

Clozapine-induced Myocarditis - Monitoring Protocol

Summary Clozapine is an effective antipsychotic for the management of treatment-resistant schizophrenia. All patients taking clozapine are registered at an approved clozapine monitoring service where ongoing monitoring primarily occurs for the detection of neutropenia and agranulocytosis. A range of cardiac disorders has been associated with the use of clozapine, the most serious being myocarditis and cardiomyopathy. Myocarditis is most commonly observed early in treatment. The protocol put forward in the policy recommends a way to actively monitor mental health patients on clozapine. It encourages continuation of clozapine in the presence of mild illness, but defines a threshold for cessation and how to manage this. NOTE: A correction was made on 1 February 2012 to the second sentence of the second paragraph in this Summary. Cardiomyopathy replaced with Myocarditis.

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

Audience Nursing;clinical;emergency depts;mental health units

MONITORING PROTOCOL FOR CLOZAPINE-INDUCED MYOCARDITIS

PURPOSE

The protocol put forward in this policy recommends a way to actively monitor mental health patients on Clozapine.

Clozapine is an effective antipsychotic for the management of treatment-resistant schizophrenia. All patients taking Clozapine are registered at an approved Clozapine monitoring service where ongoing monitoring is required for the detection of neutropenia and agranulocytosis.

The policy encourages the continuation of Clozapine in the presence of mild illness, but defines a threshold for cessation and how to manage this.

MANDATORY REQUIREMENTS

Gaining a better understanding of the potential risks associated with Clozapine will enable NSW Health staff to ensure that appropriate protocols and guidelines for the effective monitoring and management of patients taking Clozapine are in place.

IMPLEMENTATION

Implementation of this Policy Directive will be guided by the NSW Health Monitoring Protocol for Clozapine Induced Myocarditis Procedures.

The document outlines a range of cardiac disorders that has been associated with the use of Clozapine, recommends the typical clinical course of myocarditis and puts forward the recommended monitoring protocol for the detection of neutropenia and agranulocytosis.

Local Health Districts and other NSW Health organisations will be required to regularly report on the progress of the monitoring protocol.

REVISION HISTORY

Version	Approved by	Amendment notes
January 2012 (PD2012_005)	Deputy Director-General Strategy and Resources	New policy

ATTACHMENTS

1. Monitoring Protocol for Clozapine-Induced Myocarditis: Procedure

Monitoring Protocol for Clozapine-induced Myocarditis



Issue date: January 2012

PD2012_005

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1 BACKGROUND

Clozapine is an effective antipsychotic for the management of treatment-resistant schizophrenia. All patients taking clozapine are registered at an approved clozapine monitoring service where ongoing monitoring primarily occurs for the detection of neutropenia and agranulocytosis.

A range of cardiac disorders has been associated with the use of clozapine, the most serious being myocarditis, cardiomyopathy and death. Myocarditis is most commonly observed early in treatment.

This procedure recommends active monitoring for the first 4 weeks, relying on assessing clinical symptoms and signs, as well as investigations such as troponin and C-reactive protein results. It encourages continuation of clozapine in the presence of mild illness, but defines a threshold for cessation.

Recommended ongoing monitoring for cardiac disorders should include:

- BP- admission at week 6, week 18, 6 months and thereafter unless problematic
- ECG - 6 months and annually thereafter unless clinically indicated
- ECHO - 6 months, then thereafter if clinically indicated
- Troponin & CRP – Pre, first 4 weeks, week 6, week 18, at 6 months and thereafter 6 monthly unless clinically indicated
- CK-MB and NT-proBNP also advised should myocarditis be suspected.

2 DEFINITIONS

Troponin I or T- The 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. The more damage there is to the heart, the greater the amount of troponin T and I there will be in the blood. *Range: <14ng/L*

CRP- 'C- reactive protein'- is produced by the liver. The level of CRP rises when there is inflammation throughout the body. *Range: <5mg/L*

NT-proBNP- 'N-terminal B-type natriuretic peptide' 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.

CK-MB- 'Creatine Kinase'- Myocardial Band' is a cardiac marker used to assist diagnoses of an acute myocardial injury.

