

# Fever, tachycardia, and tachypnea during a psychotic exacerbation

Joseph Benert, MD, Arnaud Wautlet, MD, Edwin Meresh, MD, MPH, and Murali Rao, MD



## How would you handle this case?

Answer the challenge questions at [MDedge.com/psychiatry](http://MDedge.com/psychiatry) and see how your colleagues responded

Mr. C, age 23, has a 4-year history of schizophrenia. He is brought to the ED with worsening psychosis and altered vital signs. Is it an infection, or something else?

### **CASE** Posing a threat to his family

Mr. C, age 23, who was diagnosed with schizophrenia with daily auditory hallucinations 4 years earlier, is transferred from an outside psychiatric hospital to our emergency department (ED) after developing fever, tachycardia, headache, and nasal congestion for the past day. He had been admitted to the psychiatric hospital 3 weeks ago due to concerns he was experiencing increased hallucinations and delusions and posed a threat to his sister and her children, with whom he had been living.

Mr. C tells us that while at the psychiatric hospital, he had been started on clozapine, 250 mg/d. He said that prior to clozapine, he had been taking risperidone. We are unable to confirm past treatment information with the psychiatric hospital, including exactly when the clozapine had been started or how fast it had been titrated. We also were not able to obtain information on his prior medication regimen.

In the ED, Mr. C is febrile (39.4°C; 102.9°F), tachycardic (160 beats per minute; reference range 60 to 100), and tachypneic (24 breaths per minute; reference range 12 to 20). His blood pressure is 130/68 mm Hg, and his lactate level is 2.3 mmol/L (reference range <1.9 mmol/L). After he receives 3 liters of fluid, Mr. C's heart rate decreases to 117 and his lactate level to 1.1 mmol/L. His white blood cell count is  $10.6 \times 10^3/\text{mm}^3$  (reference range 4.0 to  $10.0 \times 10^3/\text{mm}^3$ ); a differential

can be found in the **Table (page 45)**. His electrocardiogram (ECG) demonstrates sinus tachycardia and a QTc of 510 ms (reference range <430 ms), but is otherwise unremarkable. His creatinine kinase (CK) level is within normal limits at 76 U/L (reference range 52 to 336 U/L). A C-reactive protein (CRP) level was not drawn at this time. Other than marijuana and cocaine use, Mr. C's medical history is unremarkable.

Mr. C is admitted to the hospital and is started on treatment for sepsis. On the evening of Day 1, Mr. C experiences worsening tachycardia (140 beats per minute) and tachypnea ( $\geq 40$  breaths per minute). His temperature increases to 103.3°F, and his blood pressure drops to 97/55 mm Hg. His troponin level is 19.0 ng/mL (reference range <0.01 ng/mL) and CK level is 491 U/L.

As Mr. C continues to deteriorate, a rapid response is called and he is placed on non-rebreather oxygen and transferred to the medical intensive care unit (MICU).

Dr. Benert is Resident Physician in Physical Medicine and Rehabilitation, University of Minnesota, Minneapolis, Minnesota. Dr. Wautlet is Resident Physician in Internal Medicine and Pediatrics, Rush University Medical Center, Chicago, Illinois. Dr. Meresh is Associate Professor of Psychiatry, Loyola University Medical Center, Maywood, Illinois. Dr. Rao is Professor and Chairman of Psychiatry, Loyola University Medical Center, Maywood, Illinois.

#### Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.



Discuss this article at [www.facebook.com/MDedgePsychiatry](http://www.facebook.com/MDedgePsychiatry)



### What is in your differential diagnosis for Mr. C's presenting symptoms?

- myocardial infarction
- infectious endocarditis
- pulmonary embolism
- clozapine-induced myocarditis
- Takotsubo cardiomyopathy

### The authors' observations

With Mr. C's presenting symptoms, multiple conditions were included in the differential diagnosis. The initial concern was for sepsis. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>1</sup> Organ dysfunction is defined by a quick Sepsis-Related Organ Failure Assessment (qSOFA) score  $\geq 2$  and is associated with an increased probability of mortality ( $>10\%$ ). Although no infection had been identified in Mr. C, the combination of fever, altered vital signs, and elevated lactate level in the setting of a qSOFA score of 2 (for respiratory rate and blood pressure) raised suspicion enough to start empiric treatment.

