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REVIEW

Ribavirin for Treatment of Subjects with Respiratory Syncytial Virus-Related Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV)-associated diseases have caused an estimated 1.8 million hospital admissions and 40,000 deaths among children. RSV can cause lower respiratory tract infections (LRTIs) in all age groups, adults with comorbidities, and immunocompromised patients. The aim was to summarize the evidence concerning efficacy and safety of ribavirin in subjects diagnosed with RSV associated with LRTI.

Methods: A systematic review and meta-analysis were performed. Eligible studies were observational (> 10 subjects) and randomized-controlled trials of subjects with aerosol/oral ribavirin for RSV-LRTI. Comparator was supportive care or placebo. Systematic search on PubMed, Cochrane Library, and Web of Science databases was conducted between January 2001 and January 2022. PROSPERO register number: CRD42022308147.

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Results: After retrieving 907 studies, 10 observational studies and 1 randomized controlled trial were included (4/11 high quality of evidence). Seven studies included subjects with haematological malignancy/stem cell transplant, two lung transplants, and two healthy individuals. A total of 788 subjects diagnosed with RSV infection were included; 14.3% of them presented with only LRTI. Among 445 subjects treated with ribavirin, 195 (43.8%) received an aerosolized formulation. Pooled meta-analysis showed no differences in mortality [risk ratio (RR): 0.63; 95% confidence interval (CI): 0.28–1.42] in all subjects treated with aerosol/oral ribavirin compared to supportive care. In subgroup analysis, mortality was significantly lower in haematological subjects (RR: 0.32; 95% CI: 0.14–0.71), but did not differ significantly in lung transplant recipients (RR: 0.89; 95% CI 0.31–2.56). Oral ribavirin (vs. supportive care) was associated with increased viral clearance (RR: 2.60; 95% CI: 1.35–4.99). Seventeen adverse events were reported among 119 subjects, but none were severe.
Conclusion: Ribavirin should be considered for treatment of RSV-LRTI in haematological subjects. There is a lack of evidence to support its use in lung transplant recipients. Oral formulation appears to be an easier, safe, and cost-effective alternative to aerosolized ribavirin. Further advances needs to focus on newer antivirals.

Keywords: Bronchiolitis; Paramyxovirus; Pneumonia; Respiratory syncytial virus; Ribavirin

Key Summary Points

Why carry out this study?
To improve decisions based on evidence to optimize therapy for lower respiratory tract infections caused by respiratory syncytial virus
What was learned from the study?
Oral/aerosolized ribavirin therapy significantly improves survival in haematological subjects
There is a lack of evidence to support its use in lung transplant recipients and healthy infants
Oral ribavirin is an effective alternative to aerosolized ribavirin, with cost savings and potentially fewer adverse events
The most reported adverse events were related to haematological manifestations and systemic toxicity. No severe adverse events were reported

INTRODUCTION

Respiratory syncytial virus (RSV) is a single-stranded, negative sense ribonucleic acid virus from the Orthopneumovirus family [1, 2]. RSV-associated diseases have an important global clinical and financial burden, with an estimated 1.8 million hospital admissions and 40,000 deaths among children in 2020 [3]. RSV can cause upper and lower respiratory tract infections (LRTIs). Although healthy and premature infants aged < 6 weeks are the population at higher risk of RSV-associated bronchiolitis, RSV infection is also frequent in those under 2 years old [4, 5]. LRTI presenting as pneumonia requiring hospitalization occurs in all age groups, particularly in adults with comorbidities and immunocompromised subjects [1, 6–8].

Current treatment options against RSV-LRTI in hospitalized subjects include mainly

supportive care and supplemental oxygen (standard or high-flow nasal oxygen therapy), adequate hydration, and noninvasive/invasive ventilation. Antiviral therapy includes a combination of ribavirin with adjuvant therapies such as palivizumab, intravenous immunoglobulin (IVIG), or corticosteroids. European Medicines Agency (EMA) and Food and Drug Administration (FDA) approved aerosolized ribavirin for treatment of hospitalized infants and young children with severe RSV-LRTI [4, 9, 10]. Some guidelines suggest their use, especially in immunocompromised subjects [11, 12]. However, they are based on weak/moderate evidence.

There are studies that investigated the effect of aerosolized or oral ribavirin therapy among different types of subjects with RSV infection [13–17]. However, the evidence is unclear so does not allow a strong recommendation on its use. This systematic review and meta-analysis aims to summarize the evidence concerning efficacy and safety of ribavirin in subjects diagnosed with RSV-LRTI.

