



# A case report of an 18-year-old receiving nebulized lidocaine for treatment of COVID-19 cough

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## ARTICLE INFO

### Article History:

Received 11 May 2022

Revised 14 September 2022

Accepted 19 September 2022

Available online 22 September 2022

### Keywords:

COVID-19

Cough

Extracorporeal membrane oxygenation

Lidocaine

Adolescent

Child

## ABSTRACT

An 18-year-old girl presenting with respiratory and gastrointestinal symptoms was found to have COVID-19 pneumonia and severe acute respiratory distress syndrome (ARDS). She was transferred to our pediatric intensive care unit (PICU) for ongoing mechanical ventilation and initiation of venovenous extracorporeal membrane oxygenation (VV-ECMO) for management of progressive hypoxic respiratory failure. She developed a worsening cough with associated life-threatening desaturation events that impaired ECMO flow and required deep sedation. Despite multiple sedative agents, our patient continued to have frequent coughing episodes with associated tachycardia, hypertension, and hypoxemia. The PICU team started nebulized lidocaine 1% 4 mL (40 mg) every 6 hours with albuterol pretreatment, gabapentin, and scheduled ipratropium. Lidocaine levels were < 1 mcg/mL throughout the treatment duration. Nebulized lidocaine was stopped after 18 days given improvement in coughing episode severity. Our patient is one of the first reports of an adolescent patient receiving nebulized lidocaine for COVID-19 associated cough. Administration of nebulized lidocaine was well tolerated in this patient without adverse effects and was associated with decreased sedation needs. Given the widespread impact of the COVID-19 pandemic and its sequelae in pediatric, adolescent, and adult patients, additional research is warranted to explore options for management of COVID-19 associated cough.

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## Introduction

The COVID-19 pandemic has had widespread impacts on patients of all ages. Management of COVID-19 associated cough, a common complication of COVID-19 pneumonia, has presented challenges for healthcare providers.

Lidocaine, gabapentin, ipratropium and tiotropium, inhaled morphine, and aprepitant have been studied in treatment of chronic cough and have been suggested as potential options for management of COVID-19 cough.<sup>1-8</sup>

Lidocaine, a Class Ib antiarrhythmic, has well-known antiarrhythmic and local anesthetic properties. Both nebulized and intravenous lidocaine have been studied for use as a cough suppressant, primarily as single doses to prevent coughing associated with invasive procedures.<sup>9-12</sup> Limited data is available for intermittent nebulized lidocaine for the management of cough, and to our knowledge, there are

no published reports of nebulized lidocaine for management of COVID-19 associated cough in an adolescent patient.

This case report describes the use of nebulized lidocaine, gabapentin, and ipratropium in an 18-year-old patient with severe COVID-19 associated cough.

## Case presentation

An 18-year-old girl (70.6 kg) with a past medical history of mild intermittent asthma, Type 1 diabetes, and depression presented to the emergency department of an outside hospital following five days of respiratory distress, hypoxemia, and gastrointestinal symptoms. She was not vaccinated against COVID-19. Prior to admission, she was receiving fluoxetine 10 mg once daily and insulin, and she had no known drug allergies. On hospital day (HD) 1, she started dexamethasone 6 mg once daily to complete a 7-day course, as well as remdesivir 200 mg once on HD 1, then 100 mg for the next 4 days. Anakinra 100 mg IV every 8 hours was started on HD 7 due to concerns for ongoing inflammation. She developed a refractory cough on HD 7. After 8 days at the referring hospital PICU, she developed worsening hypoxemia requiring endotracheal intubation and mechanical ventilation.

