

**Clozapine rechallenge following prior index episode of Clozapine Associated Myocarditis****Keywords:****Myocarditis****CAM****Clozapine****Rechallenge****Schizophrenia****Definitions**

CRP – C- Reactive Protein

CAM – clozapine associated myocarditis

ECG – electrocardiogram

Echo- echocardiography

TRS – treatment resistant schizophrenia

PR – Pulse rate

BP – blood pressure

RR- respiratory rate

LFT- liver function test

\* - indicates initial use of pseudonym

**Abstract****Introduction**

Treatment resistant schizophrenia (TRS) is common, and can lead to significant daily distress, poor quality of life and burden on carers. Whilst clozapine is indicated for TRS, clozapine associated myocarditis (CAM) is an early risk that has resulted in clozapine cessation and for many, mental state deterioration. Rechallenge with clozapine following an index episode of CAM is increasingly being considered for some people when few other options exist for recovery.

**Main clinical findings**

We present clinical, biomarker, and physical observations in a 33 year old man with an index episode of CAM, who was successfully rechallenged three months later with clozapine, using a cautious protocol. Challenges to the titration process have been presented.

**Primary Diagnosis, interventions and outcomes**

TRS was the primary diagnosis. An index episode with high suspicion for CAM occurred using a standard Australian protocol. Subsequent cessation of clozapine followed by acute mental state deterioration in the individual led to reconsideration of clozapine and subsequent cautious rechallenge. Following exposure with low dose clozapine, there was an immediate increase in biomarkers (CRP and eosinophils), necessitating a long period of exposure to clozapine at a very low dose. Persistent eosinophilia continued for up to 6 months without any other evidence of evolving myocarditis. This eventually settled and he was able to reach a therapeutic dose of clozapine.

**Conclusion**

Rechallenge with clozapine following an index episode of CAM can be successfully achieved but requires careful physical monitoring, slow up-titration and consideration of biomarker response. More research is required to understand possible predictors of CAM in rechallenge and the role of biomarker abnormalities, particularly eosinophils, in the rechallenge process.

**Case A – Clinical information**

Mr CD\* provided informed consent use of their clinical information and date to be included in clinical publications. Mr CD was a 33 year old single man with a university bachelor degree. He was first diagnosed with schizophrenia at the age of 27 years and trialled 3 different second-generation antipsychotics with partial response, meeting the threshold for TRS. TRS had caused significant functional impairment (unemployment, social isolation, and poor quality of life). Symptoms were characterised by recurrent auditory hallucinations and

exaggeration of normal sounds, irritability, sporadic verbal outbursts, and social isolation. He had been unable to work in the area of his university qualification, causing significant self-stigma. He deteriorated acutely in the community whilst continuing with olanzapine 30mg nocte.

In 2022, he was admitted to a 24-hour Brisbane psychosocial mental health rehabilitation unit with experience in clozapine titration, for the purpose of a clozapine trial. There were no premorbid cardiology conditions with the exception of antipsychotic induced weight gain and hyperlipidemia (total cholesterol 7.1 mmol/L) and no contraindications to clozapine. He had normal baseline echocardiography, ECG, physical observations and normal biomarkers (CRP, troponin, eosinophils, monocytes). He was a lifelong non-smoker and did not take any illicit drugs or alcohol. His BMI was 35.08.

Medications at baseline:

- olanzapine 20mg nocte
- sertraline 200mg nocte
- aripiprazole 400mg IMI monthly
- Metformin slow release 2g nocte
- Coloxyl and senna 2 tablets nocte

He was prescribed a clozapine titration using standard Australian guidelines. After 14 days of clozapine titration, he experienced significant improvement in his auditory hallucinations, irritability and anxiety.