METHODS

Registration and Protocol

This systematic review and meta-analysis was registered in PROSPERO (CRD42022308147). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline [18, 19]. See Table S1 in the electronic Supplementary Material for PRISMA checklist details.

Search Strategy

A systematic search on PubMed, Cochrane Library, and Web of Science databases was conducted between January 2001 and January 2022. Additional search was performed of ClinicalTrials.gov, FDA, and EMA databases. Literature search was limited to human subjects, with no language restrictions. Alerts were created to capture any new study published after performing the initial search. See Table S2 in the electronic Supplementary Material for search strategy details.

Eligibility Criteria

Randomized-controlled trials (RCT) and observational studies of > 10 subjects (at any age) diagnosed with RSV-associated with (1) only LRTI or (2) upper plus LRTIs, were considered for inclusion. Treatment with aerosolized and systemic (oral or intravenous) ribavirin alone or plus adjunctive therapies (IVIG, pavilizumab, RSV neutralizing antibody, and steroids) were included. Comparator was supportive care or placebo.

Pre-defined outcomes were overall mortality, length of hospital stay (days), mechanical ventilation requirement, viral clearance at the end of treatment, bacterial coinfection, bronchiolitis in lung transplant recipients, adverse events related to study drug (psychological effects, systemic toxicity, haematological), and severe adverse events.

Studies were excluded in the following cases: (1) without LRTI; (2) ribavirin for prophylaxis; (3) no comparing arm; (4) a mix of community-acquired respiratory viruses (e.g., parainfluenza virus, influenza A and/or B) and hospital-acquired respiratory viruses.

Data Collection

References were screened based on title and abstract by two independent authors (ST and HNK). Selected articles underwent a full-text assessment. Adjudicated disagreements were resolved by a third author (RMR). Using Rayyan software, any duplicate article was identified and deleted. A standardized form in Excel was used to collect data. Data on exclusion criteria, study design, subjects, intervention, comparator, and outcomes were extracted.

When results were not reported, we attempted to contact the study's authors to obtain the relevant missing data. When results were not reported in a format suitable for meta-analysis, methods recommended in the Cochrane collaboration tool to extract or estimate effects were used [20, 21]. Number of subjects and

denominator were extracted for dichotomous outcomes. Sample size, mean [standard deviation (SD)], or median [interquartile range (IQR)] were extracted for continuous outcomes.

Quality Assessment

The quality assessment was performed for each included study independently by two authors (ST and HNK). Adjudicated disagreements were resolved by a third author (RMR). Quality assessment was assessed using the Newcastle Ottawa Scale for observational studies [22]. Risk of bias was assessed using the Cochrane risk-of-bias tool for RCT [23].

Statistical Analysis

Outcomes that did not present enough numerical results for the intervention and comparator from studies were not analysed in the meta-analysis.

Statistical analyses were performed by RevMan version 5.3. The pooled effects were analysed using risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes. All statistical measures were calculated with 95% confidence interval (CI). The Mantel-Haenszel method was used for the random-effects model to generate pooled treatment effects across studies. Results were presented as forest plot.

Higgins I^2 statistic [24] was used to assess heterogeneity between studies ($I^2 \leq 30\%$ for low; 30–60% for moderate; 60–75% for substantial and $\geq 75\%$ for considerable). No funnel plot was applied because of the small number of studies (< 10 studies) included in the meta-analysis [25]. Sensitivity analysis was conducted to probe influence factor. Planned subgroup analysis was conducted based on population (children or adults), route of administration (aerosolized or systemic), and underlying condition such as heart/lung transplantation, haematological stem-cell transplant (HSCT), and haematological malignancy (HM).

Statement of Ethics Compliance

Ethics committee approval was not applicable. The present article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection

The search identified 907 potentially relevant studies. Of these, 11 studies [26–36] met the inclusion criteria, and only 7 [26–29, 32, 34, 35] were suitable for the quantitative meta-analysis. PRISMA flow diagram is shown in Fig. 1.

Study and Subjects' Characteristics

Ten observational studies and one RCT [36] met the eligibility criteria (see details in Table 1). Seven studies were conducted in adults [26–32], three included both adults and children [33–35], and one only included healthy infants [36]. With the exception of two studies [32, 36], all were focused on immunocompromised subjects, mainly with HSCT/HM ($n = 7$) [28–31, 33–35] and lung transplant recipients ($n = 2$) [26, 27]. Four studies [27–29, 32] diagnosed RSV infection only by polymerase chain reaction (PCR) in respiratory specimens, which were from nasopharyngeal swabs or bronchoalveolar lavage. Laboratory tests of the remaining six studies are detailed in Table 1.

