Clozapine in the Medically Ill, Between a Rock and a Hard Place: A Case Report of Initiating Clozapine in a Burn Patient

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Background

- Different international guidelines have been developed for clozapine treatment in the general population (1). No specific guidelines exist for the medically ill taking clozapine, despite facing multiple obstacles in managing this population.

Objectives

- To describe the challenges in management of patients on clozapine when they are admitted to medical units.
- To formulate a framework to address these challenges.
- To propose changes in the current clozapine guidelines to aid in management of clozapine patients when they become medically ill.

Case

Mr. C is a 38-year-old male with schizoaffective disorder. He presented to the Emergency Department (ED) with third-degree burns covering 65% of his total body surface area. He had doused himself with gasoline and set himself on fire.

Mr. C had 10 previous psychiatric hospitalizations due to aggression, manic symptoms, suicide attempts, mass-shooting threats, hallucinations and persecutory delusions. Home medications included lithium 600mg, haloperidol 20mg, olanzapine 30mg daily and monthly intramuscular injections of haloperidol decanoate 100mg.

Upon arrival to ED, he was admitted to the Burn Intensive Care Unit (B-ICU) for surgical management and stabilization. His B-ICU course was complicated by pneumonia, respiratory failure with subsequent intubation, wound infections, and osteomyelitis. Psychiatric medications were continued except for lithium.

Four weeks after admission to B-ICU, when the patient was extubated, he became agitated, responding to internal stimuli and endorsed paranoid delusions. He recalled setting himself on fire and was ambivalent about surviving his suicidal attempt.

Medically, he continued to have intermittent fevers and had several surgical excisions. He developed C. difficile colitis and screened positive for delirium on CAM-ICU multiple times. Haloperidol and olanzapine were continued.

Two months into his hospitalization, Mr. C was stepped down from the B-ICU to the general Burn Unit but continued to have wound infections with intermittent fevers. His psychiatric symptoms did not change, except for delirium which improved. As he continued to require surgical care, no discharge was imminent.

Given the acuity of psychiatric symptoms and the failure of a 2-month-long trial of combined antipsychotics, he was started on clozapine while he was in the Burn Unit. After a baseline work-up, clozapine dose was titrated up leading to significant improvement in psychotic symptoms and suicidal ideations. Meanwhile, he continued to have intermittent fevers related to wound infections and surgical procedures.

As the total daily dose of clozapine reached 175mg/day, we noticed deterioration with worsening hallucinations, social withdrawal, and increased sedation in the context of worsening delirium, despite an overall improvement in other medical problems. A thorough work-up did not reveal a cause for the worsening of delirium. Clozapine was gradually decreased to 100mg daily which resulted in improvement in his psychotic symptoms and eventual resolution of delirium.

For the remainder of his hospitalization, Mr. C remained psychiatrically stable on clozapine 100mg, and his medical problems improved. He was discharged to a physical rehabilitation center.

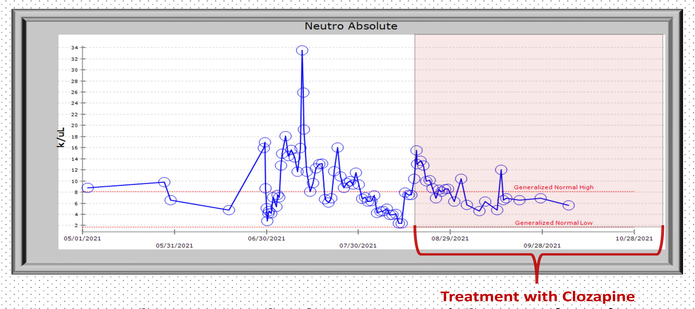


Figure 1: Changes in Absolute Neutrophil Count (ANC).
The changes in CBC/ANC due to severe medical illnesses sometimes affect their validity in monitoring for clozapine-induced agranulocytosis.