ULN- Upper Limit of Normal

LV- Left Ventricular

3 TYPICAL CLINICAL COURSE OF MYOCARDITIS

- 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*).
- C reactive protein (CRP) usually begins to increase around this time (*point 2, Figure 1*).
- Troponin I or T typically increases with a delay of as much as 5 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 patient 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 crepitations, 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 function (*Point 3, Figure 1*).
- Heart rate typically increases a few days following initiation of clozapine in all patients including those not developing myocarditis.
- It 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 10*).
- In some cases myocarditis may develop *without* accompanying symptoms.

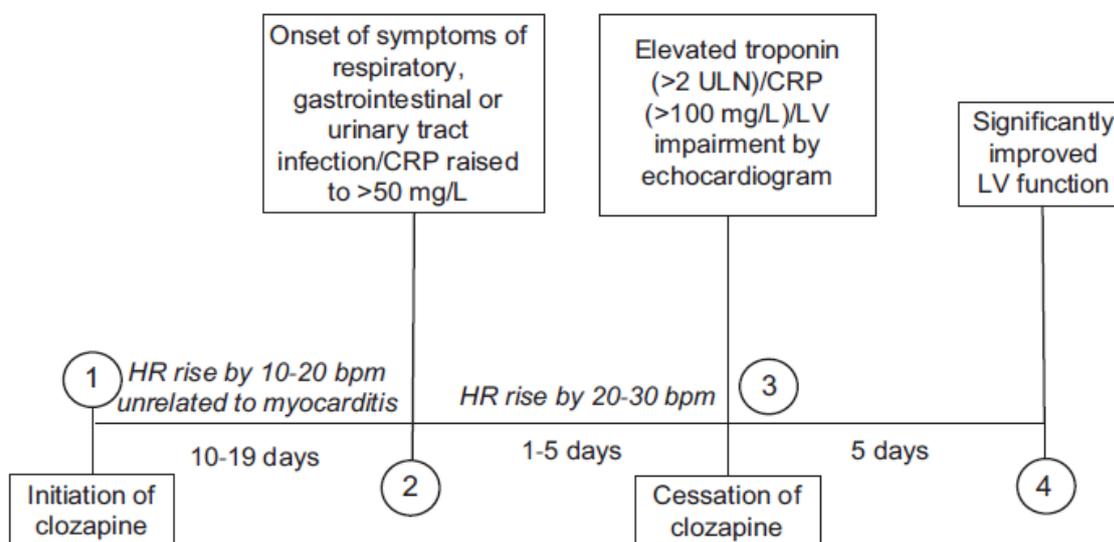


Figure 1- The typical evolution of clozapine-induced myocarditis (Ronaldson, KJ, etal)

4 MONITORING PROTOCOL

- The monitoring protocol recommends obtaining baseline troponin I or T, CRP, ECG and ECHO.
- Subsequently CRP and troponin should be monitored weekly for the first four weeks of treatment.

- During the first four weeks, vital signs and direct enquiry regarding symptoms ought to 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 troponin and CRP be measured daily and the patient monitored for developing illness.
- If 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 troponin is in excess of twice the normal maximum or CRP is more than 100 mg/L.
- Routine monitoring for myocarditis up to day 28 is recommended, in comparison to the previous guidelines which extend monitoring only to day 14.
- With a high proportion of cases of myocarditis occurring during week 3, this recommendation for actively monitoring for myocarditis during the first 4 weeks proposes that this regime will have sufficient sensitivity to pick up all symptomatic cases of myocarditis developing between days 14 and 21.

Heart rate as an indicator of myocarditis

- 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 in early diagnosis

- This protocol suggests measuring CRP along with 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 CRP of more than 50mg/L may foreshadow the onset of myocarditis.

ECG and Echocardiography (ECHO)

- Monitoring guidelines do not recommend using ECG as a means of detecting the development of myocarditis.
- Clinicians may choose to monitor heart rate by ECG and 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.

