Clozapine-induced Myocarditis Monitoring Guideline

REVISION HISTORY

Version	Approved by	Amendment notes
August 2021	Clozapine Expert Reference Group	Focus of document narrowed to clozapine-induced myocarditis.
October 2021	Clozapine Expert Reference Group	Document streamlined for better reading flow. Ongoing Monitoring moved to an appendix. Addition of retitration to Section 6. Managing Myocarditis.
November 2021	Clozapine Expert Reference Group	Addition of reference to document. Minor wording changes to Section 2. Baseline Measurements and Section 6. Managing Myocarditis.

CONTENTS

1 BACKGROUND

This Clozapine-induced Myocarditis Monitoring Guideline provides recommendations for best practice safe and effective monitoring and management of clozapine-induced myocarditis. The Guideline provides guidance for NSW Health staff responsible for the monitoring and management of clozapine-induced myocarditis.

All mental health consumers taking clozapine are enrolled in a clozapine monitoring service and have regular blood tests for the detection of neutropenia and agranulocytosis. Sound clinical judgement and knowledge are essential in the implementation of this Guideline to ensure safe monitoring and use of clozapine in mental health consumers.

1.1 Key definitions

Agranulocytosis

A rare disorder resulting in reduced white blood cells produced in the bone marrow resulting in impaired ability to fight infections.

Cardiac MRI (CMRI)

A non-invasive scan that uses a magnetic field and radio waves to take detailed pictures of the heart and tissues. It is the gold standard non-invasive test to diagnose myocarditis.

Cardiomyopathy

A condition of the heart that inhibits adequate contraction.

C- reactive protein (CRP)

Produced by the liver and can be detected by blood tests. CRP level rises when there is inflammation throughout the body. *Range: <5mg/L*

Dysuria

Painful or difficult urination.

Echocardiograph (echo)

A diagnostic device using ultrasound waves to investigate the action of the heart.

Electrocardiogram (ECG)

A test used to measure the electrical activity of the heart.

Eosinophilia

A type of disease-fighting white blood cell. An increased amount of Eosinophils in the blood can be detected when there is a parasitic infection, allergy or cancer.

High sensitivity cardiac troponin I or T (hs-CTn)

The high sensitivity cardiac troponin test measures the levels of one of two proteins, troponin T or troponin I, in a blood sample. These proteins are released when the heart

muscle has been damaged, such as during a heart attack or in myocarditis. The more damage there is to the heart, the greater the amount of troponin T and I there will be in the blood.

Fever

An increase in body temperature above the normal range of 36 - 37 degrees. A temperature above 38 degrees indicates a fever caused by illness or infection.

Left Ventricular (LV)

The left ventricle is one of four chambers of the heart.

Myocarditis

Inflammation of the heart muscle that may lead to cardiomyopathy. Myocarditis can be life-threatening if not detected and treated early.

Neuroleptic Malignant Syndrome (NMS)

A life-threatening idiosyncratic reaction to some antipsychotic drugs including clozapine. Symptoms may include fever, altered mental state, muscle rigidity, and autonomic dysfunction.

Neutropenia

A low number of neutrophils; a type of white blood cell that helps fight infection. Neutrophils are the most common white cell that can be affected by clozapine and requires regular blood test monitoring.

N-terminal B-type natriuretic peptide (NT-proBNP)

NT-proBNP is released by the ventricular wall in response to increased wall stress and reflects the haemodynamic status of the heart. Useful for detecting early and initially asymptomatic myocarditis.

QT Interval

Represents time taken for ventricular depolarisation and repolarisation.

QTc

Rate that QT intervals are measured - c is the formula used.

Sialorrhea

Also known as hypersalivation. An excess production of saliva that can be a common side effect from the early phase of clozapine therapy.

Tachycardia

An abnormally rapid heart rate.

Treatment-resistant schizophrenia (TRS)

The persistence of positive symptoms despite ≥2 trials of adequate dose and duration of antipsychotic medication with documented adherence.

