Technical Issues
Haematopoietic Progenitor Cells-Apheresis (HPC-A) and Therapeutic T Cell (TC-T) Apheresis

Spectra Versus Optia

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Spectra versus Optia

We love COBE Spectra

We also love Spectra Optia

Big
Bulky
Old
Simple

Slim
Sleek
New
Clever
We all like to upgrade our phones to have the newest in technology. In some ways we could say the same applies to the machines we use for our procedures.

In the next few slides we will discuss the differences between Spectra and Optia, the pros and cons of each of the technologies and how best to optimise the collection of stem cells on each of these machines.
## Spectra versus Optia
### pros, cons and differences

<table>
<thead>
<tr>
<th>Spectra</th>
<th>Optia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong>&lt;br&gt;- 2 protocols &amp; 2 fillers&lt;br&gt;-AutoPBSC collection or MNC collection&lt;br&gt;-Single or dual stage channel&lt;br&gt;-Weight (177 kg)&lt;br&gt;-Computer - simple</td>
<td><strong>Design</strong> – 1 protocol &amp; 1 filler&lt;br&gt;-MNC collection&lt;br&gt;-Channel and Chamber&lt;br&gt;-Weight (92 kg)&lt;br&gt;-Computer – more complex but intuitive</td>
</tr>
<tr>
<td><strong>Functionally closed set</strong></td>
<td><strong>Functionally closed set</strong></td>
</tr>
<tr>
<td><strong>Manual colour coordination</strong> – Colourgram (Plasma Pump flow Rate, PPFR)</td>
<td><strong>Automated Interface Management system (AIM) and Collection Preference (CP) settings</strong></td>
</tr>
<tr>
<td><strong>Variable product volumes dependant on process chosen</strong></td>
<td><strong>Variable product volumes dependant on WBC and number of chambers collected</strong></td>
</tr>
<tr>
<td><strong>Collection efficiency versus purity</strong></td>
<td><strong>Collection efficiency and purity</strong></td>
</tr>
<tr>
<td><strong>Time. MNC shorter than AutoPBSC for 2 x TBV</strong></td>
<td><strong>Time. Longer than MNC but shorter than AutoPBSC</strong></td>
</tr>
</tbody>
</table>
Design

- Larger bulky machine
- Heavier more challenging to transport
- Removable IV pole challenging for transporting
- Optional seal safe system
- More complicated loading, issues with training and time
- Neat, compact takes up less space
- Great mobility, light
- Compact IV pole and screen for storage or travel
- Built in seal safe system
- Easy loading, compact cassette
Design

- Graphical User interface- GUI
- Intuitive Touch Screen
- Tabs and icons, similar to a PC with drop down menus and different ‘windows’

- Simple LED display
- Old fashioned technology
- Limited information
- Information hidden e.g. AC infusion rate
Plasma Pump Flow Rate, the AIM System and Collection Preference

- **Spectra**
- Interface position is operator dependant
- Manual manipulation of the Plasma Pump Flow Rate (PPFR) is required to achieve and maintain optimal collection from the buffy coat layer.

- **Optia**
- AIM – Automated Interface Management system
- Manages interface position automatically
- More precise
- Collection preference (CP) allows operator manipulation within buffy coat layer to achieve optimal collection.
Product Volumes and Cell Content

- **Spectra MNC**
  - Relatively large volume based on collect pump flow rate, AC infusion rate and length of procedure. (default collection 1ml/min)
  - Typically 150 – 250mls. Increased volume in large volume apheresis.
  - Red cell content dependant on haematocrit chosen using the colourgram

- **Spectra AutoPBSC**
  - Volume dependant on harvest and chase volume settings
  - Smaller volume, concentrated product 60 - 100mls (dependant on MNC percentage)
  - Purer product low granulocyte and red cell contamination

- **OptiaMNC**
  - Dependant on WBC count, in particular mononuclear and lymphocyte percentage
  - Dependant on number of collection phases
  - Variable from low product volume to large product volume 20 - 300mls
  - Relatively pure product low granulocyte and red cell contamination
Collection Efficiency*

