ACUTE LIVER FAILURE IN DCCM - STANDARD OPERATING PROCEDURE

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1. Purpose of Standard Operating Procedure

This guideline describes this expected management of adult patients in DCCM who have acute liver failure or primary graft non-function within Auckland District Health Board (ADHB).

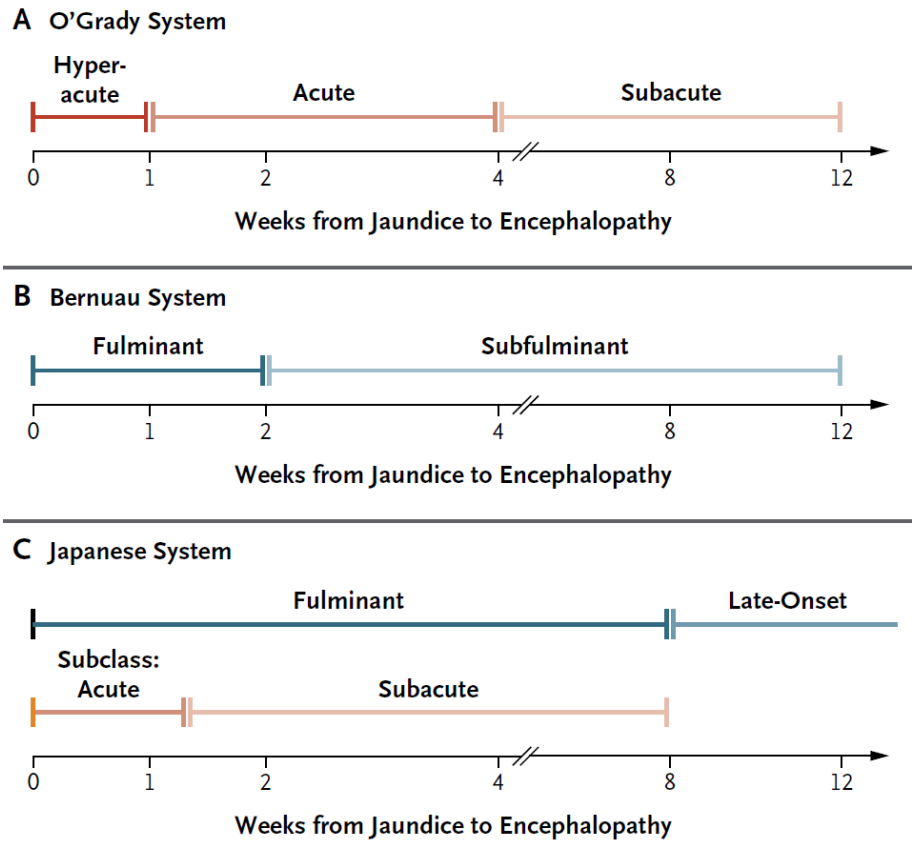
It should be read in conjunction with the more complete "Liver - Acute Liver Failure & Primary Non-Function (Adult)" guideline which is available on the ADHB intranet.

2. Terminology

2.1 Acute Liver Failure (ALF)

Acute liver failure refers to patients with encephalopathy (and other signs of liver failure) occurring within a short time of the onset of jaundice in a patient with previously normal liver function.

Figure 1. Classification Systems for Acute Liver Failure



Data are from O'Grady et al. Bernuau et al. and Mochida et al. In the Japanese system, the late-onset period is 8 to 24 weeks. (Bernal, 2013)

Table 1. Primary or secondary causes of ALF

Disease Group	Hepatic/primary ALF	Extrahepatic/secondary liver failure and AoCLF

Acute Liver Failure	• Drug related
	• Acute viral hepatitis
	• Toxin-induced ALF
	• Budd-Chiari syndrome
	• Autoimmune
	• Pregnancy related
		• Ischaemic hepatitis
		• Systemic diseases
		  ○ Haemophagocytic syndromes
		  ○ Metabolic disease
		  ○ Infiltrative disease
		  ○ Lymphoma
		  ○ Infections (e.g., malaria)

Chronic liver disease presenting with a phenotype of ALF	• Fulminant presentation of Wilson disease • Autoimmune liver disease • Budd-Chiari • HBV reactivation	• Liver resection for either secondary deposits or primary liver cancer • Alcoholic hepatitis

2.2 Primary Graft Non-Function (PNF)

Primary non-function (PNF) of a liver graft is a retrospective diagnosis for the clinical syndrome in which a newly transplanted liver does not function and there is no discernible cause. It occurs in around 5% of transplanted livers. Liver enzymes are markedly elevated, there is little or no bile output and encephalopathy, coagulopathy, renal failure and cerebral oedema develop. PNF is fatal without re-transplantation.

