Serotonin Syndrome After Methylene Blue Administration: A Case Report
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DEFINITION
- Toxidrome due to excessive serotonin receptor activities in central nervous system
- Normally due to medications and drug interactions
- Several drug classes have serotonergic effects
- Wide range of clinical presentation
- Life-threatening
- Mortality around 11%

EPIDEMIOLOGY
- First noted in 1960s in studies of single and combination antidepressants usage
- All age groups involved
- Incidence of syndrome parallels with increased use of serotonergic agents
- Most likely drug class associated with syndrome: serotonin reuptake inhibitors
- Might be more common among chronically and/or critically ill patients due to multiple drug use and decreased drug metabolism
- Incidence difficult to assess due to misdiagnosis and dismissal of mild symptoms

COMMON CAUSES
- SSRI, bicyclic antidepressants, tramadol, buprenorphine, carbamazepine, valproate, ondansetron, metoclopramide, St. John’s wort
- MAOI, linezolid, methylene blue
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- SSRI, tricyclic antidepressants, tramadol, metoclopramide, St. John’s wort
- Benzodiazepines for agitation
- Neurology consultation: determined likely serotonin syndrome
- Neurology consultation: agreed with likely serotonin syndrome
- Physical and neurological exam
- Patient’s medication history
- Hunter Serotonin Toxicity Criteria considered as gold standard
- Improved sensitivity and specificity to 84% and 97%, respectively
- Systematic review of 412 cases showed that Hunter criteria miss 37% of cases while other criteria miss only 10 or 24% of cases

CLINICAL PRESENTATION
- 62-year-old male with history of ischemic cardiomyopathy status post left ventricular assist device (LVAD), prostate cancer, transient ischemic attack, type 2 diabetes mellitus, hypertension, obesity, obstructive sleep apnea, chronic obstructive pulmonary disease, chronic kidney disease, general anxiety disorder and depression
- Presented to emergency department for low flow alarms from LVAD
- Admitted to advanced heart failure service
- Approved for heart transplant and removal of LVAD
- Vasopleria during surgery requiring methylene blue for vasopressor
- After surgery, worsening kidney function with creatinine level to 2.1 mg/dL from baseline of 1.6-1.8 mg/dL
- On post-op day 1, patient have difficulty following commands
- Shaking or dorsiflexion of ankles and feet
- Fever at maximum temperature of 38.7 degree Celsius
- Tachycardia at 100 bpm
- Differential diagnoses for symptoms include infection, seizure, anticholinergic toxicity, neuroleptic malignant syndrome, serotonin syndrome
- Neurology consultation: determined likely serotonin syndrome
- Neurology consultation: agreed with likely serotonin syndrome
- Symptom resolution on post-op day 2
- Improved creatinine level and urine output
- Tachycardic at 100 bpm
- Hyperthermia above 39°C
- Worsening hyperthermia
- Shaking or dorsiflexion of ankles and feet
- Extremity clonus, increased patellar reflex, rigid dorsiflexion of calcaneal tendon, Babinski’s sign, roving extraocular movements
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TREATMENT
- Symptomatic treatment
- Discontinue all serotonergic agents
- Cooling methods for hyperthermia and IV fluids for tachycardia and hypertension/hypotension
- No use for antipsychotic medications
- Benzodiazepines for agitation
- Medications preferred over physical restraints to avoid risk of rhabdomyolysis and worsening hyperthermia
- Hyperthermia above 41°C should be intubated and paralyzed to address muscle rigidity
- Mild cases may just need close observation
- Can consider ciprofloxacin if refractory

REFERENCES
Cung, T., & Perman, S. (2022). Methylene blue and the risk of serotonin toxicity?search=serotonin%20syndrome&source=search_result&selectedTitle=1~128&usage_type=default&display_rank=1#H10