GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH ACUTE CORONARY OCCLUSION IN KAWASAKI DISEASE

The incidence of Kawasaki Disease is increasing and the development of giant coronary arterial aneurysms is a feared complication of Kawasaki Disease[1]. Patients with giant coronary arterial aneurysms are at an increased risk of coronary arterial thrombosis and acute myocardial infarction, with the risk highest within the first six months of development of Kawasaki Disease. This document is a guideline for the management of patients with acute coronary occlusion presenting to KK Women's and Children's Hospital.

Acute Coronary Arterial Occlusion

Patients with acute coronary arterial occlusion can present with symptoms of cardiac ischemia, such as irritability, persistent crying, pallor, increased sweatiness and collapse. Patients can also present with new thrombus formation or a recent development of regional wall motion abnormalities on 2D Echocardiography. These patients should be admitted to the Children's Intensive Care Unit for treatment and monitoring. To date, there have been no clinical trials on the dosing of thrombolytic therapy for the treatment of myocardial infarction in Kawasaki pediatric patients[2]. However, local guidelines are required for the expeditious management of acute coronary arterial occlusion in these patients. The following are general and specific recommendations for the management of acute coronary arterial occlusion at KK Women's and Children's Hospital.

General Management of Acute Coronary Arterial Occlusion

Supplemental Oxygen

Supplemental oxygen can be administered via nasal cannulae or face-mask. Patients admitted in cardiovascular collapse should be intubated and ventilated.

Intravenous Morphine

Uncontrolled ischemic pain increases myocardial oxygen consumption. Intravenous morphine should be administered for pain relief and sedation. Intravenous morphine can be prescribed for non-intubated patients as intravenous boluses of 4-6 mcg/kg with increments of 4-10 mcg/kg repeated at 5 – 15 minute intervals, or up to 40mcg/kg/hr for intubated and ventilated patients.

Aspirin

Oral aspirin should be administered 5 mg/kg orally. Oral aspirin should be administered at a dose of 3~5 mg/kg/day once daily (maximum dose of 100 mg)[3]

Clopidogrel

Oral clopidogrel 1 mg/kg per day[3] is recommended in adult patients with STEMI[4] and should continue for 14 days.

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Sublingual Nitroglycerin

Sublingual Nitroglycerin may be given at 7-8 mcg/kg every 5 minutes for a total of 3 doses[2]. Alternatively, 1/3 to 1/2 tablet/dose sublingual (0.3 mg tablets) may be given[3]

Specific Management of Acute Coronary Arterial Occlusion

Systemic Thrombolysis

(a) Tissue plasminogen activators (t-PAs)- Alteplase
The recommended first line therapy for acute coronary arterial occlusion at KK Women's and Children's Hospital is intravenous Alteplase for coronary thrombosis[1]. Alteplase (Actilyse™),which is produced by recombinant DNA technique using established mammalian cell cell-line, is a recombinant human tissue-type plasminogen activator, that activates plasminogen directly to plasmin. When administered intravenously, Alteplase remains relatively inactive in the circulatory system. Once bound to fibrin, it is activated, inducing the conversion of plasminogen to plasmin leading to the dissolution of the fibrin clot.

1 vial with powder contains:

10 mg Alteplase (corresponding to 5,800,000 IU) or
20 mg Alteplase (corresponding to 11,600,000 IU) or
50 mg Alteplase (corresponding to 29,000,000 IU) respectively

There have been various infusion guidelines for Alteplase (Actilyse) in paediatric coronary thrombosis[2]. At KK Women's and Children's Hospital, for acute myocardial infarction, we recommend IV 0.5 mg/kg in the first hour, administering 10% of initial dose over 1~2 minutes intravenously and infusing the remainder of the initial dose over 60 minutes. This is followed by IV 0.5 mg/kg per hour for up to another 5h. The patient will be assessed for haemorrhagic complications and response to treatment. The decision to continue with the infusion will be made by cardiologist depending on the adequacy of treatment and the occurrence of haemorrhagic complications.

In patients, who have coronary thrombosis without acute myocardial infarction, we recommend intravenous Alteplase at 0.5 mg/kg/hr for 6 hours (290,000IU/kg/hr for 6 hours).

Intracoronary route: Administer at a dose of 0.4×10^4 units/kg over 10 minutes. Administration may be repeated at most four times

[1] Although there are no direct comparative trials for Alteplase versus Streptokinase in the management of paediatric acute myocardial infarction at the time of writing, At KKH, Alteplase is recommended as firstline thrombolysis as adult trials have demonstrated increased patency rates[1]. In addition, in paediatric myocardial infarction it is the most commonly used thrombolytic in literature. The KKH experience is also that intravenous Alteplase resulted in coronary patency when intravenous Streptokinase had not been successful.