3. Management principles and goals

Patients who are expected to meet transplant criteria or develop grade I or II encephalopathy (Table 2) should be discussed with the NZLTU and consideration should be given to transfer for management and assessment for transplant. If transfer is deemed to be appropriate, then these transfers should be organised as soon as possible, as the patient's condition can deteriorate rapidly, potentially increasing the risk of inter-hospital transfers and decreasing the probability of transplantation occurring before irreversible deterioration precludes this.

Table 2. Modified Parsons-Smith scale of hepatic encephalopathy

Grade	Clinical features	Neurological signs	Glasgow Coma Scale
0	Normal	Only seen on neuro-psychomatric testing	15
1	Trivial lack of awareness, shortened attention span	Tremor, apraxia, incoordination	15
2	Lethargy, disorientation, personality change	Asterixis, ataxia, dysarthria	11-15
3	Confusion, somnolence to semi-stupor, responsive to stimuli	Asterixis, ataxia	8-11
4	Coma	+/- decerebration	<8

Table 3. King's College Criteria

Paracetamol induced liver failure	Non-paracetamol induced liver failure
Arterial pH <7.3 after adequate fluid resuscitation (regardless of hepatic encephalopathy grade)	PR > 6.5 (regardless of hepatic encephalopathy grade)
OR all 3 of the following on the same day • PR > 6.5 • Creatinine >300 µmol/l or dialysis • Hepatic encephalopathy (grade 3 or 4)	**OR** 3 of 5 of the following (regardless of hepatic encephalopathy grade) • Age <10 or >40 years • Etiology: indeterminate, drug-induced • Time interval jaundice to encephalopathy > 7 days • PR > 3.5 • Bilirubin >300 µmol/l

4. Referral of patients

Referral is usually received by the hepatologist, who will assess the following:

- Severity of both liver failure and extra hepatic organ failure
- Likely prognosis without liver transplantation
- Suitability as candidate for either emergency transplantation or aggressive medical management

If the patient is deemed suitable for transfer to the Auckland City Hospital then the hepatologist will discuss this case with the intensivist (or fellow) in the Department of Critical Care Medicine.

Further details regarding this process are available in the "Liver - Acute Liver Failure & Primary Non-Function (Adult)" guideline which is available on the ADHB intranet.

5. Management principles

Supportive care of the patient with acute liver failure involves standard care of the critically ill patient together with specific support of the failing liver. In particular this involves the avoidance of, and treatment when required, of hypoglycaemia, bleeding, infection, shock and intracranial hypertension. Usual supportive targets are described in the text below and summarised in Table 4. These targets may be altered for individual patients.

All medications that are potentially hepatotoxic should be stopped and all medications that require hepatic metabolism or clearance should be reviewed.

Table 4. Usual physiological targets in acute liver failure

Oxygen Saturation (SpO_2)	92 - 96%
$PaCO_2$	4.6 – 5.3 kPa (low normocarbia – for ventilated patients only)
Mean Arterial Blood Pressure	70 – 90 mmHg (higher target in suspected raised ICP)
Heart rate	60-100 beats/min
Serum sodium	140 – 150 mmol/L
Temperature	Normothermia unless elevated intracranial pressure
Coagulation	Avoid correction unless active bleeding or ICP monitor in place
Haemoglobin	70 - 100 g/L (haematocrit 0.21-0.30)
Platelets	≥ 30 x 10^9/L (higher for interventions or in the presence of ICP monitor)
Glucose	6.0 – 11 mmol/L