ULN

Upper Limit of Normal

White cell count

Measures the number of white blood cells.

2 BASELINE MEASUREMENTS

Clozapine is an effective antipsychotic medication for the management of treatment-resistant schizophrenia. A range of cardiac disorders have been associated with the use of clozapine, the most serious being myocarditis and cardiomyopathy. Myocarditis is most commonly observed early in treatment. However, it should be noted in rare occasions myocarditis may develop spontaneously throughout treatment (Ronaldson et al., 2015). This Guideline recommends a way to actively monitor mental health consumers for clozapine-induced myocarditis and includes a threshold for cessation and how to manage this.

Baseline testing is required prior to commencing a mental health consumer on clozapine.

BASELINE MEASUREMENTS:		
Full blood count (FBC)	Blood group	Urea / electrolytes
Fasting glucose and lipids	Liver function tests	C-reactive protein (CRP)
High sensitivity cardiac troponin	Echocardiogram (Echo)	Electrocardiogram (ECG)
Weight	Waist circumference	

Pre-treatment/baseline white blood cell and neutrophil counts and blood group must be reviewed and provided in accordance with Clopine Central or Clozaril Patient Monitoring System (CPMS). Recommended ongoing monitoring for cardiac disorders associated with clozapine is detailed in Appendix 1.

3 CLINICAL COURSE OF MYOCARDITIS

Myocarditis is most commonly observed early in treatment. The first indications of the onset of myocarditis are non-specific symptoms of illness such as fever with features commonly associated with influenza, but symptoms may include severe diarrhoea and vomiting or dysuria (*point 2, Figure 1*). However, in some cases myocarditis may develop *without* accompanying symptoms.

C reactive protein (CRP) usually begins to increase around this time *(point 2, Figure 1)*.

High sensitivity cardiac troponin I or T typically increases with a delay of as much as five days after both the onset of symptoms and commencement in the rise of CRP *(Point 3, Figure 1).*

A sudden drop in systolic blood pressure may occur around this time and the consumer may report chest pain *(Point 3, Figure 1).*

The first appearance of non-specific electrocardiogram (ECG) changes also occurs at this point *(Point 3, Figure 1).*

Basal crepitation's, third heart sounds, peripheral oedema and raised jugular venous pressure also may develop *(Point 3, Figure 1).*

An echo may show impairment of left ventricular (LV) function (*Point 3, Figure 1*).

Heart rate typically increases a few days following initiation of clozapine in all consumers including those not developing myocarditis.

Heart rate may increase again with the onset of fever and elevation in CRP (*Point 2, Figure 1*) or it may suddenly increase with the first development of high troponin (*Point 3, Figure 1*).

