Monitoring Clozapine-induced Myocarditis

Summary Various cardiac disorders have been associated with the use of clozapine, the most serious being myocarditis, cardiomyopathy and death. This Guideline provides guidance for NSW Health staff in the detection, monitoring and management of clozapine-induced myocarditis.

Document type Guideline

Document number GL2022_011

Publication date 17 October 2022

Author branch Mental Health

Branch contact (02) 9461 7074

Replaces PD2012_005

Review date 17 October 2027

Policy manual Not applicable

File number H22/78345

Status Active

Functional group Clinical/Patient Services - Medical Treatment, Mental Health
Corporate Administration - Governance

Applies to Ministry of Health, Public Health Units, Local Health Districts, Government Medical Officers, NSW Ambulance Service

Distributed to Ministry of Health, Public Health System, Divisions of General Practice, Government Medical Officers, NSW Ambulance Service

Audience Clinical Nursing;Medical;Mental Health;Emergency Department;Cardiology

NSW Health

GUIDELINE

Monitoring Clozapine-induced Myocarditis

GUIDELINE SUMMARY

This Guideline provides guidance for NSW Health staff in the monitoring, detection and management of clozapine-induced myocarditis. It includes a threshold and guidance for cessation where clinically indicated.

KEY PRINCIPLES

Clozapine is an effective antipsychotic medication for the management of treatment-resistant schizophrenia. It is associated with various cardiac disorders including myocarditis, cardiomyopathy and death.

Myocarditis is most commonly observed early in treatment. Consumers receiving clozapine must be monitored carefully throughout treatment to minimise the risk of adverse cardiac events.

There is to be a collaborative care approach to monitoring and management of clozapine-induced myocarditis. Treatment must be person-centred and consumers and family/carers are to be actively involved in the provision of care. Consumers must be informed of the benefits of treatment with clozapine as well as the associated risks.

Sound clinical judgement and knowledge are essential in the implementation of this Guideline to ensure safe monitoring and use of clozapine in consumers.

Local Health Districts and Specialty Health Networks must have local procedures in place to establish roles and responsibilities in relation to clozapine monitoring, including pathways for medical escalation, onward referral and transfer of care.

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

REVISION HISTORY

Version	Approved By	Amendment Notes
GL2022_011 October-2022	Deputy Secretary, Health System Strategy and Planning	Changed from a Policy Directive to a Guideline. Recommendations for screening extended to first six weeks of clozapine treatment.
PD2012_005 January-2012	Deputy Director-General Strategy and Resources	New Policy Directive

CONTENTS

1. BACKGROUND

This Guideline provides guidance for NSW Health staff in the monitoring, detection and management of clozapine-induced myocarditis. Sound clinical judgement is essential in the implementation of this Guideline to ensure safe monitoring and use of clozapine in consumers.

Clozapine is an effective atypical antipsychotic medication primarily used to treat treatment-resistant schizophrenia. A range of cardiac disorders has been associated with the use of clozapine, the most serious being myocarditis, cardiomyopathy and death.

All consumers taking clozapine are enrolled in a clozapine monitoring service.

1.1. About this document

This Guideline recommends a way to actively monitor consumers for clozapine-induced myocarditis, including when to cease clozapine and how to manage this.

1.2. Key definitions

Agranulocytosis	A rare disorder resulting in reduced white blood cells produced in the bone marrow resulting in impaired ability to fight infections.
Cardiomyopathy	A condition of the heart that inhibits adequate contraction.
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.
High sensitivity C-reactive protein (hs-CRP)	The high-sensitivity C-reactive protein test is a blood test that finds lower levels of C-reactive protein (CRP).
High sensitivity cardiac troponin (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.
Neuroleptic Malignant Syndrome (NMS)	A life-threatening idiosyncratic reaction to antipsychotic drugs including clozapine. Symptoms may include fever, altered mental state, muscle rigidity, and autonomic dysfunction.

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.
Sialorrhea	Also known as hypersalivation. An excess production of saliva that can be a common side effect from the early phase of clozapine therapy.
Treatment-resistant schizophrenia (TRS)	The persistence of symptoms despite ≥2 trials of adequate dose and duration of antipsychotic medication with documented adherence.
ULN	Upper Limit of Normal

2. BASELINE MEASUREMENTS

Baseline testing is required prior to commencing a patient on clozapine. Baseline measurements may be described in local protocol and are to include:

- Investigation of any physical symptoms
- Blood group
- Blood pressure
- C-reactive protein (CRP) or High sensitivity C-reactive protein (hs-CRP)
- Echocardiogram (Echo)
- Electrocardiogram (ECG)
- Fasting glucose (a common blood test that measures the level of glucose in the blood after an overnight fast)
- Lipids (a blood test that measures the levels of cholesterol and other fats in the blood)
- Full blood count (FBC) (a common blood test that measures the number and status of different blood cells, such as red cells, white cells and platelets)
- High sensitivity cardiac troponin
- Liver function tests (blood tests used to help diagnose and monitor liver disease or damage. The tests measure the levels of certain enzymes and proteins in blood)
- Pulse
- Waist circumference
- Weight
- Urea / electrolytes (a common blood test that measures chemicals called electrolytes in the blood, such as sodium, potassium and magnesium).