*Abbreviations:* acute respiratory distress syndrome, ARDS; dextrose 5% in water, D5W; hospital day, HD; neutrophil extracellular traps, NETs; pediatric intensive care unit, PICU; propofol-related infusion syndrome, PRIS; venovenous extracorporeal membrane oxygenation, VV-ECMO; veno-veno-arterial extracorporeal membrane oxygenation, VVA-ECMO

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<https://doi.org/10.1016/j.hrtlng.2022.09.009>

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On HD 8 she was transferred to our hospital for VV-ECMO for worsening hypoxemia and air-leak syndrome. Her anakinra was increased to 300 mg IV every 8 hours on HD 8. She remained on VV-ECMO for 14 days and was then transitioned to veno-veno-arterial extracorporeal membrane oxygenation (VVA-ECMO) on HD 22 due to severe right ventricular dysfunction. She was also placed on continuous renal replacement therapy on HD 23.

Over the first 3 weeks of the patient's ECMO course, the PICU team worked to optimize sedation through a combination of scheduled opioids, benzodiazepines and a dexmedetomidine infusion. Despite maximized doses of sedative agents, the patient required initiation of a cisatracurium infusion on HD 22 to minimize coughing and metabolic demand. On HD 26, her coughing episodes worsened, and she began to experience tachycardia, hypertension, and significant desaturation events multiple times per day with minimal relief from as-needed ipratropium. She was trialed off cisatracurium on HD 27. Due to continued coughing episodes, propofol 30 mcg/kg/min was initiated on HD 27 to provide additional sedation and prevent coughing-associated decreases in ECMO flow which led to severe desaturation episodes. She received one dose of rocuronium 1 mg/kg for coughing episodes on HD 26, 27, 28, and 30 (2 doses) due to minimal relief with ipratropium. She was extubated on HD 29 and continued to experience coughing episodes that led to severe desaturations (SpO<sub>2</sub> 50%). These coughing episodes were somewhat improved with intermittent increases in ECMO sweep to minimize her drive to breathe.

She received one dose of dextromethorphan 10 mg on HD 30 with minimal relief. Given the patient was receiving trazodone at bedtime, as well as linezolid for *Staphylococcus aureus* bacteremia, there was hesitation to continue dextromethorphan due to risk of serotonin syndrome with concomitant administration of these medications. Her propofol was titrated up to 90 mcg/kg/min on HD 30, and she received multiple 35–70 mg boluses as needed for sedation and for coughing episodes that led to impaired ECMO flow and associated desaturation events (Figs. 1 and 2). Her high sedation needs prohibited participation in occupational and physical therapy sessions critical to her rehabilitation plan. There were concerns regarding the risk of propofol-related infusion syndrome (PRIS) given the extended course and high rates required; however, PRIS monitoring labs remained within normal limits. Given the potential deleterious effects of a prolonged sedation course and the frequency of these life-threatening desaturation events, the team explored alternatives to manage her cough.

Nebulized lidocaine 1% 4 mL (40 mg) every 6 hours was started on HD 31, along with albuterol 5 mg every 6 hours administered prior to lidocaine to prevent bronchospasm. Nebulized lidocaine 1% was prepared by mixing 1 mL of lidocaine 4% with 3 mL normal saline in a syringe for nebulization. While lidocaine 1% is a commercially available product, the diluent at our institution for lidocaine 1% was

dextrose 5% in water (D5W) and previous studies had only used normal saline as a diluent for nebulized lidocaine. Lidocaine was administered via positive pressure to optimize medication delivery given concerns for decreased pulmonary compliance and low patient tidal volumes. Gabapentin 300 mg TID and ipratropium 500 mcg q6h were also started to target other potential mechanisms of cough (Fig. 2).<sup>1–4</sup>

Serum lidocaine levels were drawn to monitor for systemic absorption. The lidocaine level drawn 12 hours after the first dose was <1 mcg/mL. Levels were drawn daily for three days after the first dose and remained <1 mcg/mL. After these results, the team reduced the serum lidocaine monitoring frequency to once weekly, and levels remained <1 mcg/mL for 2 weeks, which was below the 5 mcg/mL threshold above which the risk for lidocaine toxicity is significantly increased.<sup>13</sup> Nebulized lidocaine was discontinued after 18 days given decreased frequency and severity of coughing episodes and reduced incidence of severe cut-outs in her ECMO flow.