With Mr. C's subsequent deterioration on the evening of Day 1, we considered cardiopulmonary etiologies. His symptoms of dyspnea, hypotension, tachycardia, tachypnea, and fever were nonspecific and thus required consideration of multiple life-threatening etiologies. Thygesen et al<sup>2</sup> published an expert consensus of the definition of myocardial infarction, which was of concern given our patient's elevated troponin level. Because there was already concern for sepsis, the addition of cardiac symptoms required us to consider infectious endocarditis.<sup>3</sup> Sudden onset of dyspnea and a drop in blood pressure were concerning for pulmonary embolism, although our patient did not have the usual risk factors (cancer, immobilization, recent surgery, etc.).<sup>4</sup> Additionally, in light of Mr. C's psychiatric history and recent stressors of being moved from his sister's house and admitted to a psychiatric hospital, coupled with dyspnea and hypotension, we included Takotsubo cardiomyopathy in

Table

### Differential for Mr. C's initial white blood cell lab results

	Total number (thousands/mm <sup>3</sup> )	Percentage
Granulocytes	9.2	86%
Lymphocytes	0.6	6%
Monocytes	0.6	6%
Eosinophils	0.2	2%
Basophils	0.0	0%

the differential.<sup>5,6</sup> This disease often occurs in response to an emotional or physical stressor and is characterized by transient systolic dysfunction in the setting of ventricular wall-motion abnormalities reaching beyond the distribution of a single coronary artery. Acute ECG and biomarker findings mimic those of myocardial infarction.<sup>6</sup>

Finally, we needed to consider the potential adverse effects of clozapine. Clozapine is a second-generation antipsychotic (SGA) used to treat patients with schizophrenia for whom other antipsychotic medications are ineffective. Clozapine has been shown to be more effective than first-generation antipsychotics (FGA) in reducing symptoms of schizophrenia.<sup>7</sup> It has also been shown to be more effective than several SGAs, including quetiapine, risperidone, and olanzapine.<sup>7</sup> In fact, in patients with an insufficient therapeutic response to an SGA, clozapine proves to be more effective than switching to a different SGA. As a result of more than 20 years of research, clozapine is the gold-standard for treatment-resistant schizophrenia.<sup>7</sup> Yet despite this strong evidence supporting its use in patients with treatment-resistant schizophrenia, the medication continues to be underutilized, especially in patients at risk for suicide.<sup>7</sup>

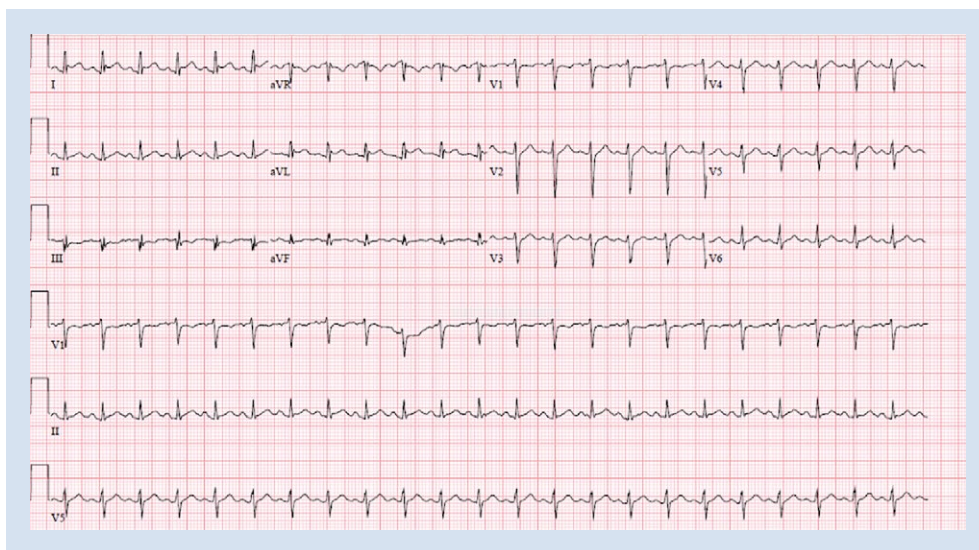
It appears that clozapine remains a third-choice medication in the treatment of schizophrenia largely due to its serious adverse effect profile.<sup>7</sup> The medication includes several black-box warnings, including severe neutropenia, orthostatic

