

New Monitoring Guidelines for Clozapine-Induced Myocarditis

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Context

Clozapine is an exceptionally effective treatment for schizophrenia, but its use is limited by its side effects, including myocarditis.

In Australia, despite a widespread practice of monitoring for myocarditis, fatal cases continue to occur.

Clozapine-induced myocarditis :

- ❖ Drug hypersensitivity reaction
- ❖ Incidence about 2%
- ❖ About 10% of cases are fatal
- ❖ Typically occurs in the third week of clozapine therapy
- ❖ Effectiveness of current monitoring guidelines never been investigated

Aim

To develop evidence-based monitoring guidelines for clozapine-induced myocarditis, based on an analysis of 75 cases and 94 controls.

Methods

Data collection:

- ❖ Documented from patient's medical record, and autopsy report for fatal cases.

Control definition:

- ❖ Took clozapine for at least 45 days with adequate documented evidence (no tachycardia, no rise in troponin, normal echocardiography) to exclude myocarditis

Current monitoring guidelines

(circulated by Novartis and Hospira)

Baseline, Days 7 & 14:

ECG, troponin I or T (or CK MB)

Six months: echocardiography

Be vigilant for symptoms and signs of heart failure

Diagnosis of cases

Nine fatal cases:

- ❖ Mixed inflammatory infiltrates on cardiac histology

66 surviving cases:

Clinical criteria

- ❖ 63 persisting tachycardia
- ❖ 3 basal crepitations / peripheral oedema

Diagnostic evidence

- ❖ 58 troponin I/T \geq 2 ULN
- ❖ 8 LV impairment by cardiac imaging
- ❖ 1 also confirmed by MRI

Six cases were asymptomatic, and 3 of these were fatal

Controls

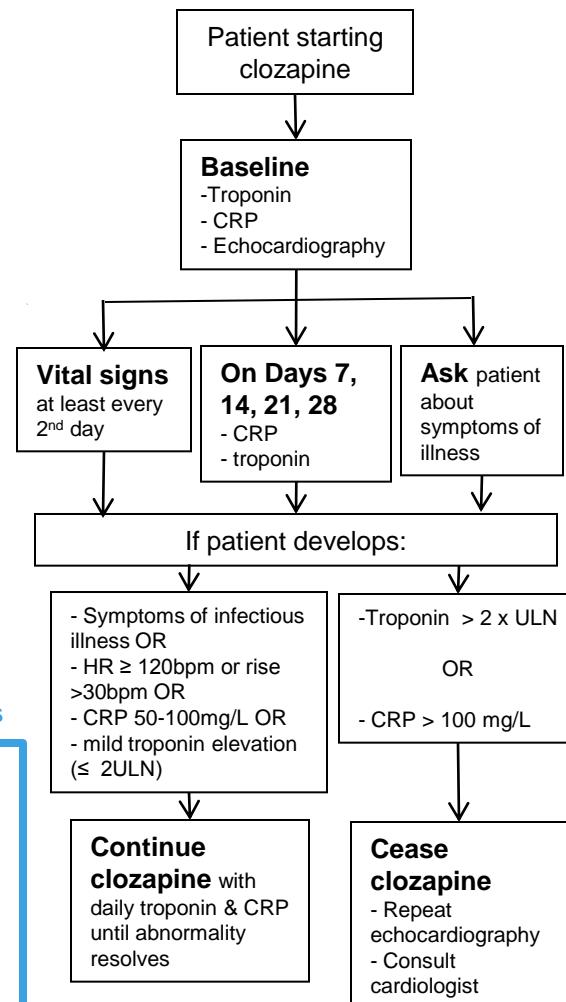
94 patients were documented as controls

Abbreviations: CK, creatine kinase; CRP, C-reactive protein; HR, heart rate; LV, left ventricular impairment; ULN, upper limit of normal.