Our institution does not routinely utilize a specific tool for assessing cough frequency and severity, so an assessment of her sedation needs was one way our team measured efficacy of nebulized lidocaine. Four days prior to initiating nebulized lidocaine (HD 28), she started receiving propofol boluses 35–70 mg as needed per physician instruction for coughing episodes. She received an average of 5.5 boluses per day (range 3–8 boluses/day, 85 mg–325 mg/day) (Fig. 2). Her mean total daily dose of propofol boluses (not including her propofol infusion rate) was 211 mg/day, or 3 mg/kg/day. After starting nebulized lidocaine on HD 31, she received propofol for 7 more days until it was discontinued. During the 7 days after starting, she received an average of 2.4 propofol boluses per day of 50 mg (range 0–8 boluses/day, 0–400 mg/day). Her mean total daily dose of propofol boluses over the 7-day period was 121 mg/day (1.7 mg/kg/day), and she did not receive any boluses for 3 days (HD 35, 36, and 37). Her infusion rate decreased after starting lidocaine as well (Fig. 2). Her dexmedetomidine infusion was weaned off on HD 47 (day 16 of nebulized lidocaine) due to concern for bradyarrhythmias.

Additionally, the PICU attending reported that coughing spells associated with desaturations improved in the 48 hours following initiation of inhaled lidocaine. The PICU attending progress note on HD 32 reported “coughing spells associated with desaturation improving over [the] last 24–48 h” and on HD 33 reported “coughing spells associated with desaturations persistent but improving.” On HD 34 and 35, the note reported “initially tolerated sedation weans to be more participatory in cares but this has resulted in persistent coughing fits – initially tolerated reasonably well, but now with worsening coughing fits and migration of cannula distally.”

Albuterol prior to lidocaine nebulization was administered for the first 7 days and then discontinued after the patient did not demonstrate any bronchospasm with lidocaine administration. She did not experience any bronchospasm after albuterol discontinuation. Scheduled ipratropium was continued for 8 days and then discontinued due to lack of perceived benefit. Gabapentin was up-titrated to 300 mg in the morning, 300 mg in the afternoon, and 900 mg in the evening.

The patient underwent rehabilitation with ongoing VV-ECMO support, and she experienced intermittent coughing episodes that were not associated with impaired ECMO flow nor severe desaturation events. She ultimately chose to withdraw life-sustaining treatments and passed peacefully on HD 161.

## Discussion

To our knowledge, our patient is one of the first adolescent patients to receive nebulized lidocaine for management of COVID-19-associated coughing episodes.

It has been proposed that the sodium and calcium channel blockade from lidocaine could offer anti-inflammatory properties.<sup>14–17</sup> A study by Lai et al. reported that the activation of sodium channels

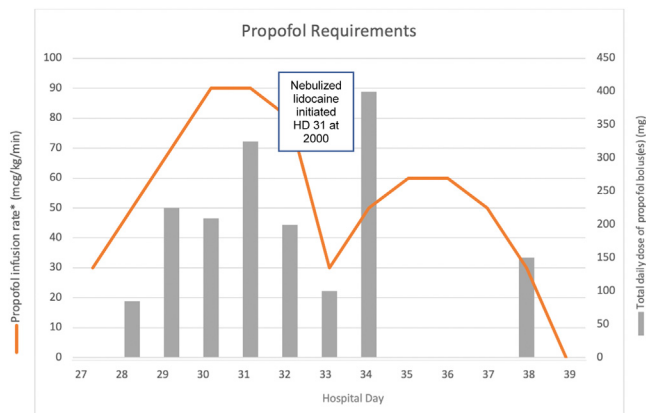


Fig. 1. \*Median daily rate of propofol infusion.