### Clinical Point

**Clozapine is effective for patients with treatment-resistant schizophrenia but has a serious adverse effect profile**

## Figure

Electrocardiogram taken on Day 1 of Mr. C's admission demonstrates sinus tachycardia and nonspecific ST elevation in lateral leads



## Clinical Point

Clozapine-induced myocarditis is more likely to develop early on during treatment

hypotension, bradycardia, syncope, seizures, myocarditis, cardiomyopathy, and mitral valve incompetence.<sup>8</sup> Tachycardia, bradycardia, and orthostatic hypotension are all clozapine-related adverse effects associated with autonomic dysfunction, which can result in serious long-term cardiac complications.<sup>9</sup> With regards to the drug's neutropenia risk, the establishment of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program has allowed for safer use of clozapine and reduced deaths due to clozapine-induced agranulocytosis. Clinicians and pharmacists must be certified in order to prescribe clozapine, and patients must be registered and undergo frequent absolute neutrophil count (ANC) monitoring.

Clozapine-induced myocarditis, a condition observed in up to 3% of patients started on the medication,<sup>9</sup> is more likely to develop early on during treatment, with a median time of detection of 16 days following drug initiation.<sup>10</sup> Myocarditis often presents with nonspecific signs and symptoms that include chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, and/or hypotension.

What laboratory/imaging tests would you next order for Mr. C?

- arterial blood gas (ABG) analysis
- cardiology consult
- ECG
- all of the above

## The authors' observations

Initial workup in the MICU for Mr. C included an ABG analysis, ECG, and cardiology consult. The ABG analysis demonstrated metabolic alkalosis; his ECG demonstrated sinus tachycardia and nonspecific ST elevation in the lateral leads (*Figure*). The cardiology consult team started Mr. C on treatment for a non-ST-elevation myocardial infarction (NSTEMI), which it believed to be most likely due to myocarditis with secondary demand ischemia, and less likely acute coronary syndrome. The cardiology consult team also recommended performing a workup for pulmonary emboli and infectious endocarditis if Mr. C's symptoms persist or the infectious source could not be identified.

**EVALUATION** Gradual improvement

Mr. C demonstrates gradual improvement as his workup continues, and clozapine is held on the recommendation of the cardiac consult team. By Day 2, he stops complaining of auditory hallucinations, and does not report their return during the rest of his stay. His troponin level decreases to 8.6 ng/mL and lactate level to 1.4 mmol/L; trending is stopped for both. The erythrocyte sedimentation rate (ESR) is elevated at 59 mm/hr (reference range 0 to 22 mm/hr), along with a CRP level of 21 mg/L (reference range <8.0 mg/L). An echocardiogram demonstrates a 40% ejection fraction (reference range 55% to 75%) and moderate global hypokinesis. The cardiology consult team is concerned for Takotsubo cardiomyopathy with sepsis as a source of adrenergic surge vs myopericarditis of viral etiology. The cardiology team also suggests continued stoppage of clozapine, because the medication can cause hypotension and tachycardia.