Table 5. Initial therapies in ALF

Proton Pump Inhibitor	Omeprazole 40mg IV q24h (because of higher risk of GI bleeding)
Antimicrobials	Not routinely indicated but low threshold for use (Section 5.10)
Nutrition	Enteral if tolerated (Section 5.11)
NAC infusion	6.25mg/kg/hr. Start as soon as practicable. (Section 6.1)
Vitamin K	10mg IV q24h, for 3 days (Section 6.2)
Folic acid	Give if platelets are less than 100 x 10^9/L. Give 5mg enterally q24h. If unable to tolerate enteral formulation then 5mg IV q24h. (Section 5.6)

5.1 Baseline investigations

These investigations are performed to guide supportive care and should be performed in all patients with acute liver failure (including those with PNF):

Table 6. Baseline investigations

Biochemistry	Glucose; sodium; potassium; chloride; phosphate; urea; creatinine; ammonia (send on ice); lactate; lipase; bilirubin; ALT; AST; GGT; ALP; albumin; calcium; magnesium; osmolality
Arterial blood gas	Arterial blood gas (ABG) with lactate
Haematology	Haemoglobin and blood film; white cell count and differential; platelets; haptoglobins; reticulocyte count
Coagulation	Prothrombin ratio; APTT; Factor V level; fibrinogen
Blood bank	Blood group and antibody screen
Bacterial cultures	Blood culture; urine culture; tracheal aspirate (if intubated). If ascites are present then culture of ascitic fluid should also be performed.
Other	Paracetamol level (on admission and after 6 hours); CMV and EBV serology (to determine risk of viral disease post transplant); pregnancy test (in patients of child bearing potential)

5.2 Assessment of aetiology

Aetiology is an important factor for guidance of further therapy and determines prognosis (2, 3). In addition to a thorough medical history and clinical examination, the below investigations can help diagnose the aetiology of acute liver failure (Table 7).

History will be almost always diagnostic for pregnancy-induced or drug or toxin-induced disease including fatty liver of pregnancy, paracetamol, some anti tuberculous medications, anaesthetic agents, HIV medications, tricyclics, anticonvulsants, antimicrobials, NSAIDS, amanita phalloides, 3,4-methylene dioxymethlyamphetamine (3,4-MDMA).

Lymphoma can present with hepatic infiltration and subsequent acute liver failure. As this would be a contraindication to transplant it is important to consider this condition particularly in patients with hepatomegaly and/or abnormal blood counts, with or without lymphadenopathy.

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It is a rare cause of acute liver failure. If suspected, a ferritin level and bone marrow aspirate may be indicated to aid in the diagnosis of HLH.

Liver biopsy is not used in acute liver failure to determine regeneration and prognosis. It is used in exceptional circumstances to aid in diagnosis, particularly to identify a treatable cause, and to exclude lymphoma.

Primary non function (PNF) is suspected when coagulopathy worsens or does not improve after transplant. Transaminases are markedly elevated and there is little or no bile production. Such patients will have urgent Doppler ultrasound of the hepatic artery and portal vein performed to exclude hepatic artery or portal venous thrombosis which, if present, should be treated by immediate re-vascularisation. PNF is confirmed by continuing failure of the graft on the second postoperative day without evident cause and should be treated by re-transplantation.

Table 7. Investigations for the assessment of aetiology in ALF

Toxicology	Urine toxicology screen; paracetamol level; creatinine kinase (CK) level (in selected patients with suspicion of heat stroke or 3, 4-MDMA toxicity)
Viral serology and markers	Anti HAV IgM; HBsAg; Anti-HBc IgM; Anti-HCV; Anti-HEV IgM; HSV1 IgM; HSV PCR; anti-VZV IgM; VZV PCR
Autoimmune markers	Anti-nuclear antibody (ANA); anti-smooth muscle antibody (ASMA); immunoglobulin levels
Biochemistry	Copper and caeruloplasmin level; ferritin
Radiological investigations	Imaging of the liver should be obtained to exclude veno-occlusive disease or malignancy. Depending on the condition of the patient and stability this can be done either by contrast enhanced CT Abdomen or ultrasound of liver including Doppler examination of hepatic veins (to exclude acute Budd-Chiari syndrome);
Other	Echocardiography may be useful to exclude significant pulmonary hypertension or structural heart disease. These would potentially be a contraindication to liver transplantation.

