



# Human metapneumovirus infection in the cardiac paediatric ICU before and during COVID-19 pandemic: a retrospective cohort analysis

## Original Article

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### Abstract

**Introduction:** This study investigates the hygiene standards in the context of the COVID-19 pandemic and their impact on the perioperative incidence of human metapneumovirus as well as the typical symptom burden of human metapneumovirus-infected children with CHDs. **Materials and methods:** Between March 2018 and July 2021, all patients of a cardiac paediatric ICU of a German university hospital were included in this retrospective cohort analysis. **Results:** A total of 589 patients with CHD were included in the analysis. Three hundred and fifty-two patients (148 females and 204 males) were admitted before the introduction of social distancing and face masks between March 2018 and 15 April 2020 (cohort A). Two hundred and thirty-seven patients (118 females and 119 males) were admitted after the introduction between April 16 and July 2021 (cohort B). In cohort A, human metapneumovirus was detected in 11 out of 352 patients (3.1%) during their stay at cardiac paediatric ICU. In cohort B, one patient out of 237 (0.4%) tested positive for human metapneumovirus. Patients who tested positive for human metapneumovirus stayed in cardiac paediatric ICU for a median of 17.5 days (range, 2–45 days). Patients without a detected human metapneumovirus infection stayed in the cardiac paediatric ICU for a median of 4 days (range, 0.5–114 days). Nine out of 12 (75%) human metapneumovirus-positive patients showed atelectasis. **Conclusion:** Perioperative human metapneumovirus infections prolong cardiac paediatric ICU stay in children with CHD. In affected patients, pulmonary impairment with typical symptoms appears. Under certain circumstances, a complication-rich perioperative infection with human metapneumovirus could be prevented in paediatric cardiac high-risk patients by prophylactic hygiene intervention.

Perioperative viral respiratory infections are associated with prolonged invasive ventilation<sup>1,2</sup> and worse outcomes<sup>3</sup> in children undergoing cardiac surgery. While severe infections with respiratory syncytial virus or influenza virus can be prevented by active or passive immunisation, there is no preventive treatment for human metapneumovirus.

Human metapneumovirus infections almost always result in symptomatic illness, with a symptom burden ranging from mild upper respiratory tract infections to severe lower respiratory tract infections such as pneumonia or obstructive bronchiolitis.<sup>4,5</sup> The virus has been found to be a common cause of respiratory infections in children of all ages. Almost every child has had infectious contact with human metapneumovirus by the age of five.<sup>6</sup> Severe, even fatal, infections are observed, particularly in young children and immunocompromised patients.<sup>7</sup> Annually, 1 in 1000 children under the age of five are hospitalised with human metapneumovirus infection.<sup>8</sup> Patients with CHDs are more likely to have severe disease attributable to human metapneumovirus infection and more likely to die from infectious lung disease.<sup>9–11</sup> Apart from symptomatic supportive treatment, there are currently no causal therapies.<sup>12</sup>

Due to the COVID-19 pandemic, face masks and social distancing have been mandatory since the beginning of 2020. Cardiac paediatric ICU respiratory admissions have been substantially reduced during the COVID-19 pandemic.<sup>13</sup>

In the present study, we demonstrate a series of human metapneumovirus infections in children suffering CHD and retrospectively analyse the impact of COVID-19-related contact restrictions and intensified hygiene standards on perioperative human metapneumovirus infections.

## Materials and methods

### Ethics committee approval

This retrospective study was approved by the responsible ethics committee (No: 21-1179) of the University Hospital of Cologne, Cologne, Germany (Chairperson Prof. Dr R. Voltz). The medical records of all children who were admitted to cardiac paediatric ICU from March 2018 to July 2021 were reviewed. In accordance with hospital ethics, written informed consent was obtained for each medical procedure. The ethics committee waived the requirement to obtain informed consent from parents to review the data. The study was conducted in accordance with the Helsinki Declaration on Patient Safety in Anaesthesiology.<sup>14</sup>

### Patient and data selection

The medical records of all children admitted to the cardiac paediatric ICU of a single tertiary centre (University Hospital of Cologne) between March 2018 and July 2021 were reviewed to identify all patients with human metapneumovirus infection detected by polymerase chain reaction (PCR). Patients were divided into two cohorts: admission between March 2018 and 15 April 2020 (cohort A) and admission between April 16 and July 2021 (cohort B). Thus, cohort A was admitted to the cardiac paediatric ICU before and cohort B during the stricter COVID-19 pandemic hygiene standards. All patients with CHD were included and analysed. Patients without CHD were excluded from the analysis. Subsequently, all cases with human metapneumovirus infection were analysed in terms of individual symptom burden, therapy, and outcome: For example, the diagnosis of atelectasis was confirmed by analysing the ultrasound and radiographic findings in the individual medical records, and the presence of pulmonary hypertension was taken from the admission report (echocardiographic findings) for the ICU stay in question. Furthermore, information on syndromal diseases or chromosomal anomalies was extracted from the medical records.