Pre-treatment/baseline counts of white blood cells and neutrophils as well as blood group must be reviewed and provided in accordance with ClopineCENTRAL™ or Clozaril Patient Monitoring System (CPMS).

3. MYOCARDITIS ONSET AND COURSE

Myocarditis is an inflammation of the heart muscle that may lead to cardiomyopathy. It can be life threatening if not detected and treated early. Myocarditis is most commonly observed early in treatment. However, in rare occasions myocarditis can develop spontaneously throughout treatment.

The first indications of the onset of myocarditis are non-specific symptoms of illness such as fever with features commonly associated with influenza, including shortness of breath and fatigue but symptoms may include chest pain, severe diarrhoea, vomiting or dysuria (painful or difficult urination). However, in some cases myocarditis may develop *without* symptoms.

C-reactive protein (CRP) usually begins to increase around this time. CRP is produced by the liver and can be detected by blood tests. CRP level rises when there is inflammation throughout the body (range*: <5mg/L*).

High sensitivity cardiac troponin typically increases with a delay of as much as five days after both the onset of symptoms and commencement in the rise of CRP or high sensitivity C-reactive protein (hs-CRP).

A sudden drop in systolic blood pressure may occur around this time and the consumer may report chest pain.

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

An echo may show impairment of left ventricular (LV) function (see Figure 1, point 3). The left ventricle is one of four chambers of the heart. The left ventricle contracts to force oxygenated blood through the aortic valve to be distributed to the entire body.

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 or hs-CRP (see Figure 1, point 2) or it may suddenly increase with the first development of high troponin (see Figure 1, point 3).

4. INITIAL MONITORING PROTOCOL

Most cases of myocarditis occur within the first six weeks of treatment and routine monitoring for myocarditis up to day forty-two is recommended. Consumers with pre-existing cardiac and metabolic risks treated with clozapine will require close monitoring.

Cardiac concerns can also occur where titration occurs too fast or at a higher dose. Refer to the Australian Commission on Safety and Quality in Health Care's *National Inpatient Medication Chart (NIMC) - Clozapine Titration guide* for further information.

Consumers with mild signs and symptoms of unidentified illness will require closer monitoring while continuing with clozapine treatment. The only known potential risk factors for myocarditis are rapid titration and possible concomitant use of Valproate.

C-reactive protein (CRP) or high sensitivity C-reactive protein (hs-CRP) and high sensitivity cardiac troponin must be monitored weekly for the first six weeks of treatment then six monthly thereafter or earlier if clinically indicated.

During the first four weeks, vital signs and direct enquiry regarding symptoms must be assessed daily.

In the presence of relevant symptoms, such as an abnormally increased heart rate or raised CRP (50 - 100 mg/L), measure high sensitivity cardiac troponin and CRP daily, as well as performing daily electrocardiograms (ECG) and monitoring the consumer for any 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 echo is advised if either high sensitivity cardiac troponin is in excess of twice the normal maximum or CRP is more than 100 mg/L.

Refer consumers early to cardiologist services for cardiology assessment if there are clinical and/or biomarker blood test concerns regarding clozapine-induced myocarditis.

Figure 2 provides an overview of the protocol for monitoring consumers for clozapine-induced myocarditis.

Recommended routine monitoring for cardiac disorders associated with clozapine is detailed in Appendix 9.1.

4.1. Early indicators of myocarditis

C-reactive protein

Measuring CRP or hs-CRP along with high sensitivity cardiac troponin is part of the routine monitoring for myocarditis.

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

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

Cardiac magnetic resonance imaging

A cardiac magnetic resonance imaging (MRI) is 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. In consumers suspected of clozapine-induced myocarditis, early consultation to a cardiology team will determine ongoing cardiac needs, including if a cardiac MRI is indicated.

Electrocardiograms and Echocardiograph

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

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

Eosinophilia

Eosinophilia is an increase in eosinophil count. An eosinophil is 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.

Elevation of eosinophil count is typically delayed in the course of myocarditis and must not be used to screen for myocarditis after the initiation of clozapine.

Fever

Fever above 38 degrees Celsius 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. Clinicians may wish to use forehead sensing thermometers as an alternative to oral or auxiliary thermometers to measure temperature.