5.3 Instrumentation, lines, and monitoring

Usual monitoring and lines for all patients with acute liver failure in DCCM:include arterial line, arterial line, central venous line, urinary catheter, and nasogastric tube.

Endotracheal intubation — Indicated in patients with partial airway obstruction, impaired airway protection, respiratory failure or shock, but, most commonly,

	in this setting it is to allow safe management of patients with Grade III or IV encephalopathy and to facilitate safe instrumentation
Arterial line	All patients.
Central venous line	Central venous access should preferably be performed. Subclavian approach is relatively contraindicated due to the increased bleeding risk in these patients
Urinary catheter	All patients.
Nasogastric tube	All patients.

5.4 Circulation, fluids, and shock

Initial orders for maintenance fluid are for **10% glucose in water (G10W)** run at a rate of **1ml/kg/hr**.

Hypotension or shock should be treated with appropriate resuscitation fluid (blood products, isotonic crystalloids, or 4% albumin) while mean arterial pressure (MAP) is raised with inotropic support or vasopressors as a temporising measure. If blood products (red cells, fresh frozen plasma, platelets or cryoprecipitate) are indicated for other reasons, they should be given first. MAP should be maintained in the range of **70-90mmHg**.

Should hypotension (MAP<70mmHg) persist, further volume challenges should be repeated, if effective. Persistent hypotension should be treated with an infusion of vasopressors. Noradrenaline is the first choice for this indication.

If elevated intracranial pressure is suspected then the MAP target may be adjusted to target a MAP of **80 - 100mmHg**. The aim is to maintain a cerebral perfusion pressure of 60 – 80 mmHg and in the absence of ICP monitoring this MAP target will approximate this.

5.5 Hypertension

Hypertension (MAP>100) in the ventilated patient should be treated with increasing propofol infusion (up to 0.15mL/kg/hr) in the first instance, followed if necessary with opioid (fentanyl 10 – 20 micrograms as required). Hypertension which persists after sedation (or in un-intubated patients) should be investigated as to cause (intracranial hypertension or hypervolaemia). If intracranial hypertension is suspected the situation should be discussed with the NZLTU as to the appropriate MAP, the appropriateness of intracranial pressure monitoring and the timing of liver transplantation. Hypervolaemia should be treated with furosemide, in 10 - 20mg doses in patients who have normal serum creatinine. Patients with elevated serum creatinine should receive larger doses (40-80mg) and those receiving renal replacement therapy should have intensive ultra-filtration.

5.6 Blood products and coagulopathy

Haemoglobin should be maintained between 70 and 100 g/L in most patients (corresponding to a haematocrit of 0.21 – 0.30). This target may be adjusted by the treating intensivist if clinically indicated.

Use of blood products should be guided by the clinical situation (evidence of bleeding), and coagulation profiles. Because PR is used as a guide to liver synthetic function and as an important

predictor of transplant-free survival, replacement of coagulation factors is avoided in the absence of active bleeding.

Platelets will be given if required to maintain a platelet count above 30 x 10^9/L. For invasive procedures (e.g. line placement, paracentesis, chest drain insertion) a platelet count of >50 x 10^9/L is appropriate.

For insertion of ICP monitor a target of 100 x 10^9/L is appropriate. If the PR is markedly elevated then correction of PR to minimise procedural risks is appropriate. If there is uncertainty over the potential hyper or hypo coagulability of the patient then TEG is suggested prior to procedures, with targeted correction of coagulopathies if needed.

In active bleeding a platelet target of > 100 x 10^9/L is appropriate with correction of PR in addition to this.

The situation of combined thrombocytopaenia (e.g. <30 x 10^9/L) and marked elevation of PR (e.g. > 5) should be viewed with caution. Attention should be paid to scrupulous avoidance of hypertension and platelet transfusion should be given with consideration of partial correction of PR.

Prothrombinex® (Factors II, IX and X concentrate) may be considered if FFP is ineffective or when the risk of pulmonary or cerebral oedema limits the amount of FFP that can be safely given.

Factor rVIIa (40µg/kg) corrects coagulopathy efficiently for up to 2 hours. In a patient with coagulopathy persisting after the use of FFP and cryoprecipitate it should be given prior to very high risk invasive procedures including ICP monitor insertion. For other invasive procedures further FFP and cryoprecipitate may be used.