The drug dilution guide for Alteplase is shown in Annex A. In the event that Alteplase is not available for use, intravenous Streptokinase may be used as an alternative.

(b) Streptokinase
Streptokinase is a highly purified protein derived from the culture filtrate of beta haemolytic streptococci of Lancefield Group C. Streptokinase then combine with human plasminogen to form plasminogen activator-the streptokinase –plasminogen activator complex. This complex is a high-specificity protease that proteolytically activates other plasminogen molecules to plasmin.

Streptokinase can be administered up to an intravenous bolus of 1000–4000 U/kg over 30 min[1]. Streptokinase should not be used in patients who have a history of streptococcal infection within 6 months of the presentation for coronary occlusion. We recommend the same dosing with Streptokinase for acute myocardial infarction and coronary thrombosis. The drug administration guide of Streptokinase is shown in Annex. In general, the agent that is most readily available should be used for systemic thrombolysis[1].

Systemic Thrombolysis however has its attendant risks. These are intracranial haemorrhage, gastrointestinal haemorrhage, mucosal haemorrhage. Thrombolytics may also induce anaphylactic shock. Parents should be informed of these risks. Thrombolytic therapy may also be associated with reperfusion arrhythmias and patients should be monitored carefully following thrombolytic therapy.

Intra-coronary Arterial Thrombolysis[5]

Patients with significant occlusive residual coronary arterial thrombus, who are within the "golden time" period, should be brought to the cardiac catheterization laboratory for cardiac catheterization, delineation of thrombus and intracoronary arterial thrombolysis KIV thrombosuction. This critical time period in children has not been determined[5] but the managing cardiologist can be guided by electrocardiographic changes and by trending the cardiac enzymes. The femoral venous and arterial access can be initially obtained in the usual way with the standard sheaths being used. Coronary angiograms are performed with selective angiography in the right and left coronary arteries to delineate the coronary arterial supply and to demonstrate the extent of the thrombus. Intracoronary Alteplase (Actilyse) can be administered into the coronary arteries. Up to 800 000 units of tPA has been administered intracoronary over a 10 minute period.

Angiojet Thrombosuction

Angiojet thrombosuction has been used for dissolution and removal of clot in patients with thrombosis within giant coronary arteries in Kawasaki Disease. The Angiojet device is available in Singapore. At the time of writing, the device can be loaned from the vendor (Transmedic Singapore) or from the National Heart Centre. The contact numbers are appended in Annex C. The Angiojet device is sized 4 French and requires a 6 French guiding catheter. A 6 French Femoral Arterial Sheath is therefore required for access. Consultation with an adult interventional cardiologist familiar with coronary arterial interventions is preferable.

Treatment of Complications

Complications of acute myocardial infarction such as heart failure, cardiogenic shock and arrhythmia should be treated accordingly. Extra-corporeal Membranous Oxygenation may be required to support the cardiovascular system post- myocardial infarction

Continued Anticoagulation

Intravenous heparin should be infused continuously at 10~20 units/kg/hr[3] after the administration of thrombolytic therapy, targeting PTT between 60 -80 s.

Conclusion

Acute coronary arterial occlusion is a rare but devastating complication of Kawasaki Disease. These guidelines aim to facilitate the expeditious and effective management of patients with acute coronary occlusion presenting to KK Women's and Children's Hospital.

Recommended drug dosing and monitoring[2,3]:

Drug	Dosing	Adverse drug reactions (ADRs) and precautions
Aspirin	PO 3–5 mg/kg/day once a day. (max=100mg)	Gastrointestinal ulcer (6% to 31%), duodenal ulcer, dyspepsia, epigastric distress, gastritis, heartburn, nausea, stomach pain, vomiting, hypoglycemia, cardiac arrhythmia, edema, hypotension, tachycardia
Alteplase (Actilyse™)	**(a) Myocardial Infarction** IV 0.5 mg/kg in the first hour,. administering 10% of initial dose over 1~2 minutes intravenously and infuse the remainder of the initial dose over 60 minutes. This is followed by IV 0.5 mg/kg per hour for up to another 5h. The patient will be assessed for haemorrhagic complications and response to treatment. Decision to continue with the infusion will be made by cardiologist depending on the adequacy of treatment and the occurrence of haemorrhagic complications **(b) Systemic Thrombolysis** The dose for systemic thrombolysis is IV 0.5 mg/kg/hour for 6 hours. Decision to continue with the infusion will be made by cardiologist depending on the adequacy of treatment and the occurrence of haemorrhagic complications	Significant bleeding complications including intraventricular haemorrhage requiring transfusion have been reported in pediatric patients receiving systemic tPA therapy for thrombolysis. Hypotension, GI hemorrhage, nausea, vomiting, angioedema (orolingual), epistaxis, AV block, asystole, bradycardia, cardiac arrest, cardiac tamponade, cardiogenic shock, pericardial effusion, pericarditis, pulmonary edema, seizure, thromboembolism, ventricular tachycardia