Heart rate

Clozapine frequently causes benign tachycardia (an abnormally rapid heart rate). Monitoring heart rate daily (as inpatient) and weekly (in community mental health) from baseline during the first 4 weeks of treatment will mean that trends and tendencies for the individual consumer can be identified and an abnormal increase associated with the onset of myocarditis is more likely to be correctly interpreted.

High sensitivity cardiac troponin

High sensitivity cardiac troponin is a sensitive and specific marker of myocyte damage and is raised in conditions such as myocardial infarction and myocarditis, pulmonary embolism and other medical conditions. Elevated high sensitivity cardiac troponin must prompt early review with a cardiology service.

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

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

If deciding to continue clozapine treatment, it is important to ensure that cardiac function is not at risk. This can be further assessed by checking high sensitivity cardiac troponin, and/or echo and/or cardiac magnetic resonance imaging (MRI). A cardiologist is to be consulted. This consult will determine whether an echo is an appropriate alternative where a cardiac MRI is not available.

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 is to be conducted promptly following the withdrawal of clozapine. A cardiologist is to 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. Post cessation monitoring will be as per ClopineCENTRAL™ protocols.

However, where the echo or cardiac magnetic resonance imaging (MRI) reveals moderate or severe left ventricular impairment a cardiology consult is to be sought to further assess the need for drug or mechanical intervention.

Any future retitration of clozapine following myocarditis is to be done under the supervision of a cardiologist in consultation with the treating team, the consumer and their family/carer. An informed consent process with the consumer and their family/carer must be followed, outlining risks and benefits of retitration. Past clozapine-induced myocarditis is a risk factor for future myocarditis and is to be noted in the eMR and any relevant discharge summaries and referral documents.

7. RELATED POLICIES, LITERATURE AND RESOURCES

- Australian Commission on Safety and Quality in Health Care. National Inpatient Medication Chart (NIMC) - Clozapine Titration guide
- Clozapine Hub for online resources and information: http://www.clopinehub.com.au
- Layland JJ, Liew, Prior DL. Clozapine-induced cardiotoxicity: A Clinical update *MJA* 2009: 190: 190-192.
- NSW Health Policy Directive *Mental Health Clinical Documentation* (PD2021_039)
- NSW Health Guideline *Physical Health Care for People Living with Mental Health Issues* (GL2021_006)
- Meyer, J and Stahl, S. (2020) The Clozapine Handbook. Cambridge University Press: Cambridge.
- 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)

8. REFERENCES

1. Knoph KN, Morgan RJ 3rd, Palmer BA, Schak KM, Owen AC, Leloux MR, Patel M, Leung JG. Clozapine-induced cardiomyopathy and myocarditis monitoring: A systematic review. *Schizophr Res*. 2018 Sep;199:17-30.
2. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. *Acta Psychiatr Scand*. 2015 Oct;132(4):231-40.
3. 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.

9. APPENDICES

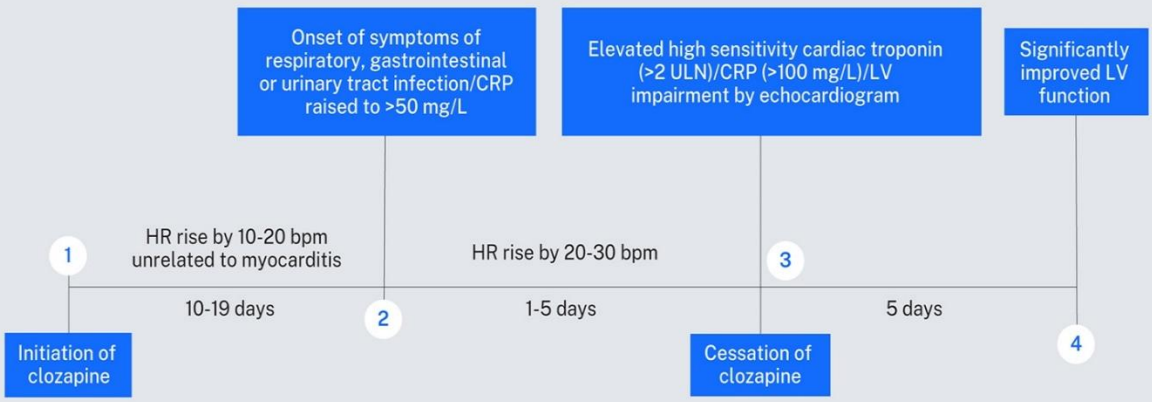
9.1. Routine Monitoring

Recommended ongoing monitoring for clozapine-induced cardiac disorders is to include:

