Clinical Use of a Vibrating Mesh Micropump for Aerosolized Ribavirin During Invasive Mechanical Ventilation: Extension of an In Vitro Model

To the Editor:

Recently, Walsh et al[1] reported that ribavirin can be effectively aerosolized using a vibrating mesh micropump in a pediatric test lung model during both spontaneous breathing and mechanical ventilation. We recently applied this information in an immunocompromised patient receiving invasive mechanical ventilation for severe ARDS from human metapneumovirus. This patient was able to receive ongoing treatment with inhaled ribavirin using a vibrating mesh micropump and minor modifications to the ventilator circuit and respiratory therapist practice. Here we aim to describe in detail how the ventilator circuit was adapted for ribavirin delivery and the additional maintenance steps that were taken to avoid circuit occlusion from crystallized medication.

A teenage male with relapsed leukemia developed worsening acute hypoxemic respiratory failure on day +16 after hematopoietic stem cell transplant after diagnosis with human metapneumovirus. Similar to infection with respiratory syncytial virus,[2] human metapneumovirus infection can be fatal in the immunocompromised,[3-5] and currently, ribavirin is the only therapeutic agent that may have therapeutic benefit.[6] There is more clinical experience with aerosolized ribavirin compared with enteral or intravenous delivery, which currently is limited to small case series.[7-9] The infectious disease consult service recommended ribavirin via the inhalational route for this patient. He received 13 d of intermittent aerosolized ribavirin before intubation but progressed to lower respiratory tract infection. He was admitted to the pediatric ICU with worsening respiratory distress and hypoxemia and was ultimately endotracheally intubated. He continued to receive aerosolized ribavirin with the equipment described here (Fig. 1), which is similar to that tested by Walsh et al.[1]

The patient was placed on the Servo-i (Maquet Medical Systems, Wayne, New Jersey) ventilator rather than the typical Dräger V500 ventilator (Dräger, Lubeck, Germany) used for most large pediatric patients in our pediatric ICU. This choice was made because the Dräger manufacturers recommended against the use of ribavirin with this ventilator. Ribavirin in normal saline was delivered on a syringe pump at 11 mL/h over 2 h through the Aerogen Solo nebulizer (Aerogen, Galway, Ireland) into the inspiratory limb before the humidifier. The Aerogen Solo is the same vibrating mesh mircopump evaluated by Walsh et al,[1] and the rate of ribavirin is similar to that suggested by the authors. The ventilator circuit was modified to contain 2 high-efficiency particulate air (HEPA) filters placed before the expiratory cartridge. The filter proximal to the patient with the highest exposure to ribavirin was discarded and replaced after the first hour of treatment. The new HEPA filter was put in the distal position closest to the expiratory cartridge. This arrangement ensured that the cleanest filter was placed closest to the ventilator (Fig. 2). After each ribavirin dose, the vibrating mesh micropump was cleaned and replaced within the circuit. The patient received 13 doses of ribavirin through the ventilator circuit. The patient had one episode of crystallization of ribavirin in the humidifier that occluded the ventilator circuit, occurring after several ribavirin doses. A small amount of sterile water instilled into the inspiratory side of the humidifier after each ribavirin dose ameliorated the issue. Eighteen hours of ribavirin delivery occurred without obstruction of the ventilator circuit. At the end of ribavirin treatment on the ventilator, there was no buildup of crystalized ribavirin on the expiratory cartridge protected by the 2 filters. Of note, for each dose of ribavirin admin-

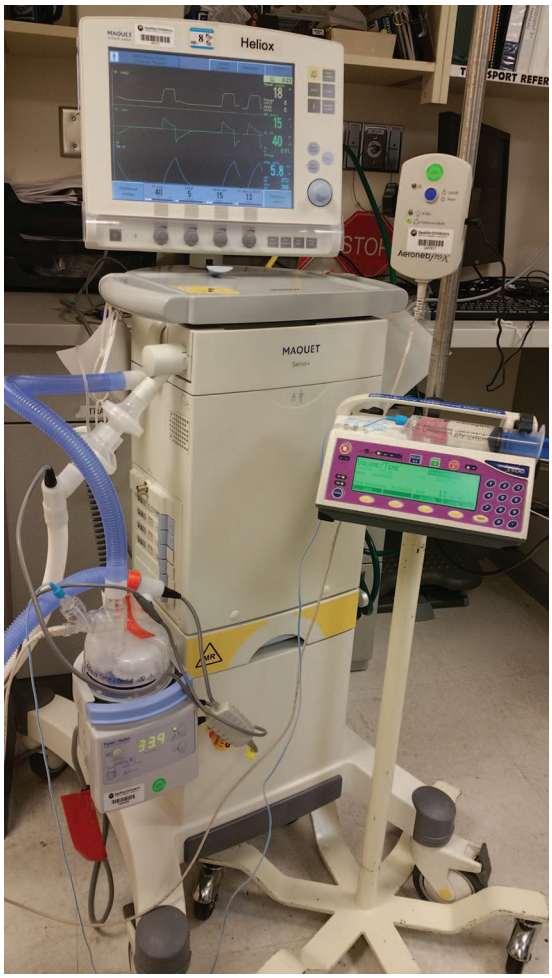

Fig. 1. Ribavirin was delivered to an intubated immunocompromised patient with the following equipment: a syringe containing the medication ribavirin (labeled), a syringe pump, a vibrating mesh micropump (Aerogen Solo nebulizer, labeled) in the inspiratory limb, a Servo-I ventilator, and 2 separate high-efficiency particulate air (HEPA) filters in the expiratory limb before the expiratory cartridge.