A total of 788 subjects diagnosed with RSV infection were included, 14.3% of them presented only with LRTI (see details in Table 2). See Table S3 in the electronic Supplementary Material for definitions of upper and LRTI from each individual study's details. Intensive care unit (ICU) stay and mechanical ventilation requirement were documented in 62 subjects (7.8%) and 72 subjects (9.1%), respectively. Of the 788 subjects with RSV infection, 445 were treated with ribavirin. Time from diagnosis or disease onset to ribavirin start was reported in

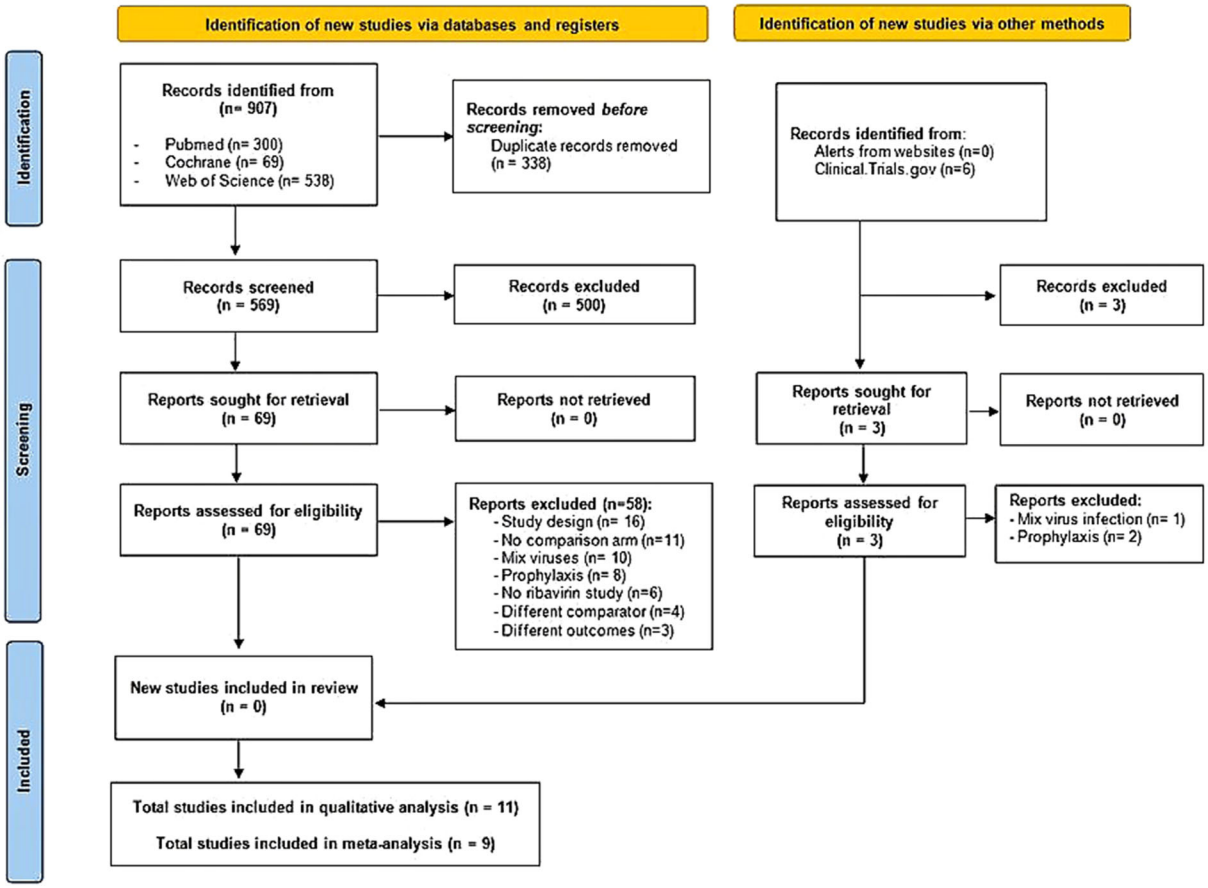

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of the study selection

110 subjects (range: 0–17 days). Ribavirin was administered via oral (n = 203, 45.6%), aerosolized (n = 195, 43.8%), oral plus aerosolized (n = 19, 4.3%), and oral plus intravenous (n = 28, 6.3%) routes. All studies had supportive care as comparator, whereas in the RCT ribavirin was compared to placebo.