By day 15, he had developed clinical signs suggestive of evolving myocarditis with early biomarker abnormalities (CRP rise) and subsequent troponin rise and he was admitted to a cardiology unit for monitoring (available investigations from his chart are presented in Table 1). Blood cultures, urine culture, and other infective screens were negative (influenza A, B, COVID), and no alternative causes for the presentation were found. Biomarker abnormalities and the timing of these changes met Clozapine Patient Monitoring System (CPMS) thresholds suggestive of CAM -CRP >100mg/L and troponin > 2\* upper limits of normal, day 18 post titration – at a daily dose of 200mg of clozapine, which is within the expected time period for CAM diagnosis in past literature. Clozapine was ceased on day 18 and a formal diagnosis made at day 20 of CAM.

Cardiac MRI was performed on day 38 post clozapine titration (20 days post clozapine cessation), and revealed Normal LV size and function (LVEF 58%), mild myocarditis (epicardial and right ventricular insertion point enhancement), involving adjacent pericardium in the basal mid segments with pericardial effusion.

There were no adverse cardiology sequelae.

Table 1: Clozapine titration findings – Index Episode

Dose	Time	Temp, °C/ clinical al Sx	BP	PR/min + RR/min	Trop onin	CRP	Eosino -phils (0.04- 0.4)	Mono - cytes 0.2- 1.)	WCC/ Neut s	LFT	Echo	ECG
0mg	Base -line	Afebrile, N obs	120/8 3	79/min	Trop T<5, N	<5, N	N	N	N		N LV size and function, EF 57%	N
25mg/ 75mg	Day 7	Afebrile, N obs	113/8 6 no drop	PR 94/min RR 16/min	Trop T 5, N	<5, N	N	N	N	N		N
50mg/ 125mg  Clozapi- ne level - 120 nor cloz -120	Day 13	Afebrile, N, obs		115/min	Trop T <5, N	<5, N	<b>0.41</b> (mild elevatio n, ULN 0.40)	0.5 N	N			N

50mg/ 150mg	Day 14	Afebrile, N obs										N
50mg/ 150mg	Day 15	<b>Febrile, head- ache</b>										N
50mg/50 mg/150 mg	Day 16				N	<b>65mg/L</b>						
200mg	Day 17	<b>Head- ache</b>										N
Clozapin e  Ceased, 0mg	Day 18	<b>38.2 C, nausea, headache</b>  <u>Admitted to inpatient</u>	122/7 5	PR <b>118/min</b>  RR <b>20/min</b>	<b>29</b> ng/L troponin T,  Troponin I <b>126</b> ng/L	<b>90mg/L,</b> <b>126</b> later that day  Blood culture - negative	0.34, N	0.9, N	WCC- <b>11.5</b> Neuts <b>8.84</b>			Wides- pread <b>non</b> <b>specific T</b> <b>wave</b> <b>changes</b>
0mg	Day 19	<b>38.8 C</b>	<b>105/7 3</b>	PR <b>115/min</b>  RR <b>20/min</b>	<b>1038</b> ng/L troponin I							<b>Inferolateral T wave inversion</b>
0mg	Day 20				<b>694</b> ng/L troponin I							
0mg	Day 21	afebrile		PR <b>120</b>								
0mg	Day 22	Cardiology review – <b>high suspicion CAM diagnosis made</b>	124/8 1	PR 76							N LV and, LVEF ~ 55%, <b>small</b> <b>pericardial</b> <b>effusion +</b> <b>enhance</b> <b>ventricula</b> <b>r</b> <b>interdepe</b> <b>ndence</b>	
0mg	Day 24											N
0mg	Day 28				Troponin I and T - <5, N	<b>15mg/L</b>	<b>0.78</b>					
0mg	Day 38										N LV size, LVEF 55%, no pericardial effusion	

	Day 44						N	N	N	N		
0mg	Day 45				Troponin T <5	<5	0.26				CMR N LV size + function (LVEF 58%), <b>mild myocarditis</b> (epicardial and right ventricular insertion point enhancement), + adjacent pericardium ~ <b>the basal mid segments + pericardial effusion.</b>	N

Abnormal findings in **bold**. N- normal, CMR – cardiac magnetic resonance imaging, EF – Ejection Fraction, LV – left ventricular Neuts – neutrophils, WCC – white cell count LVEF – left ventricular ejection fraction, temp – temperature, Clinical Sx – clinical symptoms

#### Clozapine rechallenge

Mr CD's mental state deteriorated within a week of clozapine cessation. He was continued on oral olanzapine, 30mg nocte and aripiprazole depot 400mg IMI monthly.