- **Spectra MNC**
  - Reported as 40-52%\(^1\text{-}^3\)
- **Spectra AutoPBSC**
  - Reported as 30-40%\(^3\) – generally less than MNC Spectra\(^3\)
- **Optia MNC**
  - Reported as improved from both AutoPBSC and MNC processes on Spectra at 45-55%\(^1,^4\)

*“CE2” Collection efficiency i.e. based on pre-collection peripheral CD34+ count only

1. Reinhardt et al. Transfusion 2011; 51(6):1321-1330
3. Cooling et al. Transfusion 2010; 50:100-119
Length of Procedure

- **Spectra MNC**
  - Dependant on AC infusion rate and inlet rate
  - 2 x TBV takes approximately 3 hours

- **Spectra AutoPBSC**
  - Dependant on AC infusion rate and inlet rate (max recommended inlet rate 85ml/min)
  - Processing time ‘lost’ during harvest phase
  - 2 x TBV takes approximately 4 hours

- **Optia MNC**
  - Dependant on AC infusion rate and inlet rate
  - Processing time ‘lost’ during collection phase
  - Length of procedure variable dependant on number of collection phases which is not always apparent at the beginning of the procedure
  - 2 x TBV takes approximately 3.5 hours.
Optimising the Collection
General considerations

- Consider large volume apheresis to work towards achieving transplant dose. (e.g. 3 x TBV)
  - Extending your endpoint by increasing the length of the procedure, number of Total Blood Volumes (TBV) processed or number of harvest/collection phases
- Consider a high flow procedure by increasing the inlet flow rate to process more cells per minute
- Remember: Increasing the inlet flow rate increases the AC infusion rate to the patient
- Consider using IV calcium replacement i.e. gluconate or chloride
- Consider increasing the Inlet:AC ratio. This allows the processing of cells faster but with the same AC infusion rate to the patient (max recommended 15:1)
- Some centres may consider adding heparin to allow an increase in inlet flow but to maintain safe AC infusion rate
- Some centres may use heparin only. An appropriate anticoagulant should be added to the cells
Optimising the Collection
Spectra MNC

- Enter accurate patient Haematocrit to set interface establishment during quickstart.
- Monitor collect line using Cobe Spectra colourgram to maintain optimal interface position.
- Consider collecting at 3%-5% Haematocrit. This increases the MNC yield but may also increase RBC and granulocyte contamination.
- Choose an appropriate collect flow rate. (Default 1ml/min)
  - In paediatric procedures a lower collect flow rate may be appropriate.
  - With higher WBC counts >40 a higher collect flow rate may be appropriate (calculation tool available on TerumoBCT website).
Optimising the Collection
Optia MNC

Configuration

- Consider setting the value of the chamber chase to 4 mls. This maximises clearing of the cells between the chamber and the collect valve into the bag (improves efficiency/increases product volume)
- Choose ratio ramping. Starts at 8:1 and quickly ramps up to your pre set value. This reduces risk of clotting at the collect port.

Data Entry

- Accurate WBC, platelets and Haematocrit
- Update all above when available
- If updating count’s consider using calculation to set optimal Collection Preference
  
  $60 - \{(0.2 \times \text{WBC count}) + (0.08 \times \text{platelet count})\}$ rounded to nearest ‘10’
- This may be useful in some centres for 2\textsuperscript{nd} day collections, allogeneic donors, plerixafor collections
Optimising the Collection
Optia MNC

Optimisation guide available from TerumoBCT (v. 7)
Optimising the Collection Optia MNC

- The v7 TerumoBCT guidance document has become less prescriptive but also less specific.
- Guides our thoughts as to what to expect during an Optia procedure for example;
  - Chamber takes longer to fill the first time
  - Pump pauses and alarms will cause the system to repeatedly re-establish the interface and lengthen chamber fill time
  - Consider the patient’s lymphocytes and monocytes in relation to how quickly or slowly the chamber fills
consideration of colour of the collection. (Too dark, too light.) What will influence this? e.g. peripheral WBC count