Patients with a platelet count of less than 100 x 10^9/L will receive folate supplementation. This will be given in the form of folic acid at a dose of 5mg q24h. If enteral medications and/or feeding are tolerated then this should be given enterally. If enteral medications are not tolerated then it may be given intravenously (5mg IV q24h).

Correction of coagulopathy prior to a decision to list for urgent liver transplant should be avoided if possible and used only in the presence of active bleeding, or if required to ensure the safety of an invasive procedure. Correction of coagulopathy should be partial and sparing so as to allow for assessment of the progress of the underlying liver disorder but should be sufficient so as to minimise the risk of life-threatening bleeding.

5.7 Sodium

Serum sodium should be targeted to 140 - 150 mmol/L in patients with acute liver failure. There is a correlation between serum sodium and ICP and a higher target may be indicated for the management of increased ICP. In the setting of raised ICP, a serum sodium target of 145 – 155mmol/L has been shown to decrease ICP (Murphy N, 2004).

5.8 Glucose and glycaemic control

Blood glucose should be measured every 2 hours in acute liver failure. This should be done with a blood glucose monitor if an ABG is not required at the same time. The blood glucose should be maintained between 8.0 – 11.1 mmol/L in most patients.

5.9 Neuro-protection

These measures should be initiated in any patient with hepatic encephalopathy who require airway protection and ventilation. These measures may also be indicated in other patients.

Standard neuro-protective measures:

- Maximum head up.
- Optimise venous return from brain (release any obstruction to venous outflow in the neck e.g. endotracheal tie).
- Ventilation to normocarbia ($PaCO_2$ 4.5-5.3kPa).
- Ensure adequate oxygen delivery.
- Maintain cerebral perfusion pressure (CPP) of 60-80mmHg. In the absence of ICP monitoring, a MAP target of 80-100mmHg will approximate this.
- Maintain sodium between 140-150 mmolL
- Treat any seizures
- Avoid hyperthermia.
- Maintain temperature at 36 degrees ± 1 °C.
- Use appropriate analgesia, sedation, and neuromuscular blockade to decrease cerebral metabolic rate.
- Minimise stimulation if possible (e.g. frequent suctioning, chest physiotherapy).

5.10 Antibiotic and antifungal use

Prophylactic antibiotics, non-absorbable antibiotics, and antifungal agents have not been shown to improve survival in ALF (Rolando N, 1993), however patients with ALF are at increased risk of developing infections, sepsis, and septic shock. Functional immunosuppression is common in patients with ALF (21) and severe sepsis is an independent risk factor for mortality (up to 60%) (22).

A low threshold should be applied for starting broad spectrum antibiotics. This includes patients who are significantly unwell on presentation and who are suspected to have sepsis, as well as the deteriorating patient in whom sepsis is a possible explanation for their deterioration.

Whilst fungal infections historically appeared in up to 30% of patients with acute hepatic failure, more recent data has shown a significant decline to about 4-14%. Given this decline, the need for antifungals should be decided on clinical probability and after discussion with the Intensive Care SMO, NZLTU SMO, and the infectious diseases team (23). If antifungals are being considered then biomarkers may be helpful to guide their use (Farmakiotis D, 2015).

5.11 Nutrition

Patients with minimal encephalopathy (drowsiness only) may take free oral nutrition and should be encouraged to do so. Alternatively, patients who do not eat may have a nasogastric tube placed if this is safe and nasogastric feeding then instituted with standard enteral nutrition formula, increasing to calculated goal rate as tolerated.

Intubated patients with be given nasogastric nutrition as above if tolerated. If impaired gastric emptying precludes gastric feeding a nasojejunal tube may be placed (if possible and with only one attempt) and feeding commenced at 20 mls/hour of standard nutrition formula, increasing to calculated goal rate as tolerated.

6. Specific treatments

6.1 N-Acetyl Cysteine (NAC)

All patients with acute liver failure and those with primary non-function should receive an **infusion** of N-acetyl cysteine (NAC). This has been shown to improve transplant free survival in several prospective studies (25-27). Because time to administration is closely related to outcome, it should be started as soon as practicable (28).