Quality Assessment

Risk of bias of ten observational studies was assessed by the Newcastle Ottawa Scale tool (see Table S4 in the electronic Supplementary Material for details). Only three studies [27, 30, 32] showed high quality of evidence. Seven studies [26, 28, 29, 31, 33–35] showed a moderate-low quality of evidence, mainly because of issues in selection with inability to demonstrate "representativeness of the exposed cohort" and "adequacy of follow-up of cohorts".

Risk of bias of the RCT [36] was assessed by the Cochrane risk of bias tool (see Table S4 in the electronic Supplementary Material for details), resulting in low risk of bias (high quality of evidence).

Efficacy Outcomes

Five studies [27, 28, 32, 34, 35] reported mortality. Pooled meta-analysis showed no differences in mortality (RR: 0.63; 95% CI: 0.28–1.42) in all subjects treated with aerosol/oral ribavirin compared to supportive care (Fig. 2). Moderate heterogeneity (I^2 = 45%) was found. In subgroup analysis including immunocompromised subjects, mortality was significantly lower in haematological subjects (RR: 0.32; 95% CI:

Table 1 Characteristics of the seven included studies of subjects diagnosed with respiratory syncytial virus

Author, year [Ref.]	Study design, dates	Country	Age, median (range)	Population	Number of subjects				Laboratory test	Sample	Follow-up, median months (range)
					Total	Progress of URTI to LRTI	ICU	MV			
Adults											
Testaert, 2021 [26]	RC, 2011–2019	France	45.1 (IQR 34–53.9)	LTx	77	–	9	8	PCR, immuno-fluorescence assay	NPS	37 (19–65)
Martinez-Cerezuela, 2021 [27]	RC, NR	Spain	RBV: 36 (14–66) SC: 62 (24–67)	LTx	36	–	NR	NR	PCR	NPS/ BAL	6 months
Lehners, 2013 [28]	RC, 2011–2012	Germany	57.5 (18–78)	HSCT	56	13	NR	1	PCR	NPS/ BAL	NR
Balassa, 2019 [29]	RC, 2015–2017	UK	52 (19–73)	HSCT	49	4	3	3	PCR	NPS/ BAL	14 (1–27)
Khanna, 2008 [30]	RC, 2002–2007	Switzerland	41.7 (16.7) [1]	HSCT/HM	34	2	5	4	PCR, antigen assay, viral culture	NPS/ BAL	16 (4–64)
Azzi, 2018 [31]	RC, 2003–2013	USA	59 (18–87)	HM	181	15	24	14	Direct fluorescent antibody, viral culture	NPS/ BAL	3 months
Wongsurakiat, 2022 [32]	RC, 2014–2019	Thailand	76 (12.7) [1]	No immuno-compromised	175	NR	14	36	PCR	NPS/ BAL	NR
Adults and children											
Avetisyan, 2009 [33]	RC, 2000–2007	Sweden	40.4 (IQR 3.1–67.5)	HSCT	32	0	NR	NR	Antigen detection by immunofluorescent viral culture	NPS/ BAL	NR

Table 1 continued

Author, year [Ref.]	Study design, dates	Country	Age, median (range)	Population	Number of subjects				Laboratory test	Sample	Follow-up, median months (range)
					Total	Progress of URTI to LRTI	ICU	MV			
Small, 2002 [34]	RC, 1994–2001	USA	LRTI: 26.2 (16.5) [1] URTI: 15.4 (16.3) [1]	HSCT	58	5	NR	6	PCR, direct fluorescent antibody, antigen assay, viral culture	NPS/ BAL	56 (14–82)
Torres, 2007 [35]	RC, 2000–2005	USA	47 (1–83)	HM	52	13	7	NR	Direct fluorescent antibody, viral culture	NPS/ BAL	1 month
Children											
Evarard, 2001 [36]	RCT	UK	15–266 days	No immuno-compromised	38	NR	NR	NR	NR	NR	12 months

[1] Data reported as mean (standard deviation)

BAL: bronchoalveolar lavage; HM: haematological malignancy; HSCT: haematopoietic stem cell transplant; ICU: intensive care unit; LRTI: lower respiratory tract infection; LTx: lung transplant; MV: mechanical ventilation; NPS: nasopharyngeal swabs; NR: not reported; PCR: polymerase chain reaction; URTI: upper respiratory tract infection; RC: retrospective cohort; RCT: randomized-controlled trial; RBV: ribavirin; SC: supportive care

Table 2 Characteristics of ribavirin therapy for 788 subjects diagnosed with respiratory syncytial virus