Given few alternatives for his recovery, a cardiology consult was sought to consider rechallenge with clozapine using a recently published protocol. A collaborative risk-benefit analysis between the cardiology and psychiatry team occurred. Mr CD gave informed consent to a future clozapine rechallenge, supported by family who were in agreement with rechallenge. Mr CD was in good health, with normal baseline biomarker and clinical findings, except for antipsychotic-induced obesity and treated hyperlipidaemia (HDL 0.78 but all other lipids normalised)-for which he was receiving both a cholesterol-lowering agent and metformin. Mildly raised liver enzymes (GGT 85 (0-70) and ALT 86 (0-45) were also present but not thought to contradict clozapine,

He was advised by cardiology to wait 3 months before rechallenging clozapine to allow for a full recovery from the index episode of CAM. The protocol used described a successful case using a very slow up-titration and increased biomarker monitoring,<sup>1</sup> with principles of exposure to low dose clozapine to allow desensitisation. The main principles of the protocol<sup>1</sup> included:

1. Inpatient Setting
2. Low initiation dose (5mg clozapine syrup)
3. Very slow up-titration (5mg every 3 days provided biomarkers remained normal)
4. Pause up-titration and hold the same dose of clozapine until biomarkers (C -Reactive Protein (CRP), eosinophils, monocytes) normalise
5. Increased frequency of blood biomarker sampling (C -Reactive Protein (CRP), eosinophils, monocytes) and troponin – every day for 2 weeks, then three times per week thereafter
6. ECG monitoring – every 7/days
7. Twice daily physical observations (BP/PR/RR/temperature)

Clozapine dose was adapted to locally available preparations and started at 6.25mg as an oral tablet, increased by 6.25mg every 3 days provided normal biomarkers and ECG's.

**Table 2: Baseline health status pre rechallenge**

Physical observations	T 36.7 C Weight 95.3Kg, BMI 30.1kg RR 17/min PR 94/min 119/82 – no postural drop
Medications	Aripiprazole depot 400mg IMI Olanzapine 20mg nocte Atorvastatin 20mg mane Metformin 2g nocte nocte Sertraline 200mg nocte
Troponin	<5
CRP	<5, N
Eosinophils	N
Monocytes	N
E/LFT	N
ECG	N
Echocardiography	Normal LV size, with LVEF 50-55%, no other pathology

N- normal, ND – not detected, kg – kilograms

Despite very low initial dose (6.25mg), there was an immediate rise in CRP to 50mg/L (day 6) and eosinophils (day 11), necessitating a pause in clozapine up titration as per the protocol, see Table 3. CRP normalised after 2 weeks. There were no concerns regarding his physical health or evolving myocarditis except biomarker abnormalities. As per the protocol, he was continued on a very low dose of clozapine (6.25mg daily) for an extended period of time due to persistent eosinophilia and he was discharged back to the residential facility with ongoing distressing auditory hallucinations, irritability, and paranoia where he continued with low dose clozapine (6.25mg daily) clozapine.

Increased frequency (3/week biomarker monitoring) and weekly ECG continued for another month (total of 8 weeks). Concurrent olanzapine was continued throughout the clozapine titration. Clozapine levels were taken at monthly intervals. He remained anxious about his heart, and the possibility of myocarditis recurring throughout this time, requiring additional psychological support, however continued to consent to the rechallenge due to his desire to see mental state improvement on clozapine. Additional blood tests were perceived as burdensome and were reduced to weekly after 8 weeks.