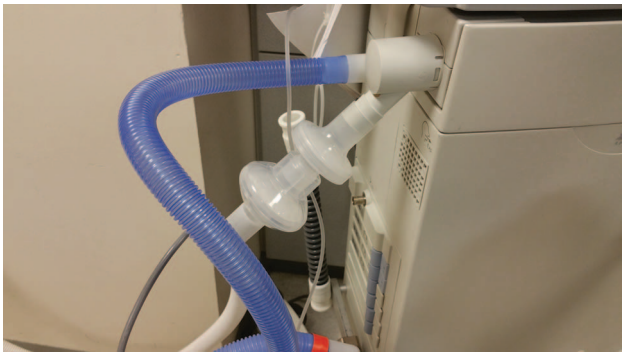

Fig. 2. Two high-efficiency particulate air (HEPA) filters are placed in sequence in the expiratory limb. The proximal filter with the highest exposure to ribavirin is discarded after 1 h of ribavirin therapy for each dose. The new HEPA filter is placed distal to the existing filter such that the filter that was previously in the distal position moves into the proximal position.

istered, the circuit was disconnected up to 3 times: once to remove the proximal HEPA filter and insert a new distal one, once to remove the vibrating mesh micropump for cleaning, and last to replace the vibrating mesh micropump after cleaning. This patient was able to tolerate the interruption in ventilator support without desaturation. He successfully extubated after 6 days and shortly thereafter discharged from the ICU.

Ribavirin delivery has some well recognized complications when administered during mechanical ventilation. These include occlusion of the ventilator circuit with crystalline deposits and the use of additional inspiratory flow to achieve delivery that impedes patients' ability to trigger the ventilator and often requires increased sedation and sometimes neuromuscular blockade for tolerance. The vibrating mesh micropump does not require the addition of inspiratory flow to deliver ribavirin, unlike the small-particle aerosol generator-2 (SPAG-2).[2] This allowed our patient to continue a spontaneous mode of ventilation with appropriate triggering and accurate tidal volume measurement. Use of the vibrating mesh micropump did not prevent circuit occlusion with crystallized ribavirin, but this issue was easily solved with additional sterile water flushes, as described above. Based on the findings of Walsh et al,[1] 0.9% NaCl could also have been used to minimize the risk of pulmonary irritation. We hypothesize that the use of a syringe to deliver ribavirin through the vibrating mesh micropump should reduce the exposure of health-care providers to ribavirin compared with the SPAG-2, where the medication needed to be poured into the reservoir before delivery, but this has not yet been studied.

Conclusions from Walsh et al[1] suggest that utilization of a vibrating mesh micropump within the ventilator circuit can deliver similar amounts of ribavirin as the SPAG-2 delivery system but without the addition of a significant amount of additional inspiratory flow that can complicate ventilator management. We confirm this observation in a pediatric patient and add pragmatic information about one method of delivering inhaled ribavirin using a vibrating mesh micropump using additional expiratory filters during mechanical ventilation.

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REFERENCES

1. Walsh BK, Betit P, Fink JB, Pereira LM, Arnold J. Characterization of ribavirin aerosol with small particle aerosol generator and vibrating mesh micropump aerosol technologies. Respir Care 2016;61(5):577-585.
2. Guerguerian AM, Gauthier M, Lebel MH, Farrell CA, Lacroix J. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. Am J Respir Crit Care Med 1999;160(3):829-834.
3. Chu HY, Renaud C, Ficken E, Thomson B, Kuypers J, Englund JA. Respiratory tract infections due to human metapneumovirus in immunocompromised children. J Pediatric Infect Dis Soc 2014;3(4):286-293.
4. Egli A, Bucher C, Dumoulin A, Stern M, Buser A, Bubendorf L, et al. Human metapneumovirus infection after allogeneic hematopoietic stem cell transplantation. Infection 2012;40(6):677-684.
5. Dokos C, Masjosthusmann K, Rellensmann G, Werner C, Schuler-Lüttmann S, Müller KM, et al. Fatal human metapneumovirus infection following allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis 2013;15(3):E97-E101.
6. Shah DP, Ghantoji SS, Mulanovich VE, Ariza-Heredia EJ, Chemaly RF. Management of respiratory viral infections in hematopoietic cell transplant recipients. Am J Blood Res 2012;2(4):203-218.
7. Molinos-Quintana A, Pérez-de Soto C, Gómez-Rosa M, Pérez-Simón JA, Pérez-Hurtado JM. Intravenous ribavirin for respiratory syncytial viral infections in pediatric hematopoietic SCT recipients. Bone Marrow Transplant 2013;48(2):265-268.
8. Kitanovski L, Kopriva S, Pokorn M, Dolničar MB, Rajić V, Stefanović M, Jazbec J. Treatment of severe human metapneumovirus (hMPV) pneumonia in an immunocompromised child with oral ribavirin and IVIG. J Pediatr Hematol Oncol 2013;35(7):e311-e313.
9. Shahda S, Carlos WG, Kiel PJ, Khan BA, Hage CA. The human metapneumovirus: a case series and review of the literature. Transpl Infect Dis 2011;13(3):324-328.

Next Logical Step

I appreciate Hartmann and colleagues' letter outlining the next logical step of our