Author, year [Ref.]	Population	N RBV/SC	Delay onset of therapy, median days (range)	Type	Dose	Frequency	Adjuvant therapies
Adults							
Testaert, 2021 [26]	LTx	19/58	NR	AER/oral	NR	NR	PZB, IVIG
Martinez-Cerezuela, 2021 [27]	LTx	19/17	NR	Oral	400–1200 mg	Daily for a median of 11.7 days	Corticosteroids, IVIG
Lehners, 2013 [28]	HSCT	36/20	NR	Oral	800 mg (< 65 kg), 1000 mg (65–80 kg), 1200 mg (> 80 kg)	Daily for 14 days	PZB, IVIG
Balassa, 2019 [29]	HSCT	24/25	NR	Oral	15–20 mg/kg	Three times daily	IVIG
Khanna, 2008 [30]	HSCT/HM	25/9	NR	Oral	10 mg/kg (loading dose), 400 mg (day 2), 600 mg (day 3)	Three times daily	PZB, IVIG
Azzi, 2018 [31]	HM	117/64	NR	AER	– 20 mg/ml (continuous) – 60 mg/ml (intermittent schedule)	Daily for 5–10 days Over a period of 3 h every 8 h for 5–10 days	Azithromycin, antibiotic, PZB, IVIG
Wongsurakiat, 2022 [32]	No immuno-compromised	99/76	NR	Oral	600 mg (loading dose) 200 mg (followed dose)	Three times a daily for 7 days	Corticosteroids, bronchodilator
Adults and children							
Avetisyan, 2009 [33]	HSCT	28/4	NR	Oral/IV	15–20 mg/kg	Three times daily	AER
Small, 2002 [34]	HSCT	34/24	1 (0–17)	AER	6 g	18 h daily	IVIG

Table 2 continued

Author, year [Ref.]	Population	N RBV/ SC	Delay onset of therapy, median days (range)	Type	Dose	Frequency	Adjuvant therapies
Torres, 2007 [35]	HM	24/28	1 (1–12)	AER	6 g	Daily for at least 4 days	Corticosteroids, PZB, IVIG
Children							
Evarard, 2001 [36]	No immuno-compromised	20/ 18*	NR	AER	6 g	18 h daily	NR

*Comparator was placebo

AER: aerosolized; HM: haematological malignancy; HSCT: haematopoietic stem cell transplant; IV: intravenous; IVIG: intravenous immunoglobulin; LTx: lung transplant; N: number of subjects; NR: not reported; PZB: palivizumab; RBV: ribavirin; SC: supportive care

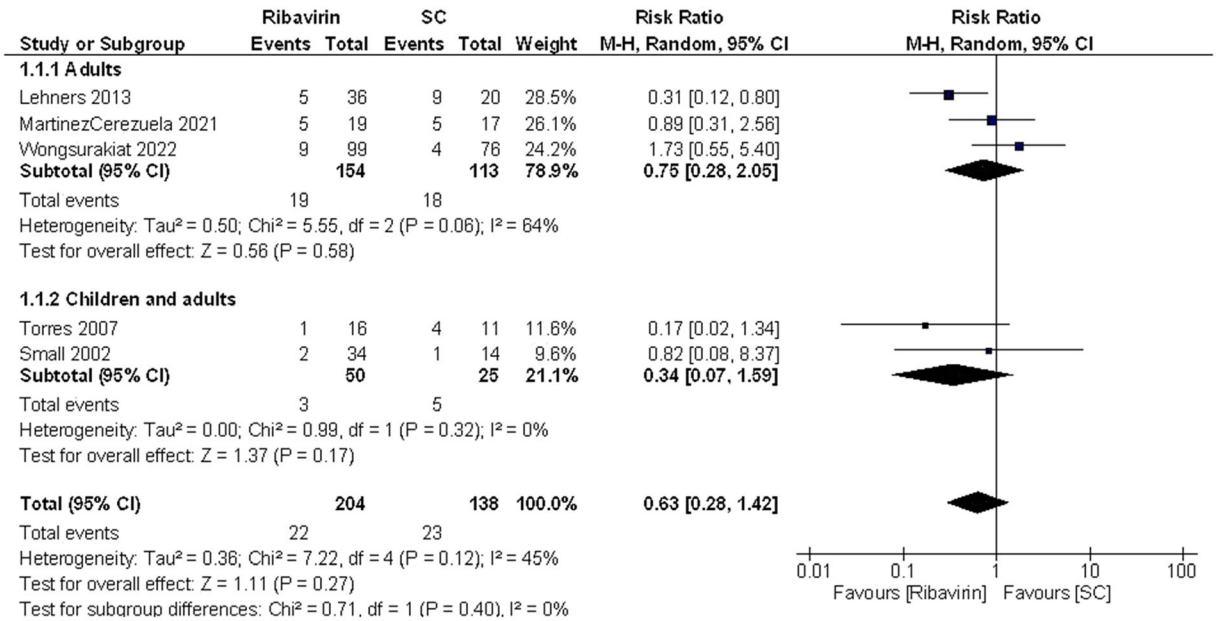

Fig. 2 Forest plot of the effect of aerosol/oral ribavirin therapy on mortality by age subgroup. The weight represents the percentage contribution of each study to the summary effect estimate. SC = supportive care; I^2 = heterogeneity; df = degrees of freedom