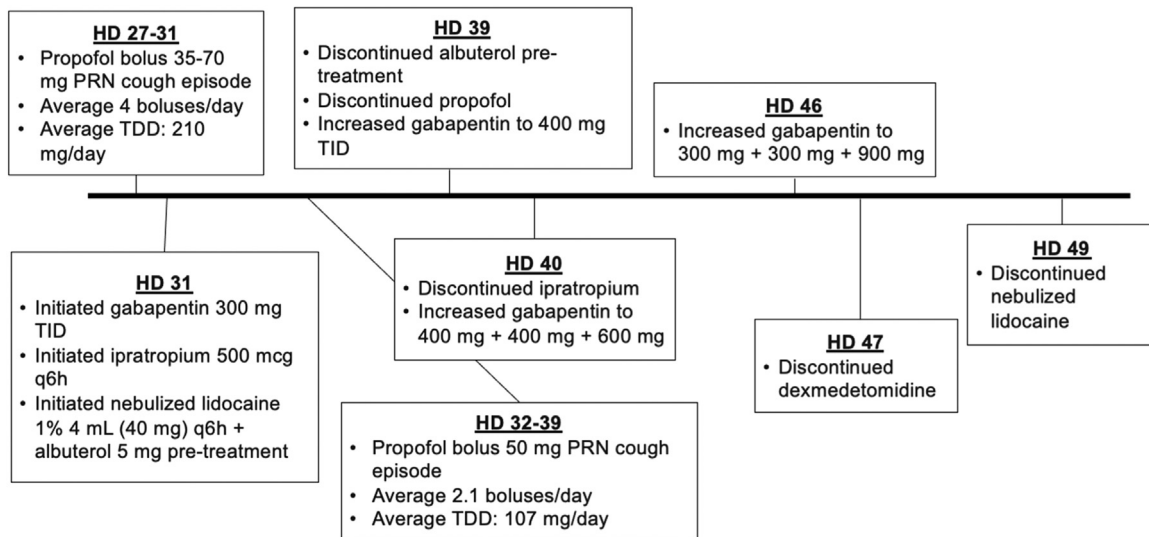


Fig. 2. HD: hospital day

and subsequent influx of sodium is an important step for a high and sustained calcium concentration during T-cell activation.<sup>18</sup> Tanaka et al. described an in-vitro model to investigate the effect of lidocaine IV on T-cells from patients with allergic asthma and found that inhaled lidocaine directly inhibited cytokine production and the proliferative responses.<sup>17</sup> The anti-inflammatory effects of lidocaine IV have been demonstrated in patients with various inflammatory states, including those with burn injuries, interstitial cystitis, ulcerative proctitis, arthritis, herpes simplex virus infections, and those undergoing laparoscopic cholecystectomies.<sup>19,20</sup> This effect may provide benefit in the multi-organ inflammatory state observed in patients with acute COVID-19. Furthermore, it has been reported that lidocaine can suppress formation of neutrophil extracellular traps (NETs), which have been observed at elevated levels in hospitalized patients with COVID-19.<sup>21</sup> This dysregulation of NET production most commonly damages the pulmonary, cardiovascular, and renal systems. Excessive NET production has also been associated with an increased risk for thrombosis and disease progression in lupus erythematosus, myocardial infarction, and sepsis.<sup>22-24</sup>

Both nebulized and intravenous lidocaine have been studied for use as a cough suppressant. One of the first reports of successful use of nebulized lidocaine was in 3 adults with intractable cough refractory to standard therapy.<sup>9</sup> A study of 21 adults with intractable cough secondary to asthma or reactive airway disease used 1-4% nebulized lidocaine (10-20 mg) every 4 to 6 hours. Patients were premedicated with albuterol 5 mg because lidocaine can cause bronchospasm in patients with asthma and received low flow oxygen throughout the nebulization.<sup>10</sup> A 2002 case series of 3 adults with intractable cough were treated with a nebulized mixture of 1 mL 1% lidocaine, 1 mL 0.5% bupivacaine, and 1 mL saline solution. Cough symptoms ceased in all 3 patients after one administration and did not recur.<sup>11</sup> Lingerfelt et al. reported improvement of cough in 2 of 4 terminally ill patients with intractable cough treated with 5 mL lidocaine 2% (100 mg) with oxygen at 4-6 L/min during the nebulization. The most common adverse events reported were oropharyngeal numbness and bitter taste.<sup>12</sup>

