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Communication

"The Aerogen® Solo is an alternative to the small particle aerosol generator (SPAG-2) for administration of inhaled ribavirin"

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Abstract: Respiratory syncytial virus (RSV) is associated with adverse outcomes among immunocompromised patients. Inhaled ribavirin has been shown to improve mortality rates. The Small-Particle Aerosol Generator delivery system (SPAG-2) is the only FDA-cleared device to deliver inhaled ribavirin. However, it is difficult to set up and maintain. We developed a method for delivery of this medication using the vibrating mesh nebulizer (Aerogen®). We did not observe any adverse events with this method.

Keywords: RSV, ribavirin, Aerogen® solo, SPAG-2, children, infection

1. Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRTI) in children. Premature infants, infants with cardiac disease and severely immunocompromised patients experience increased morbidity and mortality related to RSV infection [1, 2]. Poor outcomes are far more likely in immunocompromised patients than in non-immunocompromised individuals and include progression to pneumonia, respiratory failure, and increased mortality [3]. Among immunocompromised adults with cancer, progression to LRTI ranges from 30 to 50%; and for those who develop pneumonia, mortality can be as high as 75% [4]. Mortality associated with respiratory viruses in children undergoing HCT varies, usually ranging between 10 and 14%, but can be as high as 30% [5].

Antiviral treatment with inhaled ribavirin has been shown to improve mortality rates compared to no treatment [6]. The Small-Particle Aerosol Generator delivery system (SPAG-2) is the only FDA-cleared device to deliver ribavirin [7]. The SPAG-2 is uncommon in respiratory therapy for delivering aerosolized medications. In addition, setup of the machine is time consuming and difficult to maintain. The entire unit has to be disassembled and cleaned between each individual treatment thus decreasing availability if multiple patients require inhaled ribavirin simultaneously. Furthermore, during the 2015-2016 and 2017-2018 winter seasons, there were two FDA recalls of certain SPAG-2 units threatening the access of this treatment to our patients. [8, 9]. As a consequence, at. St. Jude Children's Research Hospital, we developed and implemented an alternative method to deliver inhaled ribavirin using the Aerogen® Solo vibrating mesh nebulizer.

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This nebulizer, which is a self-contained device, can be reused after flushing and cleaning with antimicrobial wipes. It is also smaller and easier to store in biohazard bags between use. Finally, unlike the SPAG-2 device, it allows administration of inhaled ribavirin during periods of mechanical ventilation. In this article, we describe the development and implementation of the Aerogen® Solo vibrating mesh nebulizer for inhaled ribavirin delivery.

2. Materials and Methods

During the 2017-18 winter RSV season, the SPAG-2 devices were recalled. As a result, we developed a system to deliver inhaled ribavirin with the Aerogen® Solo so that we could continue offering ribavirin to patients with proven RSV infection. Indication and duration for inhaled ribavirin treatment was performed based on institutional guidelines [10]. A total of 12 patients received inhaled ribavirin through this new method. In a subset of 5 patients with leftover respiratory samples available for testing, RSV loads were measured before and after ribavirin treatment using quantitative ddPCR [11].

Delivery of inhaled ribavirin via the Aerogen® Solo vibrating mesh nebulizer included the use of a MedFusion 3500 syringe pump, a demistifier 2000 HEPA filtration system, and a demistifier negative pressure bed enclosure with canopy around the patient's bed. Two grams of ribavirin diluted in 30 mL of normal saline were administered over 2 hours at a flow rate of 8 L/min and a pump rate of 14 mL/hr. (Figure 1). Initially, the liter flow rate was 4-6 L/min, but crystal formation in the nebulizer chamber was observed causing concern for blockage / obstruction. To correct this, ribavirin was further diluted in 100 mL of normal saline; however, this caused spillage of ribavirin at pump rates above 14 mL/hr. The flow rate was then modified to 8 L/min allowing for safe administration of 2 grams ribavirin diluted in 30 mL of saline over two hours with a pump rate of 12-14 mL/hr without observing crystallization and/or spillage. In addition, there was less wasted ribavirin in the nebulizer chamber using the Aerogen® Solo when compared to SPAG by estimation of respiratory therapy staff. Finally, we attempted dosing 6 grams of ribavirin over 12-18 hr and again noted issues with drug crystallization in the nebulizer chamber.

