

Ribavirin for paediatric patients with severe respiratory syncytial virus disease: A retrospective clinical audit

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Dear Editor,

Respiratory syncytial virus (RSV) is a single-stranded ribonucleic acid (RNA) virus of the *Paramyxoviridae* family and is one of the most common causes of lower respiratory tract infections in young children.¹ Presently, treatment of RSV infection has been limited to supportive management. Ribavirin is a guanosine analogue that has been described to have broad antiviral activity against some RNA and deoxyribonucleic acid (DNA) viruses² and has been approved since the 1980s for treatment of RSV infection in children.³ However, there remains a lack of strong evidence regarding the use of systemic ribavirin in immunocompetent paediatric patients.⁴ Currently, only a small number of paediatric studies are available demonstrating its efficacy in patients with severe disease or immunocompromised individuals⁵ and there are concerns of potential toxicity in exposed healthcare personnel.⁶ The American Academy of Pediatrics recommends against its routine use in the treatment of RSV.⁷

The authors aimed to perform an audit summarising the clinical course, and short-term outcomes of children younger than 17 years with severe RSV infection in a Singapore hospital, in particular focusing on patients who received systemic ribavirin including their clinical outcomes and any adverse effects experienced from ribavirin.

In this retrospective clinical audit of 240 children hospitalised at KK Women's and Children's Hospital (KKH) between 1 January 2018 and 31 August 2023 with severe RSV disease, data related to clinical course, patient demographics and information on ribavirin use including adverse effects were collected in February 2024. Severe RSV disease was defined as laboratory-confirmed RSV infection on nasopharyngeal swabs that were run on 1 of 3 test kits (Seeplex RV15 ACE [Seegene Inc, Seoul, South Korea], BioFire FilmArray RespPanel [BioFire Diagnostics, LLC, Utah, US] or Immunofluorescence testing), and

requiring high dependency (HD) or intensive care unit (ICU) care. Within KKH, patients in HD may receive up to supplemental oxygen or continuous positive airway pressure support. Any escalation of therapy to bi-level non-invasive respiratory support, invasive mechanical ventilation or circulatory support will require admission to ICU.

Among 240 children with severe RSV infection, 192 (80%) were admitted to HD and 48 (20%) were admitted to ICU. They had a median age of 7 months (interquartile range [IQR] 2–15.5). The most common comorbidity among patients with severe RSV infection was a background of prematurity with 33 patients (13.8%) born at 24–36 weeks' gestation, of whom 6 patients (2.5%) had a diagnosis of chronic lung disease of prematurity. The most common respiratory comorbidity was recurrent wheeze or asthma ($n=22$, 9.2%). There was no mortality from severe RSV infection during the study period. There was a decrease in the number of severe RSV cases during the COVID-19 pandemic in 2020–2021, which was particularly marked over Singapore's "circuit-breaker" period (April to June 2020) where there were strict social restrictions⁸ and no cases of severe RSV were detected in KKH.

In total, 7 (2.9%) immunocompetent patients with severe RSV received systemic ribavirin and all required ICU admission (Table 1). The decision for ribavirin administration for these 7 patients was made based on the treating physician's decision. Decisions were influenced by the presence of significant risk factors: 5 patients had major non-immunocompromised medical comorbidities, 6 patients required mechanical ventilation due to severe clinical disease, and 4 patients presented with both of these factors. Their median age was 2 months (IQR 1–8). Of patients who received ribavirin, 5 had comorbidities: 3 patients were born between 32–34 weeks' gestation and 2 had complex cyanotic heart disease. The overall median length of stay (LOS) was 15 days (IQR 9–25) and median ICU LOS was 8 days (IQR 6–11). Of these, 3 patients