Clopidogrel (Plavix™)	PO 1mg/kg/day once daily Max dose = 75 mg/day	Thrombotic thrombocytopenic purpura (TTP), gastrointestinal symptoms, malaise, myalgia, headache, rash, purpura, pruritus. Bleeding tendency may develop when used with aspirin.
Unfractionated heparin	**Loading dose**: IV 50 U/kg/dose **Infusion**: IV 20 U/kg /hour. Adjust dosage to achieve desired therapeutic level, usually plasma heparin level: 0.35–0.7 in antifactor Xa activity or aPTT 60–85 s	Allergic vasospastic reaction (possibly related to thrombosis), hemorrhage, hemorrhagic shock, thrombosis, chills, fever, headache, eczema, urticaria, purpura, hematemesis, tarry stools, thrombocytopenia , peripheral neuropathy, heparin-induced thrombocytopenia (HIT)
Low-molecular-weight heparin (enoxaparin)	**Infants <12 months** Treatment: SC 3 mg/kg/day, divided q12h Prophylaxis: SC 1.5 mg/kg/ day, divided q12h **Children/adolescents** Treatment: SC 2 mg/kg/ day, divided q12h Prophylaxis: SC 1 mg/kg /day, divided q12h Adjust dose to achieve desired therapeutic level, usually antifactor Xa 0.5–1.0 U/mL	Shock/anaphylactoid reaction, bleeding, thrombocytopenia /thrombosis associated with heparin-induced thrombocytopenia
Streptokinase	**Loading dose:** IV 1000-4000 units/kg over 30 minutes. Maximum loading dose: 250,000 units **Infusion dose**: 1000-1500 units/kg/hour	Angina pectoris, arrhythmias, hypotension (at initiation), tachycardia/bradycardia (at initiation), cardiogenic shock, congestive heart failure, flushing, pericarditis, chills, fever, headache, malaise ,allergic reaction, bleeding, haemorrhage (0.5%), deep vein thrombosis, pulmonary embolism, Increased serum bilirubin/serum transaminases **#Note:** Streptokinase should be avoided in patients with a history of streptococcal infection or recent streptokinase administration (within 5 days to 12 months) because of the increased likelihood of resistance due to anti-streptokinase antibodies
Urokinase	**(a)Systemic thrombolysis:** IV Bolus: 4400 U/kg over 10 min Infusion: 4400 U/kg/hour Administer intravenously over 30~60 minutes. **(b)Intracoronary thrombolysis** IV 0.4×10^4units/kg, administer dose over 10 minutes. Administration may be repeated at most four times.	Gingival hemorrhage, hematuria, epistaxis bleeding, gastrointestinal hemorrhage, intracranial hemorrhage, artery dissection, cerebrovascular accident, pulmonary embolism hematoma, infusion related reaction (fever, chills, rigors)
Warfarin (Marevan™)	PO 0.1 mg/kg per day once daily (0.05~0.34 mg/kg/day per AHA guidelines) Takes about 3~7 days to obtain efficacy	Dose should be adjusted to an INR of 2.0~2.5. Sensitivity to this drug, hepatic dysfunction, and bleeding ADRs are possible

Annex A: Drug dilution guideline for Alteplase
Annex B: Drug dilution guideline for Streptokinase
Annex C: Important Contact Numbers

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ALTEPLASE INFUSION GUIDELINE
(For IV Administration Only)

Brand : Actilyse (Boelringer Ingelheim®)
Content : Alteplase 50mg/vial and Solvent (Water for Injections)
Appearance : White powder

Reconstitution Steps:

1. To each vial, add 50 mL of solvent using the transfer cannula provided.
2. Concentration of the reconstituted vial = **1mg/mL**
   The reconstituted solution is a clear and colourless to pale yellow solution.