As the individual was starting to become demoralised by his lack of progress on 12.5mg of clozapine – and with no other signs of myocarditis, and in the context of uncertainty about the role and significance of the eosinophils, a decision was made to deviate from the protocol and increase his dose of clozapine by 6.25mg each week despite the eosinophilia, which he and his family consented to. Eosinophils continued to be elevated through daily doses of 12.5mg/day to 75mg /day but no other abnormalities of ECG/physical observations/troponin were detected. At 75mg (week 26) the eosinophils finally normalised.

At 5 months, a persistent symptomatic tachycardia (>120/min) necessitated echocardiography and cardiology consult which revealed no significant pathology. He was started on b blocker medication at 6 months, for persistent tachycardia with good effect and was cleared by cardiology to continue clozapine.

His mental state and overall functioning continued improving approximately 6 months after the titration. He was eventually stabilised on 350mg nocte of clozapine, which was attained 46 weeks (~11 months) weeks post rechallenge. He was able to move into independent accommodation with support of family, exercise engagement and community activities.

Annual echocardiography and ECG have since revealed no significant abnormalities.

## Conclusion

This is a case involving slow exposure to clozapine after an initial index episode of CAM. A protocol involving very slow up-titration of clozapine based on the normalisation of biomarkers was followed. Early CRP and eosinophil elevations occurred at a very low dose of clozapine, necessitating a prolonged period of desensitisation. It is hypothesised that clinically significant myocarditis may have recurred without this cautious exposure, based on the rapid early rise in CRP to 50mg/L observed by day 8. His rechallenge was complicated by persistent mild eosinophilia and tachycardia but without any other clinical signs of myocarditis or other pathology (troponin, CRP, ECG, echocardiography, holter monitor). However a protocol deviation occurred and a decision was made to increase the dose cautiously despite mildly raised eosinophils as the individual became demoralised by delays to reach a treatment dose of clozapine.

Interestingly, the eosinophilia settled after 6 months and all biomarkers and cardiac investigations are now normal. There has been significant improvement in mental state and functioning on therapeutic doses of clozapine, and he was eventually discharged to community living.

Table 2: Rechallenge post index episode of CAM

Dose	Time point	Temp, °C	BP	PR/min	Troponin TNI <54	CRP	Eosinophils	Monocytes	Echo	ECG
0mg	Baseline	afebrile	125/85	93/min	N, 4	N	N, 0.16	N, 0.40	Normal LV size & function	N
6.25mg once daily	Day 1	N	125/85	98/min	4, N	5.8	0.34, N	0.51, N		N
6.25mg twice daily	Day 4	N			3	1.3, N	0.19, N	0.36, N		
6.25mg bd	Day 5	N			6		0.25	0.35		
<b>6.25mg twice daily</b>	Day 6	N			13	<b>22</b>	0.31	0.78		
6.25mg once daily	Day 7	N			17	<b>56</b>				N
	Day 8	N			10	<b>56</b>	0.39	0.72		
6.25 once daily	Day 10	N				<b>22</b>				
6.25 once daily	Day 11	N			7	<b>22</b>	<b>1.26</b>			
6.25mg once daily	Day 14									N
6.25mg once daily	Day 15		1287/88	<b>120/min</b>		5, N	<b>1.49</b>			
6.25mg	Day 20	N			N <5	4, N	<b>1.93</b>	0.29		N, tachycardia