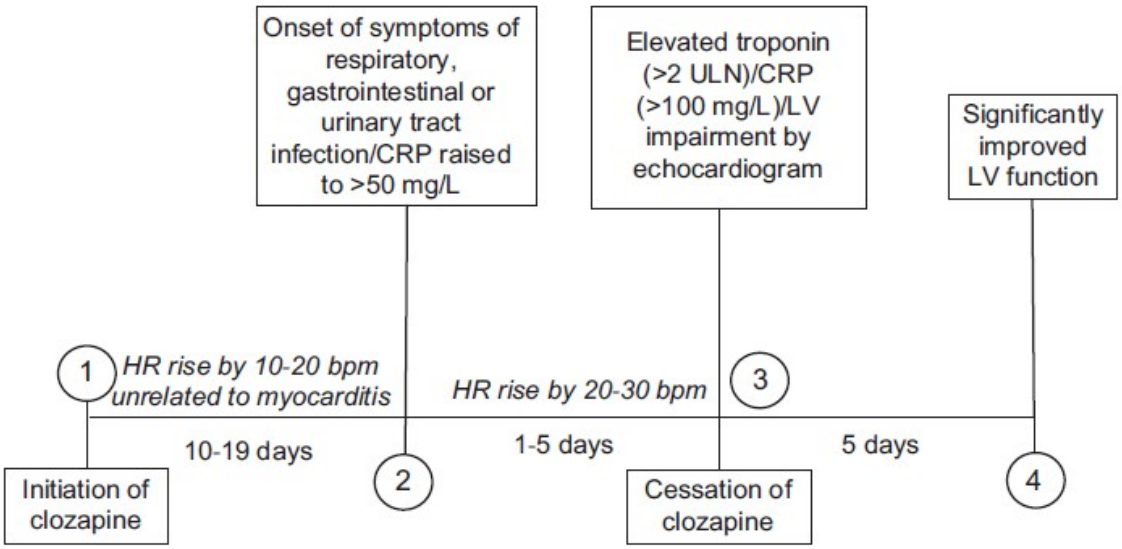

Figure 1- The typical evolution of clozapine-induced myocarditis (Ronaldson et al., 2011)

3.1 Monitoring of suspected myocarditis

Active monitoring of the mental health consumer started on clozapine is required during the first four weeks of treatment including tests i.e. high sensitivity cardiac troponin T/I, CRP and symptoms of influenza. Consumers with pre-existing cardiac and metabolic risks treated with clozapine will require close monitoring.

Cardiac concerns can also occur where retitration occurs too fast or at a higher dose (Knoph et al., 2018).

The only known potential risk factors for myocarditis are rapid titration, and possible concomitant use of Valproate.

Consumers with mild signs and symptoms of unidentified illness will require closer monitoring while continuing with treatment.

4 INITIAL FOUR WEEK MONITORING PROTOCOL

CRP and high sensitivity cardiac troponin I or T should be monitored weekly for the first four weeks of treatment then six monthly thereafter.

During the first four weeks, vital signs and direct enquiry regarding symptoms should be assessed at least every alternate day whilst the patient is an inpatient and weekly if the patient has been transferred to an outpatient clinic.

In the presence of relevant symptoms, an abnormally increased heart rate or raised CRP (50 mg/L), it is recommended that high sensitivity cardiac troponin and CRP be measured daily and the patient monitored for developing illness.

If high sensitivity cardiac troponin levels are only slightly raised (less than twice the upper limit of normal) and CRP remains less than 100 mg/L, clozapine may be continued.

Discontinuation of clozapine and investigation by echocardiography is advised if either high sensitivity cardiac troponin is in excess of twice the normal maximum or CRP is more than 100 mg/L.

Early referral for cardiology assessment is encouraged if there are clinical and/or biomarker blood test concerns regarding clozapine-induced myocarditis.

Routine monitoring for myocarditis up to day 28 is recommended, as the majority of cases occur within the first four weeks of treatment.

4.1 Early indicators of myocarditis

Fever

Fever above 38 degrees may be an early indicator of myocarditis. However, this can also indicate the presence of other serious adverse reactions such as neuroleptic malignant syndrome, secondary infection due to agranulocytosis or aspiration pneumonia from sialorrhea.

Heart rate

Clozapine frequently causes benign tachycardia. Monitoring heart rate on at least alternate days (as inpatient) and weekly (as outpatient) from baseline during first 4 weeks will mean that trends and tendencies for the individual patient can be identified and an abnormal increase associated with the onset of myocarditis is more likely to be correctly interpreted.

C-reactive protein

This guideline suggests measuring CRP along with high sensitivity cardiac troponin measurements in the routine monitoring for myocarditis.

CRP is generally a non-specific marker of inflammation; however, studies indicate that elevated CRP is an early diagnostic indicator of the presence of myocarditis where other cardiac biomarkers are elevated. A focal source of underlying infection (e.g. urinary tract infection, chest infection) or systemic sepsis should be excluded based on clinical symptoms.

A CRP of more than 50mg/L may foreshadow the onset of myocarditis.

ECG and Echocardiography

ECG is not recommended as a means of detecting the development of myocarditis.