0.14–0.71, $I^2 = 0\%$) treated with aerosol/oral ribavirin (Fig. 3). Impact of ribavirin on mortality was inconclusive in lung transplant recipients (RR: 0.89; 95% CI 0.31–2.56).

Wongsurakiat et al. [32] study showed that treatment with oral ribavirin was the only factor associated with reduced mortality (adjusted HR: 0.19, 95% CI: 0.04–0.9, $p = 0.03$) in non-immunocompromised adults with RSV infection. The only RCT [36] included presented no data regarding mortality and therefore could not be included in the meta-analysis. However, it reported narratively that no significant benefit could be demonstrated when using aerosolized

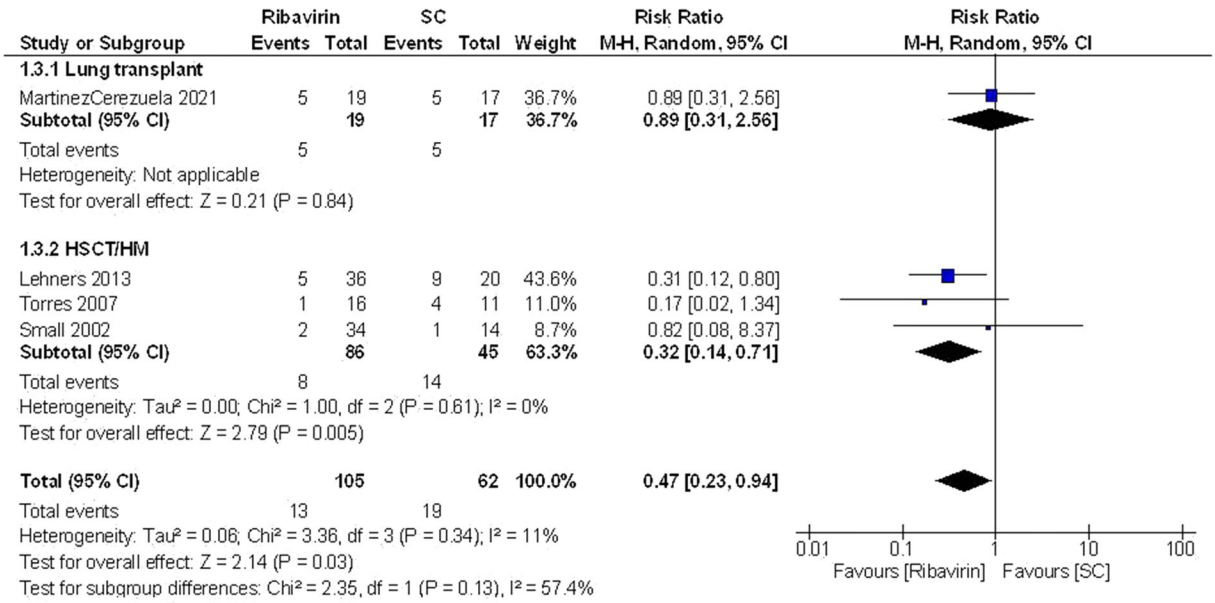

Fig. 3 Forest plot of the effect of aerosol/oral ribavirin therapy on mortality by immunocompromised subjects. The weight represents the percentage contribution of each study to the summary effect estimate. SC = supportive care; I^2 = heterogeneity; df = degrees of freedom

ribavirin to treat healthy infants admitted with moderately severe bronchiolitis.

In a sub-analysis of aerosol or oral administration arms (compared with supportive care) no statistically significant differences were found (see Figure S1 in the electronic Supplementary Material for details).

Three studies [26, 29, 32] among adult populations reported an association between the use of oral ribavirin (vs. supportive care) and increased days of hospitalization (MD 3.45; 95% CI 0.78–6.13). Two studies [27, 32] found higher viral clearance at the end of treatment in subjects treated with oral ribavirin (RR 2.60, 95% CI 1.35–4.99). No significant differences were found in the need for mechanical ventilation, bacterial coinfections, and bronchiolitis in lung transplant recipients (see Figure S2 in the electronic Supplementary Material for details).