On Day 3, Mr. C's ST elevation resolves on ECG, and his CK level decreases to 70 U/L, at which point trending is stopped. On Day 5, Mr. C undergoes MRI, which demonstrates an ejection fraction of 55% and confirms myocarditis. No infectious source is identified.

By Day 6, with all other sources ruled out, clozapine is confirmed as the source of myocarditis for Mr. C.

**The authors' observations**

Close cardiovascular monitoring should occur during the first 4 weeks after starting clozapine because 80% of cases of clozapine-induced myocarditis occur within 4 weeks of clozapine initiation.<sup>10</sup> Baseline CRP, troponin I/T, and vital signs should be obtained before starting clozapine.<sup>11</sup> Vital signs must be monitored to assess for fever, tachycardia, and deviations from baseline blood pressures.<sup>11</sup> Although eosinophil counts and percentages can also be considered in addition to a baseline CRP value, they have not proven to be

sensitive or specific for clozapine-induced myocarditis.<sup>12</sup> A baseline echocardiogram can also be obtained, but is not necessary, especially given that it may not be readily available in all clinics, and could therefore delay initiation of clozapine and limit its use. C-reactive protein and troponin levels should be assessed weekly during the first 6 weeks of clozapine therapy.<sup>11</sup> For symptomatic patients presenting with concern for clozapine-induced myocarditis, a CRP level >100 mg/L has 100% sensitivity in detecting clozapine-induced myocarditis.<sup>13</sup> Clozapine should also be stopped if troponins levels reach twice the upper limit of normal. More mild elevations of CRP and troponins in the setting of persistent tachycardia or signs of an infectious process should be followed by daily CRP and troponins levels until these features resolve.<sup>11</sup>

Mr. C's case highlights clinical features that clinicians should consider when screening for myocarditis. The development of myocarditis is associated with quick titrations of clozapine during Days 1 to 9. In this case, Mr. C had recently been titrated at an outside hospital, and the time frame during which this titration occurred was unknown. Given this lack of information, the potential for a rapid titration should alert the clinician to the risk of developing myocarditis. Increased age is also associated with an increased risk of myocarditis, with a 31% increase for each decade. Further, the concomitant use of valproate sodium during the titration period also increases the risk of myocarditis 2.5-fold.<sup>14</sup>

When evaluating a patient such as Mr. C, an important clinical sign that must not be overlooked is that an elevation of body temperature of 1°C is expected to give rise to a 10-beats-per-minute increase in heart rate when the fever is the result of an infection.<sup>15</sup> During Day 1 of his hospitalization, Mr. C was tachycardic to 160 beats per minute, with a fever of 39.4°C. Thus, his heart rate was elevated well beyond what would be expected from a fever secondary to an

**Clinical Point**

**Baseline CRP, troponin I/T, and vital signs should be obtained before starting clozapine**

**Clinical Point**

**Prompt discontinuation of clozapine should lead to spontaneous resolution of myocarditis**

**Related Resources**

- Clozapine Risk Evaluation and Mitigation Strategy [REMS] Program. What is the Clozapine REMS Program? <https://www.clozapinerems.com>.
- Keating D, McWilliams S, Schneider I, et al. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. *BMJ Open*. 2017;7(1):e013881.
- Curto M, Girardi N, Lionetto L, et al. Systematic review of clozapine cardiotoxicity. *Curr Psychiatry Rep*. 2016;18(7):68.

**Drug Brand Names**

Clozapine • Clozaril	Risperidone • Risperdal
Olanzapine • Zyprexa	Valproate • Depacon
Quetiapine • Seroquel	

infectious process. This further illustrates the need to consider adverse effects caused by medication, such as clozapine-induced tachycardia.

While clozapine had already been stopped in Mr. C, it is conceivable that other patients would potentially continue receiving it because of the medication’s demonstrated efficacy in reducing hallucinations; however, this would result in worsening and potentially serious cardiac symptoms.