Patients who have acute liver failure after paracetamol ingestion should receive (if they have not already had) the standard dose of NAC for this poisoning, irrespective of the time since ingestion. In these patients continuous infusion of NAC should continue at the terminal rate in the poisoning guideline (6.25mg/kg/hour).

Patients without paracetamol poisoning should receive NAC at a continuous rate the same as that in the terminal treatment phase of paracetamol poisoning, i.e. 6.25mg/kg/hour (150mg/kg/24 hours). This treatment is stopped at the time of transfer to the operating room for OLT or when PR is improving and is less than 2.0 in the absence of exogenous blood product support in patients not transplanted.

6.2 Vitamin K

All patients with acute liver failure should receive Vitamin K 10mg by slow IV injection daily for three days. This is to minimise the potential for Vitamin K deficiency to contribute to any coagulopathies.

6.3 Specific treatments based on Aetiology

Any specific treatment (antivirals, steroids, D-penicillamine, etc.) should be only initiated after discussion with the duty intensivist and the hepatologist.

6.4 Plasma exchange

Plasma exchange has been described in the setting of acute liver failure. The indications and evidence for this therapy are currently evolving.

Plasma exchange in patients with ALF has been shown to decrease intracranial pressure in 2 case series (Clemmesen JO, 2001) (Clemmesen & Gerbes AL, 1999). One trial in 182 patients with ALF, undertaken over 12 years (Larsen FS, 2016), randomized patients to receive either standard medical therapy or plasma exchange for three days in addition to standard therapy. This study showed a mortality benefit for patients who did not proceed to liver transplantation but who did receive plasma exchange. Criticisms of this study include the long time taken for recruitment.

Overall there is an increasing body of evidence for this therapy although the indications for it remain unclear. It is not a routine therapy.

7. Intracranial pressure monitoring and intracranial hypertension

7.1 Indications for insertion of ICP monitor

Patients who are listed for liver transplantation and who are not accessible for neurological examination, will usually require an intracranial pressure monitor (Codman®) inserted prior to surgery, unless transplant is imminent.

An ICP monitor is useful to manage intracranial pressures in these patients preoperatively and may also be useful during the liver transplantation surgery when there are significant physiological changes with potentially detrimental effects on intracranial pressure.

7.2 Insertion of ICP monitor

In the Auckland District Health Board, ICP monitors are inserted by the neurosurgical service.

Coagulation should be completely corrected prior to insertion of an ICP monitor. Commonly used targets in this setting are an PR < 1.5, fibrinogen ≥ 1.0 g/L, and platelet count ≥ 100 x 10^9/L. Liaise with the neurosurgical service. Unfortunately in patients with ALF, standard coagulation measures do not provide an accurate measure of coagulation and therefore patients proceeding to ICP monitor should also have thromboelastographic assays (TEG), with correction of coagulopathy being guided by TEG as well as standard measures of coagulation.

This procedure is preferably undertaken in the operating room, by a senior member of staff. This should be performed under general anaesthesia which will be provided by the anaesthesia service in the operating room or the DCCM otherwise. Anaesthesia should include sedation, opioid, neuromuscular blockade and generous (10mL) local scalp infiltration (in the right frontal region) with lignocaine 1% with adrenaline.

A single prophylactic dose of IV cephazolin will be given immediately prior to scalp incision.

7.3 Correction of coagulopathy for ICP insertion and use of rFVIIa – a suggested approach

Targets: PR < 1.5, fibrinogen ≥ 1.0 g/L, and platelet count ≥ 100 x 10^9/L – note that target for PR may be lower depending on the proceduralist.

Table 8. Reversal of coagulopathy for ICP insertion in acute liver failure – initial therapy

If PR is > 1.5	Give 3 factor prothrombin complex concentrate (Prothrombinex®-VF) at a dose of 50 IU/kg **AND** give one unit of FFP.
If fibrinogen is < 1.0g/L	Give 3 units of cryoprecipitate.
Once other products are given	Give rFVIIa (40mcg/kg) **AND** if platelets are < 100 x 10^9/L, give 2 adult units of platelets (pooled units).
20 minutes after rFVIIa is given	Send repeat TEG, FBC, and coagulation screen.