6.25mg once daily	Day 34	afebrile	128/84	94/min PR  18/min RR						
12.5mg	Day 54		138/91	107 – <b>120 standing</b>	N, <5	CRP, <5	<b>0.65</b>	N		
12.5mg	Day 68				N, <5	CRP, <5	<b>0.82</b>	N		N
18.75m g	6/3, 15 weeks				N	N	elevated	N		
18.75m g	10/3			<b>PR 120/min</b>	Postural drop 20mmg HG					
25mg	20/3  17.5 weeks	<b>Referral to cardiolo gist</b>	147/97 – 129/70	<b>PR 128/min</b>	7	<5	<b>1.04</b>	WCC 8.7 Neuts 5.0 Mono- N		
	3/4			<b>126/min</b>	7	1.1	<b>0.78</b>	<b>WCC11.1,</b> Neuts 7.0		
	14/4									N echo, N LV function 50-55%
50mg	17/4 21 weeks			<b>139/min</b>	6	<b>8</b>	<b>0.64</b>			
50mg	24/4	Metoprol o started 12.5mg		<b>140 – 150 standing</b>	7	1.1	<b>0.43</b>			Tachycardi a on ECG
62.5mg	16/5			94/min	6	<5	<b>0.47</b>			Holter – Normal, one PR 120/min, average rate <100
75mg	18/5 26 weeks				N	<5	N			N
87.5	30/5				N	<5	N			
100mg	31/5 28 weeks									N
137.5m g	4/7			<b>103 – 134 standing</b>	N	<5	N			
150mg  Cloz 230/ norcloz 130	11/7  33 weeks		<b>128/80 – 111/80</b>	<b>116/min – 123/min standing</b>	N	<5	N			N
175mg	25/7		<b>140/90- 129/85</b>		N	<b>25</b>	<b>N</b>	WCC 7.9 Neuts 4.6		N

200mg Cloz level 330	8/8		<b>127/87</b>	94/min, - <b>105 standing</b>	N	N	N			N
300mg	21/9				N	N	N			N
	44 weeks									
350mg  Cloz 590/ Norcloz 360	16/1		120/80, no drop	<b>111/min 116 standing</b>	N	N	N	Chol 3.9, TG – 2.5, HDL 1.2		N

### Case B – Clinical information

Mr BA\* provided informed consent use of their clinical information and date to be included in clinical publications. Mr BA was a 37 year old single man, with a history of TRS for 14 years, which had caused significant functional impairment (unemployment, social isolation, and carer burden living under the care of elderly parents).

He was first diagnosed with schizophrenia at the age of 23, and trialled a number of different antipsychotics with partial or incomplete response, meeting the threshold for TRS. 10 years ago, he was offered a trial of clozapine. He had no prior physical health conditions or premorbid cardiology history with normal baseline echocardiography, ECG, physical observations and normal biomarkers (CRP, troponin, eosinophils, monocytes). He was prescribed a clozapine titration using standard Australian guidelines in an acute mental health inpatient unit in a metropolitan hospital in Brisbane and received co-prescribed risperidone 6mg nocte.

He developed non-specific T wave changes on day 7, followed by biomarker abnormalities and clinical signs suggestive of evolving myocarditis, and eventual troponin rise (available investigations from his chart are presented in Table 1).

No echocardiography, cardiac biopsy or Cardiac MRI were performed, but high suspicion of CAM was diagnosed based on biomarker and clinical findings in relation to high-risk time for CAM (first 3 weeks). Clozapine was ceased with no adverse cardiology sequelae.

Table 1: Clozapine titration findings

Dose	Time point	Temp, °C	BP	PR/min	Troponin	CRP	Eosinophils	Monocytes	Echo	ECG
0mg	Base-line	37.1	119/76	79	N	<5	N	N	EF 55%, normal	N
	Day 7									Non specific T wave changes
	Day 14	38.0		110	N	elevated		elevated		Non specific T wave changes
	Day 15	37.9								
	Day 16	37.8	Postural drop 117/77 siting- 89/59 standing							



50mg mane/150 mg nocte	Day 17	38.8	Postural drop		N			elevated		
25mg	Day 18				elevated	elevated		elevated		Non specific T wave changes
25mg	Day 19									Non specific T wave changes
CAM diagnosed Clozapine ceased	Day 20									Non specific T wave changes

N – normal

He was lost to follow up by the public mental health services for over 5 years, disengaging from treatment but continuing to experience distressing symptoms of his illness, and significant functional impairment.