### Statistical analysis

The data analysed for this study were taken from the electronic patient record.

The statistical analysis was carried out using SPSS version 27.0 (IBM, SPSS Statistics, IBM Corporation, Chicago, IL, United States of America).

Distribution of demographic data (age, weight, etc.) is presented as median (range). Descriptive data are given as numbers (proportion). Pearson-Chi-Square-Test and Mann-Whitney-U-Test were performed to test for significant correlations/differences. All *p* values below 0.05 were considered statistically significant.

## Results

### Demographic data

Between March 2018 and July 2021, a total of 589 patients (266 females and 323 males) with CHD were admitted to cardiac paediatric ICU and all of them were included in the analysis. Three hundred and fifty-two patients (148 females and 204 males) were admitted before the introduction of social distancing and face masks between March 2018 and 15 April 2020 (cohort A). The median age in cohort A was 5.9 months (range, 0.0–307.20 months), and median bodyweight was 5.9 kg (range, 1.4–96 kg). Two hundred and thirty-seven patients (118 females and 119

males) were admitted after the introduction of social distancing and face masks between April 16 and July 2021 (cohort B). The median age in this cohort was 5.5 months (range, 0.0–283.1 months), and the median bodyweight was 5.7 kg (range, 1.6–81 kg). Mann-Whitney-U-Test showed no significant difference between cohort A and cohort B with *p*=0.136 for age and *p*=0.220 for bodyweight. Patients in cohort A had a Risk Adjustment in Congenital Heart Surgery score 1 in 131 cases (37.2%), Risk Adjustment in Congenital Heart Surgery score 2 in 71 cases (20.2%), Risk Adjustment in Congenital Heart Surgery score 3 in 99 cases (28.1%), Risk Adjustment in Congenital Heart Surgery score 4 in 25 cases (7.1%), Risk Adjustment in Congenital Heart Surgery score 5 in 1 case (0.3%), and Risk Adjustment in Congenital Heart Surgery score 6 in 25 cases (7.1%). Cohort B showed Risk Adjustment in Congenital Heart Surgery score 1 in 68 cases (28.7%), Risk Adjustment in Congenital Heart Surgery score 2 in 60 cases (25.3%), Risk Adjustment in Congenital Heart Surgery score 3 in 66 cases (27.8%), Risk Adjustment in Congenital Heart Surgery score 4 in 16 cases (6.8%), Risk Adjustment in Congenital Heart Surgery score 5 in 0 cases, and Risk Adjustment in Congenital Heart Surgery score 6 in 27 cases (11.4%). Pearson-Chi-Square-Test showed no significant difference in Risk Adjustment in Congenital Heart Surgery score between cohort A and cohort B with *p*=0.136.

### Occurrence of human metapneumovirus

In cohort A, human metapneumovirus was detected in 11 out of 352 patients (3.1%) during their stay at cardiac paediatric ICU. In cohort B, 1 patient out of 237 (0.4%) tested positive for human metapneumovirus. Pearson-Chi-Square-Test showed significant difference in occurrence rate of human metapneumovirus between cohort A and cohort B with *p*=0.023.

In the one patient tested positive in cohort B, the parents reported a pulmonary infection 2 weeks before hospital admission; the patient was completely asymptomatic upon admission. The swab was taken 1 day before the planned surgery, the positive results arrived the night after surgery, and another swab was negative 2 days after surgery. Four out of 12 (33.3%) patients were positive only after repeated testing (see Table 1).

### Human metapneumovirus-positive tested patients: summary

One patient out of 12 (8.3%) human metapneumovirus-positive patients from cohort A and cohort B belonged to Risk Adjustment in Congenital Heart Surgery score category 2, eight patients (66.7%) belonged to category 3, one patient (8.3%) belonged to category 4, and two patients (16.7%) did not undergo surgery. Pearson-Chi-Square-Test showed no significant correlation between Risk Adjustment in Congenital Heart Surgery score and human metapneumovirus infection with *p*=0.081.

### Human metapneumovirus-positive tested patients: complicating factors

In 6 out of 12 patients (50%), pulmonary hypertension was known prior (echocardiographic findings from the admission report) to the discovery of human metapneumovirus infection, and all patients with fatal outcome had pre-existing pulmonary hypertension. Two patients with a fatal outcome had an underlying syndromal disease; in total, 5 out of 12 (41.7%) patients had an underlying syndromal disease.