- Consider use of Inlet Volume control for subsequent chambers if the RBC detector is not being triggered and cells are potentially being lost into the reservoir
  - for example the alarm ‘cells are exiting the chamber too soon’
- Only collect a chamber when it is full.
Optimising the Collection
Venous Access

- Preparation - early assessment of venous access.
  (If possible by an apheresis operator)
- Assess peripheral venous access to decide if it is adequate
- Identify if placement of central access is required
- Assess central access to see if flow is sufficient, if catheter requires thrombolytic agent or possible replacement
- Choice may be to place a temporary apheresis/dialysis type catheter. Ensure this is arranged in a timely manner
Optimising the Collection
Venous Access - A stable interface

- Good peripheral or central access are required to ensure a stable interface position.
- The aim for both machines is to have minimal interruptions.
- For both machines each time the procedure is paused the interface is interrupted.
- **Spectra** - operator change to the PPFR may be required to re-establish the optimal interface position.
- **Optia** - the AIM system will re-establish the interface position however each time the procedure is stopped it will go back to ‘re-establishing interface’ mode and will be collecting at a collection preference of 80 during that period.
- For both machines interruptions mean collection efficiency is compromised.
Good peripheral or central access are required to allow adequate inlet and return flow

- Essential if considering a high flow procedure

- Essential if the patient is poorly mobilised with a low CD34 count and you are aiming to maximise the procedure

- Good continual flow will prevent clotting. Continual access flow problems may activate platelets, initiate the clotting cascade and encourage the formation of clots at the collect port

- Good access reduces time required for operator intervention
Optimising the Collection
Venous Access - Choice

- **Peripheral access**
  - Large gauge cannula or fistula needle.
  - 17 gauge steel needle. Already attached to the functionally closed set (Spectra and Optia)
  - Supercath type needles, plastic with additional holes along the sheath for improved flow
  - Return can be a smaller bore cannula but sufficient for uninterrupted return flow.
Optimising the Collection
Venous Access - Choice

- Central Access
  - Consider using tunnelled line if already in situ (for access or return)
  - Consider insertion of tunnelled line for collection if transplant is imminent
  - Consider insertion of temporary apheresis line
  - Consider using a ‘reverse Y connector’ to draw from both sides of central access to improve flow
Plerixafor

- Highly effective at minimising failed Autologous PBSC mobilisation
- Increasingly used internationally for poorly mobilised patients.
- Planned or immediate rescue/preemptive use
- Pre agreed written protocols are effective
Plerixafor Collection Considerations

- Now aiming for minimum transplant dose but higher doses may be possible
- Consider collecting the patients stem cells 11 hours post Plerixafor without waiting for a CD34 count.
- Emerging evidence to suggest Plerixafor given early evening with up to 15 hours before collection is still effective and less disrupting for the patient:\n  Randomised Clinical Trial currently open in USA looking at 6 p.m. versus 11 p.m. administration\(^1\)
- Consider a large volume apheresis to work towards achieving transplant dose (3xTBV)
- Ensure good venous access
- Consider if a second dose of Plerixafor is required or if G-CSF alone may be enough to maintain CD34 count


2. Emory University, USA study “WCI1680-09: Evaluation of Alterations in Time of Administration of Plerixafor (Mozobil ®, AMD3100) in Combination With G-CSF on Safety and CD34+ Cell Mobilization” (sponsored by Sanofi) - ClinicalTrials.gov Identifier: NCT01149863
Plerixafor and Optia Collection Considerations

- Using Plerixafor means collecting with a high WBC count.
- This is particularly true for Plerixafor plus G-CSF alone mobilisation.

- Spectra MNC - PBSC collected with a high WCC means the product is more cellular leading to high cryopreservation volumes and more DMSO.

- Optia – collects a purer product and eliminates problematic high cryopreservation volumes seen with Spectra collections with high WBC counts. This is particularly useful for Plerixafor collections.