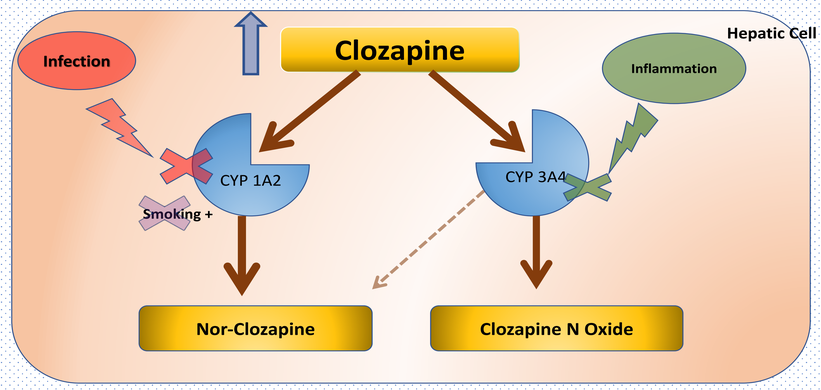
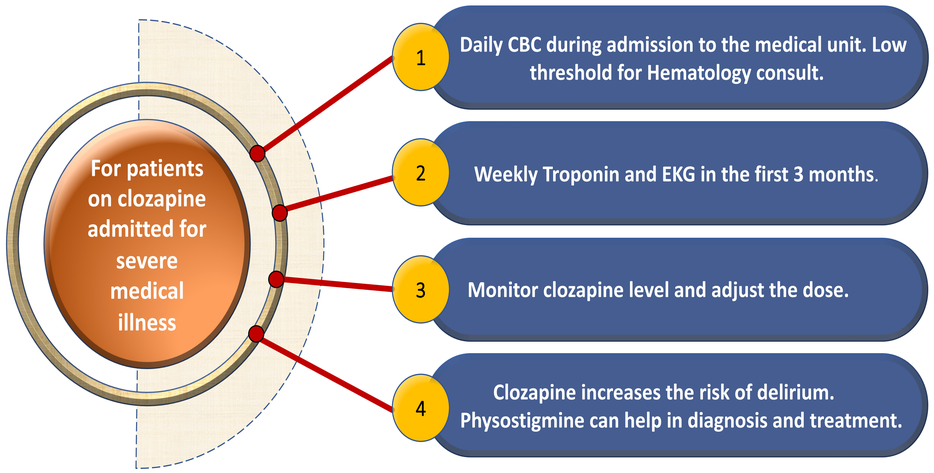


Figure 2: Clozapine Serum Level Increases in the Medically Ill.

Summary of Recommendations



Guidelines should require at LEAST one trough clozapine level obtained right after clinical stabilization of the mental disorder. This will serve as an anchor in guiding dose adjustment when patients become medically ill.

Discussion: Challenges and Solutions

1. In our patient, changes in Complete Blood Count (CBC) and ANC due to medical problems did affect their validity in monitoring for agranulocytosis (Figure 1). Clinicians should be aware of that in the medically-ill and should have a low threshold for consulting Hematology, especially in cases of benign ethnic neutropenia (BEN).

2. In the United States, detecting clozapine-induced myocarditis (CIM) depends mainly on monitoring for the signs and symptoms. In the medically ill, a variety of medical problems can produce non-specific signs and symptoms that mimic those seen in myocarditis, including fatigue, dyspnea, fever and tachycardia. Segev et al. (2) suggest that troponin, and EKG monitoring yields a specific and sensitive tool in capturing `CIM. Since almost all cases of CIM occur within 90 days of initiating treatment (3), we strongly suggest baseline, then weekly monitoring of Troponin and EKG in the first 3 months after initiating clozapine for all patients admitted to hospital for medical reasons.

3. Studies found that inflammation (4) and infection (5) cause a substantial increase in clozapine serum levels (CSL) which correlates with clozapine toxicity (6). In addition, smoking cessation during hospitalization may result in further increases in (CSL), by the removal of the CYP-1A2-inducing effect of the polycyclic aromatic hydrocarbons in tobacco (7) (Figure 2). Whereas more studies are needed to address this; for now, we suggest checking CSL frequently during admission to avoid toxicity and maintain an adequate therapeutic level. However, a baseline CSL obtained prior to the onset of medical illness can serve as an anchor in guiding dose adjustment when patients become medically ill. Thus, we propose that current guidelines should require a baseline CSL for all patients taking clozapine.

4. Clozapine is highly anticholinergic and can cause delirium even in medically-stable patients (8). This creates a dilemma in the medically-ill taking clozapine, especially if they become delirious. In these situations, it's often difficult to determine if the delirium is caused by clozapine, the medical illness itself or both. Spring et al. suggested that a physostigmine challenge test can help in the diagnosis and management of delirium in these patients (9). However, clinicians should weigh the risks and benefits of using physostigmine in this setting, especially given the serious side effects shared between clozapine and physostigmine (e.g., seizures, conduction abnormalities, etc...), and the complexity of medical problems in these patients.

5. Consultation-Liaison psychiatrists have the expertise in initiating and monitoring clozapine treatment, and they are familiar with the pathophysiology of medical illnesses which might affect that treatment. Thus, they play a pivotal role in management of patients taking clozapine when they become medically ill.

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