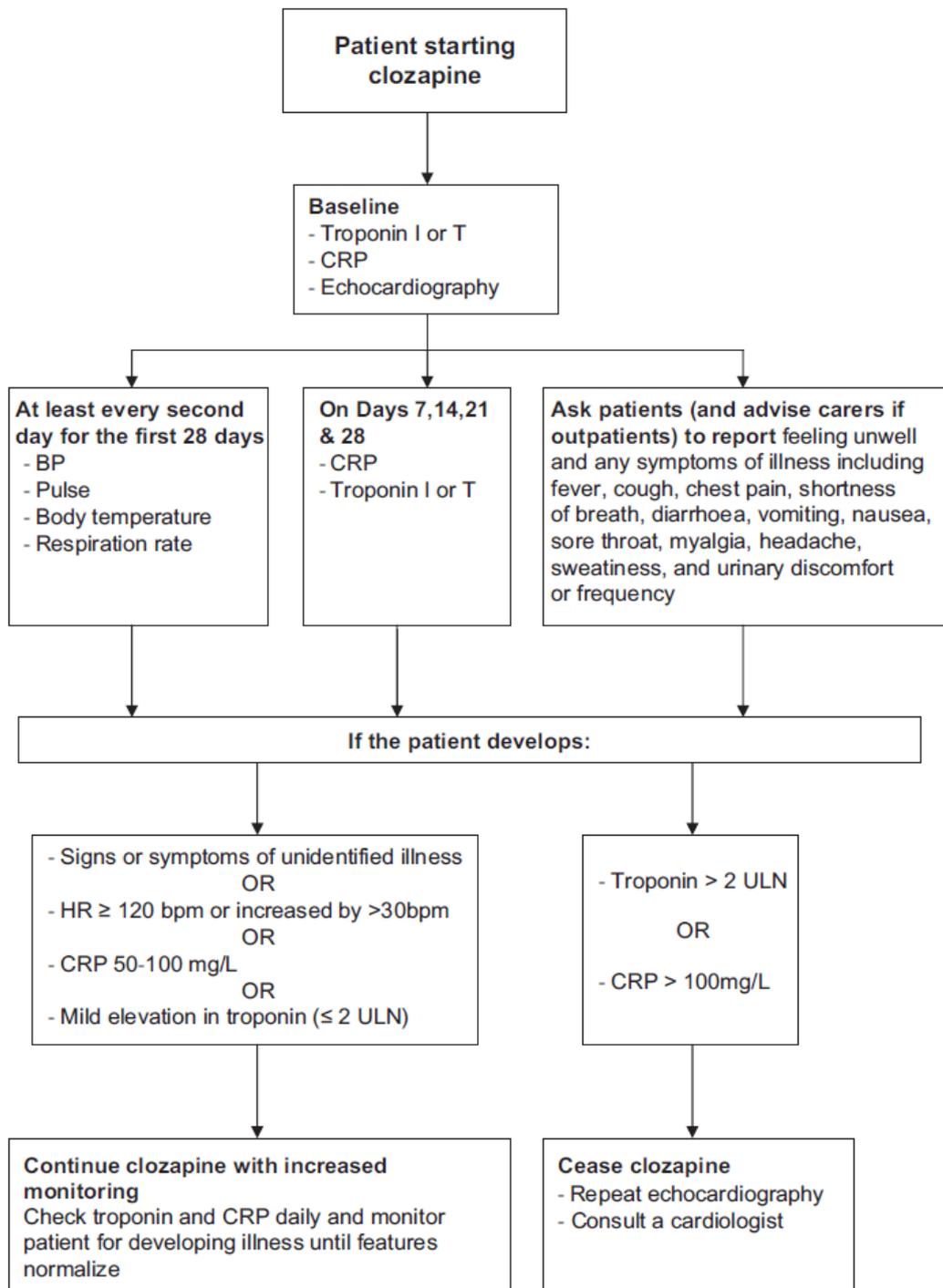


Figure 2: Proposed protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis. (Ronaldson, KJ, et al)

5 CONTINUATION OF CLOZAPINE WITH MILD DISEASE

- 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 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, certainty that cardiac function is not at risk, can be further assessed by checking CK-MB, Pro-BNP and/ or ECHO and requested a cardiologist assessment.
- Slow titration of clozapine dose is advised.

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 reveals moderate or severe left ventricular impairment a cardiology consult should be sought to further assess the need for drug or mechanical intervention.

7 ADDITIONAL INFORMATION

1. 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
2. Layland JJ, Liew, Prior DL. Clozapine-induced cardiotoxicity: A Clinical update MJA 2009; 190: 190-192.
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4. NSW Health Beat the Heat Guidelines. December 2011