- Purity is good:
  - 0.7-2.3% Haematocrit *
  - With plerixafor < Total Nucleated Count (TNC) in the bag, this
    - Less dilution
    - Less bags needed for dilution reduces time for processing
    - Less space used in the freezer
    - Less DMSO back to the patient

*local figures Glasgow collections
Donor Lymphocyte collection TC-T
Procedural Considerations - Optia

- Generally 2 x TBV processed should be sufficient for escalating DLI doses
- MNC guidance for Optimisation should be followed
- Accurate WBC, Platelet count and Haematocrit required
- The collection preference will default according to the data input.
- For non mobilised donors such as lymphocyte donors the mononuclear cell count is low and so the chambers, particularly the first chamber, may take longer to fill. For example 3-4 litres inlet volume
- Only initiate a collection phase when the chamber is full!
ECP
UVAR XTS and CELLEX

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Ammi-majus (Bishops weed)

Ancient Egyptians recognised the medicinal properties of the weed when activated by sunlight

Lerner et al (1953) demonstrated that 8-mop (methoxypsoralen) becomes a photosensitiser when exposed to ultraviolet light
History of photopheresis

- 1987 Therakos UVAR 1st photopheresis system
- 1998 Therakos UVAR XTS 2nd generation
- 2009 Therakos CELLEX 3rd generation

UVAR XTS and CELLEX which are now in use are known as closed or on-line systems
ECP is a treatment associated with virtually no systemic immunosuppressive effect.

Initially developed for treatment of cutaneous T-cell lymphomas (CTCL; mycosis fungoides/Sézary syndrome), but nowadays over half of patients treated worldwide have chronic Graft versus Host Disease after Bone Marrow or Stem Cell transplant.
Extracorporeal photopheresis: how does it work?

- The UVAR XTS machine or Cellex (Therakos) incorporates both a cell separator and an Ultraviolet (UV) light source.
- The cell separator draws blood from patient & separates off the mononuclear cell layer (lymphocytes plus monocytes) by centrifugation.
- 8-methoxypsoralen is added to the completed collection, & the cells are then exposed to UV light and re-infused.
- Re-infused apoptotic T lymphocytes “trigger” the immune system to suppress T-cell-mediated conditions like GvHD, probably via dendritic cells.
UVAR XTS
Photopheresis system

- Single unit system known as closed or on-line
- Combines a medical device with a drug treatment
- Requires manual calculation of drug dose
- Fairly large extracorporeal blood volume
- Fluid logic module
- Approximately 3-4 hour treatment time
- Manual residual blood return option
CELLEX
Photopheresis System

- Single, integrated closed or ‘on line’ system
- Reduced extracorporeal volume compared to UVAR XTS
- Suitable for paediatrics
- Significantly shorter treatment times (approximately 1.5 hours)
- System calculates drug dose
- Single or double needle configuration options
  - Double needle can again reduce treatment time
- Integrated blood return
## Comparison

<table>
<thead>
<tr>
<th>UVAR XTS</th>
<th>CELLEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal photoactivation chamber</td>
<td>Vertical photoactivation chamber</td>
</tr>
<tr>
<td>Recirculation bag latex injection port</td>
<td>Needle and latex free injection port</td>
</tr>
<tr>
<td>Latham bowl two sizes</td>
<td>Custom made single bowl</td>
</tr>
<tr>
<td>Data key</td>
<td>Smart card</td>
</tr>
<tr>
<td>Limited fluid management system</td>
<td>Sophisticated fluid system controlled by microprocessors</td>
</tr>
<tr>
<td>Not a true touch screen</td>
<td>True touch screen</td>
</tr>
<tr>
<td>Schematics do not match to actual system status</td>
<td>Schematics represent actual status of system</td>
</tr>
<tr>
<td>All alarms management from UVAR XTS manual</td>
<td>Some “simple” alarms management given on screen</td>
</tr>
</tbody>
</table>
Issues UVAR XTS

- Has a fairly large extracorporeal volume
- Single needle only procedures
- Manual blood return option
- Unable to use this machine for children
- Close monitoring required of all buffy coat cycles as the operator may need to end cycle appropriately
- Close monitoring of final buffy coat cycle is required. Operator should aim for 3 x 2-minute pauses at spaced out intervals. This helps pack the cells together before the final buffy coat is collected
- Reasonable amount of operator intervention
Issues CELLEX