### Clozapine rechallenge

10 years later he was referred to a 24 hour psychosocial residential rehabilitation despite high dose risperidone, 6mg nocte. Persistent psychotic symptoms were characterised by misidentification delusions (Capgras and Fregoli delusions), in which his parents were regularly the object of his misidentification, leading to irritability, verbal aggression and threats of violence to parents and residential mental health staff. Risperidone was changed to oral olanzapine with minor improvements in mood but persistence of psychotic symptoms meeting the criteria for TRS.

Given few alternatives for his recovery, a cardiology consult was sought to consider rechallenge with clozapine, using a recently published protocol. A collaborative risk-benefit analysis between cardiology and psychiatry team occurred and Mr BA was provided with options for future treatment. He consented to a future clozapine rechallenge. This protocol described success using a very slow up-titration and increased biomarker monitoring<sup>1</sup>. The main principles of the protocol included:

1. Inpatient Setting
2. Low initiation dose (5mg clozapine syrup)
3. Pause up-titration and prescribe the same dose of clozapine until biomarkers (C -Reactive Protein (CRP), eosinophils, monocytes) normalise
4. Very slow up-titration (5mg every 3 days provided biomarkers remained normal)
5. Increased frequency of blood biomarker sampling (C -Reactive Protein (CRP), eosinophils, monocytes) and troponin – daily for first 2 weeks, then 3/week thereafter for 8 weeks
6. ECG monitoring – every 7/days

Clozapine dose was adapted to locally available preparations and started at 6.25mg as an oral tablet, increased by 6.25mg every 3 days provided daily normal biomarkers for the first 2 weeks and weekly ECG.

Mr BA was in good health, with normal biomarker and clinical findings, except antipsychotic induced obesity and elevated total cholesterol – for which he was receiving atorvastatin and metformin.

**Table 2: Baseline health status pre rechallenge**

Physical observations	T 37.1, Weight 113.6kg RR 17/min PR 85/min 119/76 – no postural drop
Medications at baseline	Olanzapine 30mg nocte Atorvastatin 20mg mane Metformin 500mg nocte

	Sertraline 100mg mane
Troponin	ND
CRP	<5
Eosinophils	N
Monocytes	N
LFT's	N
ECG	N
Echocardiography	N LV function, EF 61%, mild mitral regurgitation

N- normal, ND – not detected, kg – kilograms

In the first month, all biomarkers remained normal throughout the rechallenge phase for every blood test, with normal weekly ECG's. There was no troponin rise or clinical symptoms of myocarditis. Physical observations remained stable, with a mild persistent tachycardia (PR 110/min), but no other abnormalities.

Mr BA's mental state began to improve within several weeks of the clozapine rechallenge, with a resolution of misidentification delusions. He was discharged to the residential facility for ongoing slow up-titration of clozapine with increased biomarker monitoring and weekly ECG for another month (total of 8 weeks). He continued weekly blood tests thereafter until he reached 18 weeks post titration, and blood tests were reduced to monthly in line with Australian clozapine prescribing guidelines for neutropenia. He was eventually stabilised on 325 mg of clozapine, which was attained at 27 weeks post rechallenge, with a clozapine level of 660 clozapine/310 norclozapine.

Rate of clozapine increase:

- 25 mg – attained at 14 days
- 50mg – 24 days
- 75 mg – 6 weeks
- 100mg – 8 weeks
- 150mg – 11 weeks
- 200mg – 13 weeks
- 300mg – 19 weeks
- 325mg – 27 weeks

His mental state and overall functioning continued to improve; he was able to move into independent accommodation and continue improved engagement with family, and engagement in community activities.

Annual echocardiography revealed no significant abnormalities.

## References

1. Shivakumar G, Thomas N, Sollychin M, et al. Protocol for Clozapine Rechallenge in a Case of Clozapine-Induced Myocarditis. *Can J Psychiatry*. Jul 2020;65(7):448-453. doi:10.1177/0706743719892709