Safety Outcomes

Three studies in haematological [28–30] and one in non-immunocompromised subjects [32] reported that oral ribavirin was generally well tolerated. Seven studies [26, 28–32, 34] reported a total of 72 subjects with RSV requiring mechanical ventilation. Precipitation of aerosolized ribavirin in ventilator circuits was not documented. Neither wheezing/bronchospasm nor gastrointestinal manifestations were reported.

Seventeen adverse events were documented among 119 subjects [27, 29, 30]. None of them were reported as severe adverse events. Fifteen haematological manifestations were reported; nine of them were haemolytic anaemia [29, 30] and six were anaemia or renal failure without details [27]. One subject with acute kidney injury [29] and one subject with liver damage [30] were also reported. In the Balassa et al. study [29], one patient had acute kidney injury and renal function returned to baseline within 3 weeks. In the Khanna et al. study [30], the bilirubin level increased from 100 to 150 mmol/l within 7 days in one patient with preexisting liver damage. A liver biopsy revealed histological characteristics that were consistent with drug-induced liver damage, but an association with ribavirin could not be excluded. According to the reports, they did not result in death, prolonged hospitalization or persistent disability/incapacity.

DISCUSSION

To our knowledge, this is the first meta-analysis assessing the efficacy and safety of aerosol/oral ribavirin (vs. supportive care) in subjects diagnosed with RSV-LRTI. Ten observational studies and one RCT (in healthy infants) were identified after an extensive literature review. Quality of evidence was high in 4/11 studies. Our findings showed that oral/aerosolized ribavirin therapy significantly improved survival in haematological subjects, but had no impact on other outcomes, such as mechanical ventilation, viral clearance, or bacterial coinfections. Oral ribavirin appeared to be well tolerated in both haematological and non-immunocompromised subjects. The effect in lung transplant recipients and healthy infants was uncertain.

Antiviral options for RSV are limited. In 1985, the FDA approved aerosolized ribavirin for treatment of hospitalized infants and young children with severe RSV-LRTI [4, 9]. EMA has approved aerosolized ribavirin for treatment of RSV bronchiolitis in infants, but it is not recommended in healthy subjects [10]. The routine use of aerosolized ribavirin is hampered by the cost, difficulty of administration, and potential teratogenic risk for healthcare professionals [37, 38]. Aerosolized ribavirin alternatives include oral or intravenous administration, but these other options have not been routinely available for RSV infection therapy [39, 40]. Although new antiviral agents such as nucleoside analogues and fusion inhibitors are being investigated, none are currently approved by regulatory agencies [41, 42].

Our findings failed to identify statistically significant differences between aerosolized and oral administration arms in five studies [27, 28, 32, 34, 35] with supportive care as comparator. The results of our meta-analysis are consistent with the results of three studies that compared aerosolized vs. oral ribavirin therapy. Foolad et al. [43] analysed 124 HSCT adult recipients diagnosed with RSV infection. They found similar rates of 30-day mortality (5% vs. 6%) and progression to LRTI (24% vs. 29%) between the two administration routes. Another retrospective cohort [44] of 46 immunocompromised adult subjects also showed no significant differences at 30-day mortality (4% vs. 15%, $p = 0.33$). Li et al. [45] reported the only retrospective cohort study in lung transplant recipients that compared aerosolized vs. oral ribavirin for RSV infection. No significant differences in overall survival were observed ($p = 0.41$).

In published literature [39–41], as well as in our systematic review [28–30, 32], ribavirin was generally well tolerated in both haematological and non-immunocompromised subjects. However, the most reported adverse events are diverse. Our study identified 17 non-severe adverse events: 15 haematological (anaemia manifestation) or renal failure, 1 acute kidney injury, and 1 liver damage. No cases of wheezing/bronchospasm, gastrointestinal manifestations or precipitation in ventilator circuits were documented. Other studies reported different adverse events [44, 45, 48–50]. Psychological manifestations associated with the feeling of extreme isolation were the most frequent in three articles [46–48], usually represented as anxiety, loneliness and ultimately depression. Six events of bronchospasm and wheezing were reported in two studies [42, 43]; whether they were associated with drug administration or disease progression remained unclear. More than five events of ribavirin precipitation in the ventilator circuit were documented in two articles [46, 47]. Respiratory therapists should know the appropriate administration technique in ventilated subjects to avoid this issue and, when using the aerosolized form, also beware of ocular and respiratory tract irritation as well as its potential teratogenic risk.