**Table 1.** Characteristics of positive human metapneumovirus swab.

Case	Month	Co-infection	TTP from surgery (days)	TTP from symptomatic disease (days)	Negative swabs before positivity
1	February	Norovirus	2	2	0
2	February	RSV	8	8	1
3	July	Rhinovirus, Staph. epidermidis	11	15	2
4	February		Surgery 9 days after positive result	2	0
5	December	Parainfluenza	13 (re-admission to ICU)	1	0
6	December	Staph. epidermidis, <i>E. cloacae</i>	18	3	0
7	June	Rhinovirus	4	2	1
8	October		1	1	0
9	August	Rhino-, Bocavirus	24	10	1
10	February		No surgery	1	0
11	March		No surgery	2	0
12	May		0	0	0

E, enterobacter; RSV, respiratory syncytial virus; Staph, staphylococcus; TTP, time to positivity.

#### Human metapneumovirus-positive tested patients: typical symptoms

Nine out of 12 (75 %) human metapneumovirus-positive patients showed atelectasis demonstrated by chest X-ray or lung ultrasound (see Table 2).

#### Human metapneumovirus-positive tested patients: ventilatory support

Median time on ventilator in human metapneumovirus-infected patients from Risk Adjustment in Congenital Heart Surgery score category 3 was 10 days (range 0–43 days).

#### Human metapneumovirus-positive tested patients: extracorporeal membrane oxygenation

Two out of 12 patients (16.7%) were put on veno-arterial extracorporeal membrane oxygenation due to acute respiratory failure and resulting circulatory decompensation, both died.

#### Human metapneumovirus-positive tested patients: infectiology

Seven out of 12 human metapneumovirus-positive tested patients (58.3%) showed a viral or bacterial co-infection during cardiac paediatric ICU stay (see Table 1).

#### Human metapneumovirus-positive tested patients: duration of cardiac paediatric ICU stay

Patients who tested positive for human metapneumovirus stayed at cardiac paediatric ICU for a median of 17.5 days (range, 2–45 days). Patients without a detected human metapneumovirus infection stayed in the cardiac paediatric ICU for a median of 4 days (range, 0.5–114 days). Mann–Whitney–U–Test showed significant difference between patients tested positive for human metapneumovirus and patients without detected human metapneumovirus infection with  $p < 0.001$ .

#### Surgery on human metapneumovirus-positive patients

Four patients tested positive for human metapneumovirus by day 4 after surgery, indicating that surgery was performed during active or fading infection.

#### Human metapneumovirus-positive tested patients: outcome

Overall, 3 out of 12 (25%) human metapneumovirus-positive patients died during their stay in the cardiac paediatric ICU. Five out of nine (55.6%) patients who survived primary cardiac paediatric ICU stay were readmitted to cardiac paediatric ICU within 90 days of discharge.

#### Discussion

In this retrospective analysis, we found a significant difference in the incidence of human metapneumovirus infections in cardiac paediatric ICU patients before and during intensified hygiene standards due to COVID-19 pandemic. In 24 months without social distancing and medical face masks, we detected 11 human metapneumovirus infections, 9 of which were perioperative. In the following 16 months, there was extensive social distancing including medical face mask obligation for all persons entering the hospital due to the COVID-19 pandemic. During this time, only one human metapneumovirus infection was detected, which remained without clinical relevance. It can be assumed that this was a fading infection, as there were no more symptoms and the second smear test was already negative.

We found that patients who tested positive for human metapneumovirus had to stay in the ICU significantly longer than patients without human metapneumovirus detection.

The need for mechanical ventilation appears to be longer and mortality higher in human metapneumovirus-infected patients than in patients without human metapneumovirus infection, as shown by recent literature looking at the Risk Adjustment in Congenital Heart Surgery score: Risk Adjustment in Congenital Heart Surgery score category 3, in this analysis, needed ventilation