Monitoring	Frequency
Postural BP, pulse, temperature, respiratory rate	• After first dose for 6 hours • Weekly for the first 18 weeks • Every 28 days • As clinically indicated
Weight	• Baseline • Weekly in an acute setting • Monthly in a community setting • Once stable, review as part of metabolic monitoring
ECG	• Baseline • 6 monthly • As clinically indicated
Echo	• Baseline • 12 months • 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 and CRP or hs-CRP	• Baseline • Weekly from week 1 to week 6 once initiated • 6 monthly or as clinically indicated
Cardiac MRI	• To be considered for confirmation of myocarditis

9.2. Figure 1: Evolution of clozapine-induced myocarditis

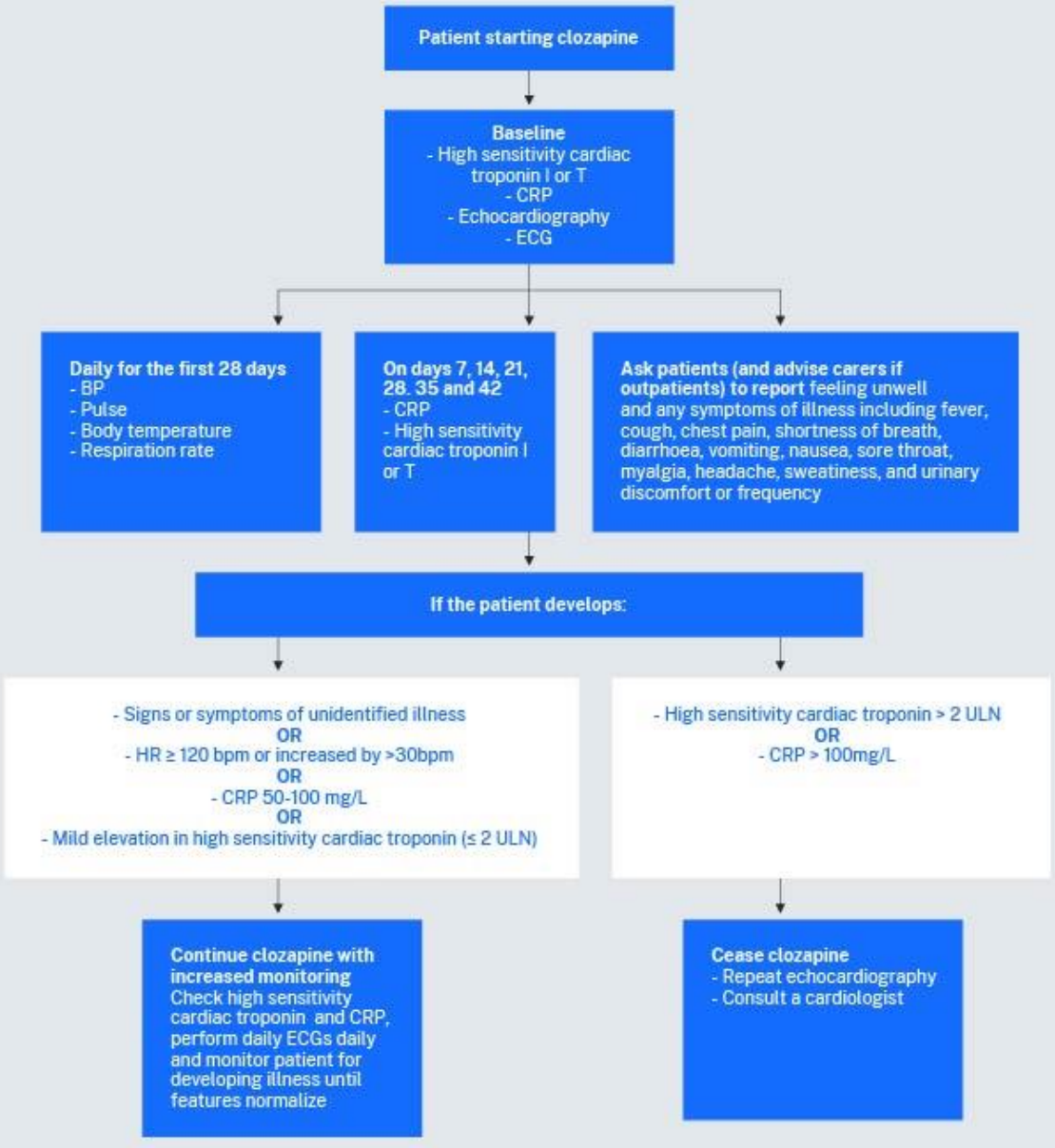
Figure 1. The typical evolution of clozapine-induced myocarditis.



(Ronaldson et al., 2011)

9.3. Figure 2: Protocol for monitoring clozapine-induced myocarditis

Figure 2. Proposed protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis.



(Based on Ronaldson et al., 2011)