At the end of each prescribed treatment, the Aerogen® nebulizer was turned off. The demistifier and any drug remaining in the nebulizer or IV tubing were placed into a red biohazard bag along with the large bore tubing, T adaptor, aerosol mask and O2 reduce, and disposed according to institutional policy. Upon completion of the last prescribed treatment, the same process was followed including the demistifier canopy, aerosol tubing and mask. The demistifier, bed enclosure, and syringe pump were cleaned with antimicrobial wipes prior to storage. After this procedure, environmental health services proceeded with decontamination of the inpatient hospital room (supplementary material).

The study was approved by the St Jude Children's Research Hospital Institutional Review Board #00000029 (FWA00004775) and determined to be secondary research and exempt under the Office for Human Subject Protection category 4 for which consent is not required (IRN number 20-0585).

3. Results

During the 2017-18 and 2018-9 RSV seasons, twelve patients were treated for RSV infection; seven in 2017-18 and eight in 2018-19 (Table 1). The median age was 9.5 years (range 5 – 19 years) and 5 were male (41.66%). All patients had leukemia with acute lymphoblastic leukemia (ALL) being the most frequent diagnosis (n=8) followed by acute myeloid leukemia (AML; n=4). Six patients previously underwent hematopoietic cell transplant (HCT) and 2 patients were undergoing HCT conditioning at the time of RSV diagnosis. Ten patients (66.7%) presented with upper respiratory tract infection (URTI); two of which progressed to LRTI. The remaining two patients (16.6%) presented with LRTI at the time of diagnosis. Eight patients (66.6%) had profound lymphopenia

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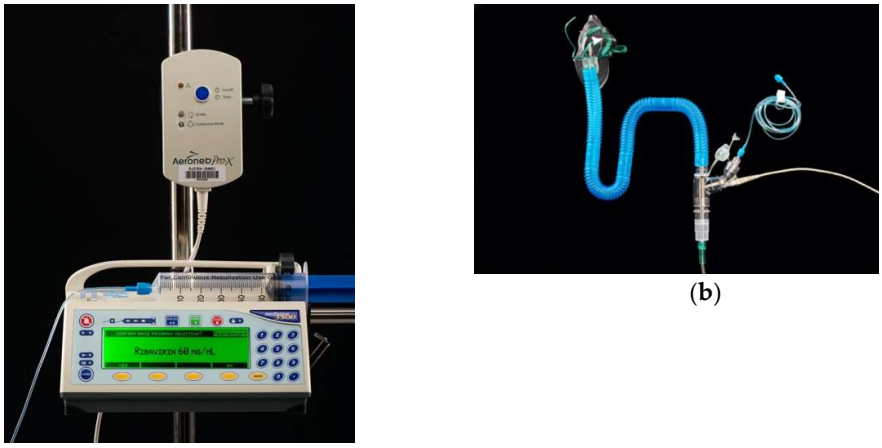
(absolute lymphocyte count < 200 cells/μL) at the time of diagnosis. The duration of ribavirin therapy ranged from 2 to 10 days. According to institutional guidelines, patients with URTI received 5 days of inhaled ribavirin and patients with LRTI received 10 days. Three patients had chronic lung disease, 2 of them presenting with or developing LRTI.



(a) (b)

Figure 1. Set up and connection to administer inhaled Ribavirin with The Aerogen® Solo **(a)** MedFusion 3500 syringe pump containing ribavirin at a dilution of 60 mg/ml connected to nebulizer; **(b)** Aerosol mask, large bore tubing and T adaptor connection.