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Table 1. Summary of demographic, ribavirin use and clinical outcome of patients receiving ribavirin between 1 January 2018 and 31 August 2023.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Demographics							
Age (months)	2	0 (11 days)	3	1	36	1	8
Sex	Male	Male	Female	Female	Female	Male	Male
Ethnicity	Chinese	Malay	Malay	Chinese	Malay	Chinese	Chinese
Risk factors							
Comorbidities	Preterm 32 weeks ^a	Preterm 34 weeks ^a	None	None	AVSD/PA ^b asplenia	Preterm 33 weeks ^a	Tetralogy of Fallot, PA ^c
Day of illness (cough) at presentation	2	2	4	3	2	2	2
Ribavirin							
Day of illness when ribavirin was administered	4	3	5	4	3	3	3
Dose of ribavirin (mg/kg)	15	20	15	25	15	15 (IV) 24 (PO)	30
Route of ribavirin	IV	PO	IV	PO	IV	IV and PO	PO
Duration of ribavirin	10	10	7	10	7	10	10
Maximum medical care required							
Ventilatory support	Conventional					HFOV	Non-invasive
Inotropic support	None	None	None	None	Inotrope	None	None
Days of ICU stay	9	7	6	11	8	20	6
Days of hospital stay	19	36	9	15	9	25	14
Outcome and follow-up							
Outcome	Survived to discharge						
Follow-up duration ^d	2 years 5 months	3 years 11 months	4 months	1 year 1 month	10 months	Did not attend	5 months

AVSD/PA: atrioventricular septal defect with pulmonary atresia; HFOV: high frequency oscillatory ventilation; ICU: intensive care unit; IV: intravenous; PA: pulmonary atresia; PO: per os ("by mouth")

^a All 3 ex-premature infants who received ribavirin did not have chronic lung disease or significant respiratory sequelae as a result of their prematurity.

^b Complete atrioventricular septal defect with pulmonary atresia and major aortopulmonary collateral arteries, cyanotic baseline saturations of 78–80%.

^c Tetralogy of Fallot with pulmonary atresia, had undergone right ventricle-to-pulmonary artery shunt creation, cyanotic baseline saturations of 80–82%.

^d This represents the duration from discharge until last follow-up or time of data collection for the audit in February 2024 if follow-up was ongoing.

received intravenous ribavirin, 3 received oral ribavirin and 1 received both intravenous and oral ribavirin. The dosage used was between 20–30 mg/kg/day for oral ribavirin and 15 mg/kg/day for intravenous ribavirin. None of the infants developed haemolytic anaemia or electrolyte abnormalities from ribavirin. All 7 patients survived to discharge, and 1 patient was subsequently diagnosed with asthma requiring inhaled corticosteroid therapy on outpatient follow-up

4 months after the admission for RSV requiring ribavirin treatment.

Of the 7 patients who were treated with systemic ribavirin over the period of this audit, a Wilcoxon rank-sum test indicated no statistically significant differences in median age ($P=0.114$) or presence of co-infection with other respiratory viruses ($P=0.10$) between patients who were not given ribavirin and those who were given ribavirin. However, individuals

who received ribavirin were more likely to have had other comorbid medical conditions ($P=0.045$) and a longer median duration of ICU ($P=0.00$) and hospital stay ($P=0.00$).

In this audit, the authors described no acute adverse effects of ribavirin with good tolerability among 7 severe RSV-infected children. This is similar to the side effect profile described in existing literature⁹ with few significant adverse effects reported. One systematic review published in 2022 of studies in adults and a small paediatric population, demonstrated insufficient evidence to support its use in lung transplant recipients and healthy infants.⁹ Reported side effects described from other studies include bronchospasm, shortness of breath, chest pain, skin rash and conjunctivitis⁴ which were not present in the patients included in this study. Due to the small cohort of children started on ribavirin in this study, the authors were unable to draw any further conclusions regarding its efficacy in use in paediatric patients. In addition, the follow-up period was limited, as patients who had been admitted in 2023 would only have been followed up for 1 year at the time of this clinical audit. Further prospective studies are required to establish the efficacy and safety of ribavirin use in immunocompetent paediatric patients.

Ethics statement

This study was performed as a clinical practice improvement audit.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any

financial interest in the subject matter or materials discussed in this manuscript. All authors have no conflicts of interest to declare.

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