Two studies [32, 36] of non-immunocompromised subjects were included in our systematic review. Wongsurakiat et al. [32] analysed the effect of oral ribavirin in a cohort of 175 adults with community-acquired RSV-associated acute respiratory illnesses. Treatment with oral ribavirin was the only factor associated with reduced mortality (adjusted HR: 0.19, 95% CI: 0.04–0.9, $p = 0.03$). The only RCT [36] included in our systematic review evaluated 38 healthy infants treated with aerosolized ribavirin compared to placebo. Evarard et al. [36] study was unable to demostrate any significant

benefit in healthy infants treated with aerosolized ribavirin in the year following admission after a RSV-bronchiolitis episode.

Our findings did not support aerosol/oral ribavirin use in adult lung transplant recipients [26, 27] because of several factors: (1) the number of subjects analysed compared to haematological subjects; (2) heterogeneity in time from transplant to ribavirin use; (3) heterogeneity of the net state of immunosuppression. Testaert et al. [26] study reported that ribavirin was significantly less prescribed among subjects with bacterial coinfection. Adjunctive treatment with palivizumab or IVIG infusion was less frequent in lung transplant (6.4%) compared to haematological subjects (range 27–41%) and it could also be a confounding factor. Further studies are needed to elucidate the convenience of ribavirin or other co-adjuvant therapies for treating RSV-LTRI in lung recipients.

Comparison between current study and the two previous systematic reviews [13, 14] that evaluated the effect of aerosolized or oral ribavirin in the treatment of RSV-LRTI, is summarized in Table S5 in the electronic Supplementary Material. Our systematic review is the only one to our knowledge performing a meta-analysis (of RCT and observational studies) on oral and aerosolized ribavirin registered in PROSPERO. Cohort studies reporting ≤ 10 cases were excluded to improve the quality of evidence. Publication period was limited to January 2001–January 2022 to focus on current care practices with increasing implementation of molecular diagnostic tests. Population included 788 subjects with no age restriction and both immunocompromised and non-immunocompromised subjects. The systematic review by Gross et al. [13] included 15 studies (516 subjects) on oral ribavirin from 1972 to 2015. Only two of them were assessed in the current study. The review reported infections by multiple respiratory viruses. Avery et al. [14] included 15 studies (303 subjects) on aerosolized ribavirin for RSV from 1966 to 2019. Only one of them was assessed in the current study. Eight additional articles were included in the current systematic review and meta-analysis, adding new insights to the topic. Differences between articles in the previous systematic reviews and the present study and reasons for exclusion are detailed in Table S6 in the electronic Supplementary Material.

This systematic review has some limitations. Sample size was relatively small and the study was underpowered to perform several subgroup analyses or identify significant differences in outcomes. Only 1 out of 11 included studies was an RCT. Furthermore, the included population was heterogeneous in various aspects: subjects of any age (adults, infants, and both adults and children); different administration routes (aerosolized, oral, and intravenous) and duration of therapy; no consensus on the optimal oral ribavirin dosage; different types of subjects (non-immunocompromised, lung transplant, and HSCT/HM); methodological differences; baseline severity; underlying conditions; onset of therapy. Diagnostic tests also differed. PCR is currently the most sensitive tool for diagnosis of RSV infection, but some studies included in this systematic review were performed in the 2001s and the diagnosis of RSV was still confirmed by viral culture, antigen assay, or direct fluorescent antibody. That implies on delay in starting therapy, which is an important weakness because time onset was not standardized and delayed ribavirin start reduces efficacy. In addition, LRTI definition varied among studies. Our findings cannot be translated to prophylaxis.

Among the strengths, our systematic review and meta-analysis provides a critical appraisal of 11 studies, which added information on aerosolized/oral ribavirin to treat RSV-LTRI. Moreover, the study period was the last 20 years. This is important for future research because the available evidence in the literature is limited. It would be important to standardize the therapeutic strategy and conduct more studies, especially given the lack of RCTs in adults. The findings from our study support that oral ribavirin appears to be an easier, safe and cost-effective alternative to aerosolized ribavirin for therapy of RSV infection in immunocompromised subjects.

CONCLUSION

Ribavirin should be considered for the treatment of RSV-LRTI in haematological subjects. There is a lack of evidence to support its use in lung transplant recipients and healthy infants. Oral ribavirin appears to be an easier, safe, and cost-effective alternative to aerosolized ribavirin for therapy of RSV-LRTI infection in immunocompromised subjects. Future research on RSV therapy needs to focus on newer antivirals.

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