Table 1: Clinical characteristics of patients with RSV infection treated with inhaled ribavirin

Case	Age (years)	Gender	Diagnosis	URTI/ LRTI	ALC	Days therapy	Transition to PO	Comments
1	13	F	ALL (s/p haplo-HCT+28)	URTI	75	5	No	
2	14	F	ALL (s/p MUD-HCT+83)	URTI	93	5	No	Chronic lung disease
3	7	F	AML (pre-HCT)	URTI→LRTI	0	10	No	
4	9	M	Relapsed ALL	URTI	0	5	No	
5	19	F	AML (s/p MUD-HCT >1 year)	URTI→LRTI	1480	7	No	Chronic lung disease
6	7	F	ALL (s/p haplo-HCT >1 year)	LRTI	1186	10	Yes	Chronic lung disease
7	9	M	ALL (s/p haplo-HCT+16)	URTI	0	5	No	
8	10	M	ALL (s/p haplo-HCT+132)	URTI	1630	5	No (initially started on PO)	
9	15	F	AML	LRTI	0	8	Yes	
10	6	M	ALL relapsed	URTI	468	5	Yes	
11	5	M	AML	URTI	0	2	NA	
12	11	F	ALL (pre-HCT)	URTI	0	10	NA	

M (male); F (female); AML (acute myeloid leukemia); ALL (acute lymphoblastic leukemia); HCT (Hematopoietic cell transplant); MUD (match unrelated donor); LRTI (lower respiratory tract infection); URTI (upper respiratory tract infection); ALC (absolute lymphocyte count); SPAG-2 (small particle aerosol generator).

No patients had received palivizumab as prophylaxis, nor did they receive it as part of their treatment regimen. During the 2018-2019 season we started utilizing oral (PO) ribavirin in selected cases and three patients (cases 6, 9 and 10) were transitioned to PO ribavirin.

In a subgroup of 5 patients we were able to measure viral loads from leftover respiratory samples before and after treatment. We observe a reduction of 3.92 log copies/ml of RSV viral load in respiratory secretions upon completion of antiviral therapy. We did not observe any bronchospasm associated with administration of ribavirin using either device.

4. Discussion

RSV infection in immunocompromised remains a challenge due to it high morbidity and mortality. Lack of novel treatment has left clinicians with very few tools as supportive treatment and inhaled ribavirin. The latter, while widely used, is expensive and has been difficult to administer to complications with the SPAG-2. Here, we developed a method that was. Here we describe an alternative for administering inhaled ribavirin with the Aerogen® Solo mesh nebulizer.

Ribavirin is a nucleoside analog with broad activity against DNA and RNA viruses that can be administered by inhalation, oral or intravenous routes (the latter only available through investigation new drug application and approval). Inhaled ribavirin can be administered by the SPGA-2 device in two dosing approaches: 2 grams diluted in 30 mL of normal saline over 2 hours, three times daily or 6 grams diluted on 100 mL over 12-18 hours per day. Although there are no clinical trials comparing these regimens, there does not seem to be any clinical benefits of either regimen based on the current literature [12-15]. Inhaled ribavirin in either approach decreases progression to LRTI and mortality in immunocompromised patients. There is a dearth of evidence regarding the efficacy of oral or intravenous ribavirin for the treatment of RSV infection. The former has poor oral bioavailability and the latter carries a greater risk of toxicity and is difficult to access [16].

Our results are limited to the small number of cases and retrospective nature of the design. In addition, leftover samples to measure viral load was only available for a subset of patients. While safety and efficacy can't be measured at this point, we will continue to monitor side effects and clinical recovery as we have widely adopted this method in the institution. Furthermore, this method has the potential to be used in patients requiring mechanical ventilation, something that is complicated and challenging with the SPAG-2 device. Although we have not used it in this situation, a detailed process is available in our institutional standard operating procedure if the need were to arise (supplementary material).

In conclusion, we present an alternative to administer inhaled ribavirin with a widely used nebulizer, The Aerogen® Solo, that can simplify the process with no additional side effects or changes in clinical outcomes.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1. Respiratory Therapy Institutional Policy & Procedure manual.

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