- Return pressure alarm on single needle mode
  - Lower return pressure limit to -100mmHg at the beginning of the procedure
  - Close monitoring of cycles
  - Manipulation of the return bag when each return cycle starts may prevent this alarm
  - Patience may be required
- Red blood cell pump alarm
  - Due to poor access – slow flow rates
  - Abnormal erythrocyte morphology combined with high flow rates
  - Interface too high – adjust optic sensor
  - Refer to technical bulletins as directed
- System pressure alarms
  - Differing solutions – complicated
  - Refer to technical bulletins as directed
- Central or peripheral access choice
Single point of access in an antecubital vein may be available for some patients and this will be suitable for the UVAR XTS procedure and the single needle option on Cellex.

Two points of access may be available for a fewer number of patients to allow use of the double needle option on Cellex.

Appropriate access needles similar to previously discussed for MNC collection can be used.
Patients with Sezary syndrome may have adequate venous access but often patients post allogenic transplant with acute or chronic GvHD have poor veins.

Hickman lines can be a longer term option. However we know these carry a significant infective risk which may be even more troublesome for someone with GvHD of the skin.

Some patients may also identify having a Hickman line re-inserted as a backwards step.

A Hickman line may impair quality of life for example body image, exercising or swimming.

Port-a-Caths are not a suitable option for apheresis due to the high flow rates required.

- The needles used in conventional ports are too narrow.
- High flow rates can cause damage to the port.
- The higher flows needed for successful apheresis cannot be achieved.
Vortex ports

- Vortex ports have been used in North America for almost 12 years\(^1,2\).
- Used successfully for paediatric sickle cell patients requiring Red Blood Cell Exchange (RBCX) and photopheresis patients among others.
- Useful for patients with venous access problems who may be at increased risk of infection with cuffed and tunnelled central catheters.
- Completely concealed under the skin, so lifestyle need not be affected.
- Vortex ports have now been marketed in the UK for a few years with increasing use.

Vortex ports

- Single port which can be either plastic or titanium
- Useful for single needle procedures

www.angiodynamics.com
Vortex ports

- Double port which can be either plastic or titanium

- Useful for double needle/continuous flow procedures

www.angiodynamics.com
Vortex ports

- Round chamber design allows fluid to reach all surfaces in the chamber
- This helps to eliminate dead space and resist sludge build-up
- Reduces risk of occlusion and infection
To achieve adequate flow rates for apheresis, Vortex ports require access by a large bore non-coring needles.

Using a needle without a special non-coring tip will damage the port by making a hole in the membrane. This can cause haematoma around the port, clotting-off of the port chamber and increased risk of infection.

A damaged port generally cannot be used and needs to be replaced.
Challenges of using vortex ports

- Insertion
  - Internal jugular method recommended
- Flow rates and occlusion
  - Challenges withdrawing blood if port had not been used for some time
  - Access pressure alarms caused by clotting during the procedures and need to flush the ports
  - Identify the most appropriate locking dose of heparin (for example 2000 iu/5mls)
  - Consider giving patients a heparin bolus

- **Most Important** – consider using urokinase or another thrombolytic
  - Consider instilling this the evening before procedure or 1 hour before procedure
  - Consider instilling this when having flow challenges during a procedure

- Using urokinase transformed our experience in using Vortex Ports successfully

- Challenges in correct positioning of large bore needle
  - Training and practice
Vortex Ports are a viable venous access option in this difficult patient group.

There is a learning curve both for clinicians carrying out port insertion and for nurses accessing the ports.

In our experience, where possible port insertion by interventional radiologists has been preferable to insertion by vascular surgeons, due to the advantage of X-ray screening in patients with “difficult” central venous access due to multiple previous lines.

Urokinase the day before each procedure has allowed increased success in completing apheresis procedures.

In addition, pausing the procedure and instilling urokinase for an hour can aid completion of a troublesome procedure when there are flow problems.
In summary

✍ Apheresis and ECP are changing globally
✍ ‘Sunset’ for the Spectra in the UK is here
✍ New machines are more technologically advanced and have sophisticated software.
✍ Operators must step up to the mark and embrace these new systems
BE BRAVE
Acknowledgments

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