ECG may be used to monitor heart rate and clinicians may find diagnostic benefit in monitoring the evolving ECG changes.

In order to use an echo as a diagnostic tool in suspected myocarditis, a baseline echo prior to clozapine treatment is advisable to exclude pre-existing dysfunction.

Eosinophilia

Raised eosinophils should not be used to monitor for myocarditis occurring following clozapine initiation. Usually used to determine parasitic infections, allergies or cancers.

Cardiac MRI

In patients suspected of clozapine-induced myocarditis, early consultation to a cardiology team is recommended to determine the ongoing cardiac needs, including if a cardiac MRI is indicated.

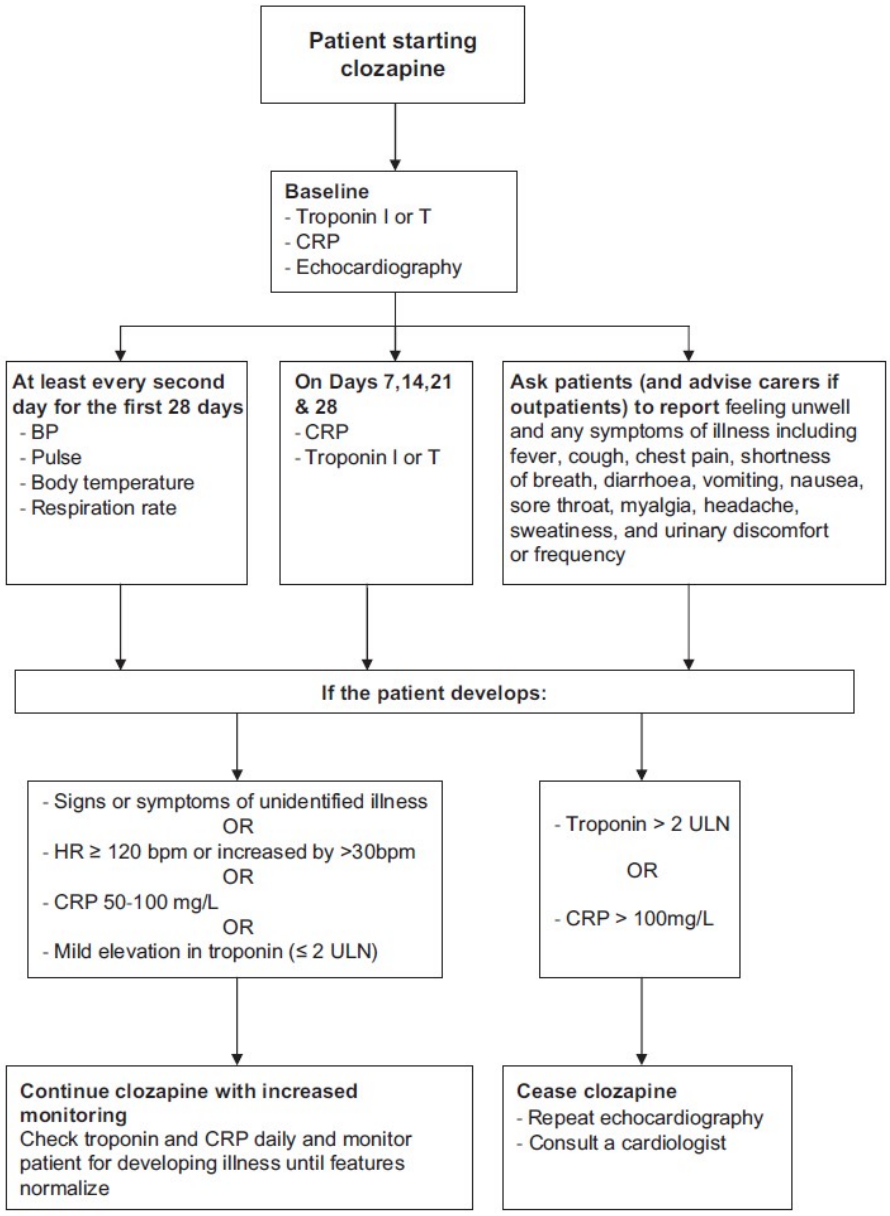

Figure 2: Proposed protocol for monitoring mental health consumer commenced on clozapine for clozapine-induced myocarditis. (Ronaldson et al., 2011)