Dilution Guide & Dosage :

Patient's Dose : _____ Weight :_____ (kg)

1. Syringe out _____ mL (_____mg) of solution from the vial.

2. Further dilute to _____mL with NaCl 0.9%.

3. Final concentration of the solution = _____ mg/mL
   Minimum concentration of solution = 0.2 mg/mL[1,2]

Please select one of the below :

☐ **Myocardial Infarction**[3]

4. Infuse _____mLs of the diluted solution over 1-2 minutes. (10% of the dose)
5. Infuse _____mLs of the diluted solution over 60 minutes. (90% of the dose)

OR

☐ **Systemic Thrombolysis**[4]

4. Infuse _____mLs of the diluted solution over 6 hours. (100% of the dose)
   Rate : 0.5 mg/kg/hour = _____mLs/hour

Stability:

1. Store unused vials at room temperature.
2. The reconstituted solution in the vial may be stored at 2-8 °C at 24 hours or up to 8 hours at room temperature if prepared under aseptic technique.[1] If not reconstituted under aseptic conditions, use immediately and discard remaining solution.

Compatibility: (with reference to patient's own medication)

Compatible with :

Incompatible with :

Filled by: _____

Checked by: _____

References

1. Product Insert (Boelringher Ingelheim)
2. Phelps SJ, Hak EB, Crill CM. Teddy Bear Book: Pediatric Injectable Drugs, 10th edition
3. JCS Joint Working Group. "Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)--digest version." *Circulation journal: official journal of the Japanese Circulation Society* 74.9 (2010): 1989.
4. Clinical Practice Guidelines : Anticoagulation Therapy(Royal Children Hospital) Last accessed 25th June 2015

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STREPTOKINASE INFUSION GUIDELINE
For IV, Intra-arterial or Intra-coronary Infusion

Brand : Streptase® (CSL Behring)
Content : Streptokinase 1,500,000 IU (1.5 MU)/vial
Appearance : White powder

Reconstitution Steps:

1. To each vial, slowly add 5 mL of NaCl 0.9% down the side wall of the vial, not onto the drug itself. [1]
2. Gently roll the reconstituted vial between the palms till powder is dissolved, taking care to avoid formation of foam. **DO NOT** shake the vial. [1]
   [Note: The reconstituted solution appears as a colourless to yellowish, clear solution] [2]
3. Concentration of reconstituted vial = **300,000 IU/mL** [2]

Dilution Guide & Dosage :

Patient's Dose : _____

1. Syringe out _____ mL (_____ IU) of solution from the vial.
2. Further dilute to _____ mL with NaCl 0.9% or D5%.[1 - 3]
3. Final concentration of infusion = _____ IU/mL
4. Infuse over _____ minutes or hours
   Recommended duration = ≥ 30 minutes [2, 3]

Stability: [1]

1. Unopened vials should be stored at room temperature (≤ 25°C).
2. The reconstituted solution in the vial and the diluted infusion solution may be stored under refrigeration (2 – 8°C) for up to 24 hours.

Special Precautions: [1, 2]

1. Flocculation of reconstituted streptokinase may occur, and if present in sufficient amounts, it may be removed by filtering the solution through a 0.8-micron or larger porosity filter.
   Discard the preparation if flocculation still remains.
2. At the beginning of therapy, fall in blood pressure, increase or decrease in heart rate is commonly observed. Therefore, infusion should be performed slowly when starting therapy.
3. Streptokinase should be avoided in patients with a history of streptococcal infection or previous streptokinase administration (within 5 days to 12 months) because of the increased likelihood of resistance due to anti-streptokinase antibodies.

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Done by: Kar Yen
Vetted by: Jess Toon

Annex C: Important Contact Numbers

1. National Heart Centre, Coronary Care Unit: 63214440

2. Transmedic Singapore Pte Ltd (Angio jet): 67371945

References:

1. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2004;110(17):2747-2771.
2. Paredes N, Mondal T, Brandao LR, Chan AK. Management of myocardial infarction in children with Kawasaki disease. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis.* 2010;21(7):620-631.
3. Group JCSJW. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. *Circulation journal : official journal of the Japanese Circulation Society.* 2014;78(10):2521-2562.
4. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation.* 2004;110(5):588-636.
5. Nakagawa M, Watanabe N, Okuno M, Okamoto N, Fujino H. Effects of intracoronary tissue-type plasminogen activator treatment in kawasaki disease and acute myocardial infarction. *Cardiology.* 2000;94(1):52-57.