should be offered by the fast track scheme, but felt it worthy of discussion at LAG.

4.3 Several solutions were discussed

Four proposals were presented with two additional suggestions made:

1. Centre A sends, with their perfusionist/fellow, and brings back centre Bs machine
2. Centre B fetches, taking their machine to centre A, and bringing back A's machine with the liver on it
3. Centre A sends, and OrganOx replace A; centre B returns machine to OrganOx. Centres would have to fund OrganOx to have 2 rental machines free to enable this.
4. Centre B fetches, and OrganOx replaces A's machine

Additional suggestions at meeting:

5. Centre A sends and waits till B finishes with A's machine and then gets "their own" machine back
6. OrganOx provides a service to move machines with one of their technicians

There was considerable discussion about this. The agreement, to be piloted for 6 months, was to follow option 2. The number of times this is likely to be necessary is not clear, with estimates ranging from twice a month to twice a year.

4.4 Items to accompany a liver

Whenever a liver was transferred an ice box should accompany the liver containing :

- The vessels from the same donor
- The sample of donor blood, lymph nodes and spleen
- The paperwork with the donor liver (HTA A form, retrieval data)
- A print out of results of biochemical parameters measured during perfusion

A standard dataset of information to be shared when offering a liver on was agreed to include:

- Lactate time points: 15, 60, 120 mins
- Glucose time points: 120, 240 mins + amount of supplementary glucose
- Bile production, volume at: ~ 4 hours
- Bicarbonate supplementation (mmol) between 15 and 240 mins to achieve target pH
- AST/ALT at 2 hours
- Bile pH & perfusate pH when measured
- Bile glucose & perfusate glucose when measured

4.5 Costs

The costs of moving a liver from centre A to centre B should be borne by centre B.
If the liver is transplanted centre B would reimburse centre A with one set of disposables (£4000).