5 CONTINUATION OF CLOZAPINE WITH SUBTHRESHOLD FINDINGS AND/OR MILD SYMPTOMS

Given the potential success of clozapine, every opportunity for continuation of clozapine should be taken provided it can occur safely.

It has been suggested that the continuation of clozapine may be contemplated if high sensitivity cardiac troponin I or T is no more than twice the upper limit of normal, provided CRP is less than 100mg/L.

If deciding to continue clozapine treatment, it is important to ensure that the cardiac function is not at risk. This can be further assessed by checking high sensitivity cardiac

troponin I or T, and/or echo and/or cardiac MRI. A cardiology consult should be considered.

Slow titration of clozapine dose is advised, in consultation with the treating team.

6 MANAGING MYOCARDITIS

Once clozapine-related myocarditis has been suspected or diagnosed, clozapine treatment must cease.

There is evidence that the early cessation of clozapine treatment with the onset of myocarditis improves clinical outcomes.

Where myocarditis is suspected, investigation for clozapine-induced impairment should be conducted promptly following the withdrawal of clozapine. A cardiologist should be consulted about the need for referral.

If no significant impairment of cardiac function is measured, no specific therapy apart from cessation of Clozapine is required.

However, where the echocardiography or cardiac MRI reveals moderate or severe left ventricular impairment a cardiology consult should be sought to further assess the need for drug or mechanical intervention.

Any future retitration of clozapine following myocarditis should be done under the supervision of a cardiologist in consultation with the treating team, the consumer and their family.

7 RELATED POLICIES, LITERATURE, AND RESOURCES

- Physical Health Care for People Living with Mental Health Issues: A Guideline (GL2021_006)
- Health Care Records - Documentation and Management (PD2012_069)
- Clopine Hub www.clopinehub.com.au
- Layland JJ, Liew, Prior DL. Clozapine-induced cardiotoxicity: A Clinical update *MJA* 2009: 190: 190-192.
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- Robinson, G., Kisely, S., Siskind, D., Flanagan, R. J., & Wheeler, A. J. (2017). Echocardiography and clozapine: Is current clinical practice inhibiting use of a potentially life-transforming therapy? *Australian Family Physician, 46*(3), 169–170. https://doi.org/10.3316/informit.673859849778400 (Original work published March 2017)
- Western Australia Department of Health (WA DoH) (2020). Guidelines for the safe and quality use of clozapine therapy in the WA health system, May 2020.

8 REFERENCES

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Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand*. 2015 Oct;132(4):231-40.

Ronaldson KJ, Fitzgerald PB, Taylor AJ, Topliss DJ, McNeil JJ. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust NZ J of Psychiatry,* 2011. Vol.45(6), 458-465.

APPENDIX 1: ONGOING MONITORING

Recommended ongoing monitoring for clozapine-induced cardiac disorders should include:

MONITORING	FREQUENCY
BP, Pulse, Temperature, Weight	• Baseline(sitting, standing, lying) • After stat dose for 6 hours • Weekly for the first 19 weeks • Every 28 days • As clinically indicated
ECG	• Baseline • 6 monthly • As clinically indicated
Echo	• Baseline • Annual • If there is no serial change in LV function then echo can be done every 2 to 5 years • As clinically indicated
High sensitivity cardiac troponin & CRP	• Baseline • Weekly from week 1 to week 4 once initiated • 6 monthly or as clinically indicated
NT-proBNP	• As advised if early and asymptomatic myocarditis is suspected
Cardiac MRI	• To be considered for confirmation of myocarditis