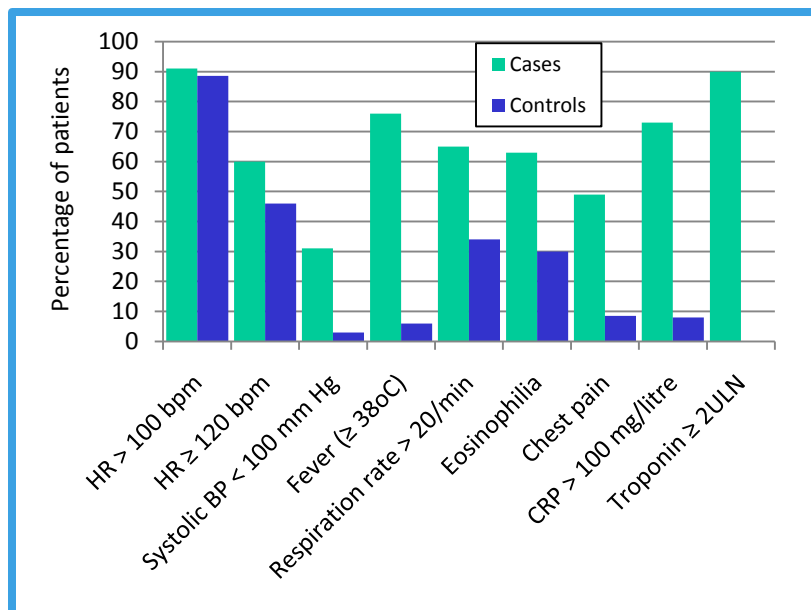
Monitoring consequences of key observations

Parameter	Observation	Consequence for monitoring
Time to onset	10-33 (mean 17.7) days	Monitor for 28 days
Troponin I/T	90% had troponin \geq 2x ULN	
CRP	87% had CRP > 50mg/L	
Troponin I/T + CRP	All symptomatic cases had troponin \geq 2x ULN or CRP > 100mg/L	Combining troponin + CRP gives 100% sensitivity for symptomatic cases
	Asymptomatic cases: none had CRP > 50 mg/L	Sensitivity for asymptomatic cases unknown
Echocardiography	LV impairment in 38 (64%) cases. Six of these without troponin rise but with CRP > 100mg/L	Echocardiography can assist in diagnosis
Eosinophils	63% cases + 30% controls with eosinophilia. Eosinophilia in cases 0-8 days after troponin peak	Eosinophils a poor measure for myocarditis diagnosis

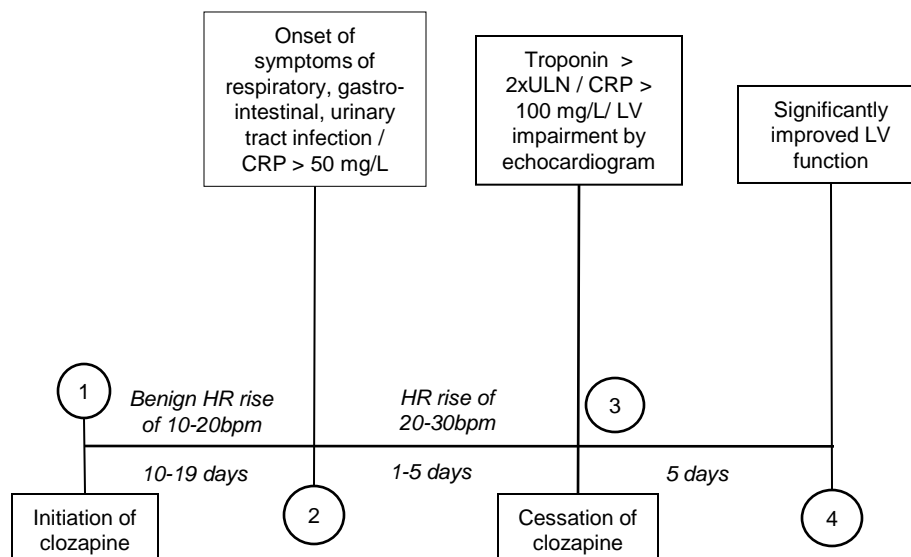
Proposed monitoring guidelines



Comparison of discriminating features of cases and controls



The typical evolution of clozapine-induced myocarditis



Differences between current and new guidelines

Feature	Current	New
Duration	14 days	28 days
Parameters	ECG troponin	CRP troponin
Symptoms / signs of:	Heart failure	Infective illness

Plus new guidelines: symptoms of illness or raised CRP a trigger to monitor CRP and troponin daily.

Conclusions

- ❖ These are the first truly evidence-based guidelines for monitoring for clozapine-induced myocarditis.
- ❖ The time to onset of myocarditis indicates the extension of monitoring to Day 28 is appropriate.
- ❖ Combining monitoring of symptoms of illness with checking troponin and CRP gives a sensitivity of 100% for symptomatic myocarditis.
- ❖ There is no guarantee that asymptomatic cases will be identified before death, even with assiduous adherence to the guidelines.