Inhaled lidocaine use in pediatric and adolescent patients is limited to one prospective, randomized, double-blind trial of 20 infants and children undergoing bronchoscopy.<sup>25</sup> Patients received either lidocaine 2% 8 mg/kg or 4 mg/kg nebulized via face mask along with oxygen 8 L/min for 15 minutes, with all patients receiving atropine 0.01 mg/kg as premedication and meperidine and/or midazolam as needed for sedation. Lidocaine was well tolerated. Serum levels were

obtained 20 minutes after starting the nebulization and the highest level obtained was 0.62 mcg/mL.<sup>25</sup>

Nebulized or inhaled lidocaine has been proposed for use in COVID-19 acute respiratory distress syndrome and associated cough given its anti-inflammatory effects.<sup>26-28</sup> However, there have been no subsequent reports of use in children with respiratory distress or failure secondary to COVID-19 infection. In our patient with COVID-19-associated cough, use of nebulized lidocaine was associated with decreased sedation needs for coughing episodes. The administration of inhaled lidocaine was well tolerated with and without albuterol pre-treatment. Lidocaine serum levels remained <1 mcg/mL throughout the duration of therapy and there were no signs or symptoms of lidocaine toxicity.

In most nebulized lidocaine studies that monitored serum lidocaine levels, levels were drawn within 2 hours of lidocaine administration. In all of these studies, the highest serum lidocaine level obtained was 1.4 mcg/mL, with most results being <1 mcg/mL.<sup>29-32</sup> This is far below the 5 mcg/mL level above which the risk for toxicity is significantly increased.<sup>13</sup> Although it has not been previously reported that nebulized lidocaine causes toxicity, we believe it is warranted to monitor for signs and symptoms of lidocaine toxicity as well as serum levels in patients receiving scheduled doses. At our institution, we obtain serum lidocaine levels 6-12 hours after initiation of therapy. We obtained daily levels, and then spaced to weekly once it was deemed that there was not a concern for toxicity. Our patient did not have levels that exceeded 1 mcg/mL throughout her duration of therapy.

Our patient experienced some relief of post-COVID-19 pain and potentially some relief of cough from gabapentin. She continued gabapentin for the remainder of her hospitalization. Ipratropium did not appear to effectively treat our patient's cough and was discontinued on HD 40.

Long-term prognosis for patients with COVID-19 is unknown. With more time and experience, we can expect to gain more understanding about the mechanism of COVID-19-associated cough and its treatment options, and the natural course of this intrusive symptom.

## Conclusion

Our patient is one of the first reports of an adolescent patient receiving inhaled lidocaine for COVID-19-associated cough. Her severe cough required increased sedation, including a trial of propofol infusion with intermittent boluses, that significantly impaired her

ability to participate in rehabilitation therapies. After initiating inhaled lidocaine her sedation needs decreased. Clinicians should be aware of the potential for lidocaine toxicity and monitor levels and signs and symptoms associated with lidocaine toxicity. Given the widespread impact of the COVID-19 pandemic and its sequelae in pediatric, adolescent, and adult patients, additional research is warranted to explore options for management of COVID-19-associated cough.

### Declaration of Competing Interest

None.

### Acknowledgements

Justin Heizer, PharmD, Abby Kim, PharmD, BCOP, Aline Maddux, MD, Katie Poplawski, RT.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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