**What is an appropriate ongoing treatment for a patient who experiences clozapine-induced myocarditis?**

- clozapine rechallenge
- another antipsychotic plus a mood stabilizer
- electroconvulsive therapy (ECT) augmentation

**The authors’ observations**

A diagnosis of clozapine-induced myocarditis should be followed by a prompt discontinuation of clozapine. Discontinuation of the drug should lead to spontaneous resolution of the myocarditis, with significantly improved left ventricular function observed within 5 days.<sup>13</sup> Historically, rechallenging a patient with clozapine was not recommended, due to fear of recurrence of myocarditis. However, recent case studies indicate that myocarditis need not be an absolute contraindication to restarting clozapine.<sup>16</sup> Rather, the risks must be balanced against demonstrated efficacy in patients who had a limited response to other antipsychotics, as was the case with Mr. C. For these patients, the decision to rechallenge should be made with the patient’s informed consent and involve slow dose titration and increased monitoring.<sup>17</sup> Should this rechallenge fail, another antipsychotic plus augmentation with a mood stabilizer or ECT may be more efficacious than an antipsychotic alone.<sup>18,19</sup>

**OUTCOME Return to the psychiatric hospital**

On Day 8, Mr. C is medically cleared; he had not reported auditory hallucinations since Day 2. He is discharged back to the psychiatric hospital for additional medication management of his schizophrenia.

continued on page 51

**Bottom Line**

Clozapine-induced myocarditis should be included in the differential diagnosis for patients who present with nonspecific complaints and have an incomplete history pertaining to clozapine use. After discontinuing clozapine, and after myocarditis symptoms resolve, consider restarting clozapine in patients who have limited response to other treatments. If rechallenging fails, another antipsychotic plus augmentation with a mood stabilizer or electroconvulsive therapy may be more efficacious than an antipsychotic alone.



## Cases That Test Your Skills

continued from page 48

### References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-2567.
3. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet*. 2016;387(10021):882-893.
4. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest*. 1991;100(3):598-603.
5. Summers MR, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): potential pre-disposing factors? *J Am Coll Cardiol*. 2010;55(7):700-701.
6. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373(10):929-938.
7. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry*. 2014;14:102.
8. Clozaril [package insert]. Rosemont, PA: HLS Therapeutics (USA), Inc.; 2016.
9. Ronaldson KJ. Cardiovascular disease in clozapine-treated Patients: evidence, mechanisms and management. *CNS Drugs*. 2017;31(9):777-795.
10. Haas SJ, Hill R, Krum H, et al. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Saf*. 2007;30(1):47-57.
11. Goldsmith DR, Cotes RO. An unmet need: a clozapine-induced myocarditis screening protocol. *Prim Care Companion CNS Disord*. 2017;19(4): doi: 10.4088/PCC.16l02083.
12. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Evolution of troponin, C-reactive protein and eosinophil count with the onset of clozapine-induced myocarditis. *Aust N Z J Psychiatry*. 2015;49(5):486-487.
13. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry*. 2011;45(6):458-465.
14. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study. *Schizophr Res*. 2012;141(2-3):173-178.
15. Davies P, Maconochie I. The relationship between body temperature, heart rate and respiratory rate in children. *Emerg Med J*. 2009;26(9):641-643.
16. Cook SC, Ferguson BA, Cotes RO, et al. Clozapine-induced myocarditis: prevention and considerations in rechallenge. *Psychosomatics*. 2015;56(6):685-690.
17. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Observations from 8 cases of clozapine rechallenge after development of myocarditis. *J Clin Psychiatry*. 2012;73(2):252-254.
18. Singh SP, Singh V, Kar N, et al. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry*. 2010;197(3):174-179.
19. Wenzheng W, Chengcheng PU, Jiangling Jiang, et al. Efficacy and safety of treating patients with refractory schizophrenia with antipsychotic medication and adjunctive electroconvulsive therapy: a systematic review and meta-analysis. *Shanghai Arch Psychiatry*. 2015;27(4):206-219.