- Give prothrombin complex concentrate and cryoprecipitate as soon as these are available. Ideally rFVIIa (40mcg/kg) and platelets are administered immediately prior to procedure and the procedure performed within the next 30 – 60 mins. This will mean that if the TEG is

satisfactory early on, then ideally the patient would be transferred to theatre at that point. The rest of the coagulation screen will become available during setup time in theatre.

- A second dose of rFVIIa (40mcg/kg) may be used if targets are not met with the initial dose. Other blood products may also be required and should be used as per the DCCM SMO instructions. A third dose of rFVIIa may be required in some cases however there is a risk of increased complications.

NOTES:

- In acute liver failure due to pregnancy and Budd-Chiari syndrome, rFVIIa is contraindicated.
- rFVIIa may increase thrombotic complications, especially after repeat dosing or higher doses (90mcg/kg).
- FFP is a potential alternative to Prothrombinex®-VF, however this will mean a larger volume of fluid is administered and there is evidence that it will take significantly longer to reverse coagulopathy without lowering the PR as much as the above strategy.

7.4 Specific care for patients with ICP monitors

Table 9. Additional care post ICP monitor insertion

Keep PR < 1.5	This may be accomplished with an **infusion of 100mls/hr of FFP** – adjusted to PR. Usual ranges for the FFP infusion are 50-200mls/hr.
Keep fibrinogen > 1.0 g/L	FFP infusion will likely achieve this however additional fibrinogen may be given in the form of cryoprecipitate as needed.
Keep platelets ≥ 50 x 10^9/L	Use platelet transfusions as necessary to achieve this.
Renal replacement therapy	If renal replacement has not yet been instituted then CVVHDF should be started now.
Monitoring of coagulopathy	Continue 6 hourly FBC and coagulation screen.

In patients with ICP monitors, the PR should be kept less than 1.5 and platelet count ≥ 50 x 10^9/L.

The correction of coagulopathy should continue as long as the ICP monitor is in place, **including** the post-operative period if the ICP monitor remains in place. In addition renal replacement therapy will usually be required at this point for both metabolic and fluid management

The ICP monitor will be removed when it is no longer necessary (prior to extubation); this is usually within the first 48 hours post-transplant. It may remain in situ for longer in patients with severe graft dysfunction (because of associated late intracranial hypertension).

Patients in whom the initial ICP is high (30mmHg or more) or in whom ICP rises to these levels within the first four hours after monitor insertion should have a repeat CT scan to establish whether monitor-related haemorrhage has occurred.

All patients with ICP monitors should receive low dose neuromuscular blockers, if required, to prevent coughing, straining and interference with ventilatory support, but not with the aim of producing complete neuromuscular blockade. Neuromuscular blockade may be withheld in patients who have received heavy sedation and who do not cough.

7.5 Management of raised intracranial pressure in the presence of ICP monitor

If ICP is below 20mmHg no specific therapy is given. Cerebral perfusion pressure is monitored and kept between 60 and 80mmHg with volume and the lowest necessary dose of noradrenaline.

ICP of above 20mmHg for more than five minutes will be investigated as to easily remediable causes (coughing, ventilatory interference, hypoxaemia, hypercarbia, kinking of cerebral venous drainage, arterial hypotension) which should be immediately corrected if present.

Persistent intracranial hypertension will be treated with further osmotherapy (4 molar saline, 1mmol Na^+/kg, given via central line lumen only over 20 minutes as long as serum osmolality is under 320mosm/kg) and mild hypothermia will be induced if not already present (core temperature 35-36°C initially, falling to 34-35°C if needed).

Persistent intracranial hypertension in patients who are both hyperosmolar (310-320) and hypothermic (34°C) will be treated with thiopentone infusion (initial bolus 5-10mg/kg, subsequent infusion rate 3-5mg/kg/hr). Thiopentone infusion will not be given longer than five days.

Temporary hyperventilation (PaCO2 30-35 mmHg) may be used for acute elevation of ICP until other measures (osmotherapy, diuresis or ultra-filtration) have been instituted.

Transplantation will not proceed in patients with bilaterally fixed pupils unresponsive to therapy, in those with persistent CPP less than 40mmHg or in those with intracerebral haemorrhage.

8. Supporting Evidence

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