**Table 2.** Patient demographics and characteristics of their human metapneumovirus infection.

Case	Vitium	RACHS-score	Age at ICU-admission (months)	Sex	Maximum therapy	Atelectasis	Pulmonary hypertension	Medical specialities	ICU/Ventilator/ECMO (days)	Hospital (days)	Outcome	Re-admission ICU during 90 days
1	Balanced AVSD	3,19	5	M	VA-ECMO, iNO, APRV	X-ray	Yes	Trisomy 21	22/22/5	22	Exitus	
2	Hypoplastic left heart, hypoplasia of aortic arch	4,13	7	M	VA-ECMO, iNO, APRV	X-ray/US	Yes		27/27/6	27	Exitus	
3	Dysplastic mitral valve with insufficiency	3,07	1	M	APRV, iNO	X-ray/US	yes	Repeated MPV-Infection	26/14/0	75	IMC	Yes
4	Dilated cardiomyopathy	3,07	8	F	CMV	X-ray/US	Yes		28/10/0	33	IMC	No
5	Balanced AVSD, AV-Block III	3,19	4	F	CMV	X-ray/US	Yes	Trisomy 21	15/07/0	39	IMC	Yes
6	Imbalanced AVSD (borderline hypoplastic left heart)	3,20	0	F	NIV	X-ray/US	No		50/26/0	59	IMC	No
7	DORV with AV-canal, malpositioning of great arteries	3,10	38	F	HFNC	No	No		13/0/0	13	IMC	Yes
8	Balanced AVSD	3,19	10	F	NIV	No	No	Trisomy 21	7/0/0	12	IMC	Yes
9	DORV, atresia of mitral valve, hypoplastic left heart, stenosis of pulmonic valve, partial mismatch of pulmonary veins	3,23	26	M	APRV, iNO, tracheotomy	X-ray/US	Yes	Kleefstra syndrome	43/43/0	43	Exitus	
10	AVSD	No surgery	32	F	APRV	X-ray/US	No	Indeterminate syndrome	10/7/0	17	IMC	No
11	Fallot's tetralogy	No surgery	29	F	HFNC	X-ray	No		19/0/0	27	IMC	Yes
12	DORV, stenosis of pulmonary valve	2,16	20	F	HFNC	No	No		3/0/0	17	IMC	No

AV-Block, atrioventricular block; AV-canal, atrioventricular canal; AVSD, atrioventricular septum defect; APRV, airway pressure release ventilation; CMV, continuous mandatory ventilation; DORV, double outlet right ventricle; F, female; HFNC, high-flow nasal cannula; IMC, intermediate care; iNO, inhaled nitric oxide; M, male; NIV, non-invasive ventilation; RACHS, Risk Adjustment in Congenital Heart Surgery; US, ultrasound; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.



for a median of 10 days (range 0–43 days). Meanwhile in current literature, it is 58 hours (range 13–135 hours)<sup>15</sup>. The mortality in category 3 was 25% in this analysis, whereas 9.5% has been previously reported.<sup>16</sup> Patient number for Risk Adjustment in Congenital Heart Surgery score category 2 and 4 was too small for comparison with literature.

In particular, children with pre-existing pulmonary hypertension appear to be at risk when acute human metapneumovirus infection and current surgery coincide, probably due to the leading pulmonary pathogenesis of human metapneumovirus. Many patients in this study who were affected by human metapneumovirus suffered from viral or bacterial co-infections during their stay in the ICU. The human metapneumovirus seems to act as a kind of door opener for these infections in the present study, as the diagnosis of the co-infections appeared days after human metapneumovirus detection. During the disease, the majority of patients showed a pronounced tendency towards atelectasis, which led to the need for highly invasive ventilation in a relevant number of cases. In some cases, it was this tendency towards atelectasis that led to repeated PCR smears and only then to a human metapneumovirus-positive result. The tendency towards atelectasis seems to be more pronounced in this paediatric cardiac collective (75%) than in paediatric collectives without CHD (around 40%<sup>17,18</sup>).

It remains unclear whether the detection rate reflects the prevalence of human metapneumovirus in cardiac paediatric ICU patients as only symptomatic patients were tested for respiratory viruses; however, human metapneumovirus very rarely remains without symptoms.<sup>5</sup> In several cases, patients were positive for human metapneumovirus only after repeated testing. Therefore, the prevalence might be underestimated and mortality might be overestimated. Nevertheless, in this retrospective analysis, human metapneumovirus infection appears to be at least an avoidable contributor to cardiac paediatric ICU morbidity, resulting in longer length of stay in the cardiac paediatric ICU.

As a result, the present study raises the question of whether paediatric cardiac high-risk patients, for example, with previously known pulmonary hypertension, can or must be protected from human metapneumovirus infection by social distancing, use of medical face masks and gloves by the parents, doctors, and nursing staff for the incubation period of human metapneumovirus and the perioperative period in hospital, even after the COVID-19 pandemic. The current studies confirming the reduction of respiratory virus distribution by the COVID-19 pandemic protective measures in the paediatric community also seem to justify these ideas.<sup>19</sup> However, the mental integrity of the already suffering and possibly socially isolated children must not be forgotten, as otherwise psychological impairments could also occur and the already stressful hospital situation could be further aggravated.<sup>20</sup>

## Conclusion

Children with human metapneumovirus and CHD suffer from typical pulmonary symptoms; in particular, their tendency towards atelectasis appears to be higher than in children with human metapneumovirus infection who do not have CHD. Human metapneumovirus infections in children with CHD appear to favour a complication-rich course and prolong their cardiac paediatric ICU stay. To prevent a complicating perioperative infection with human metapneumovirus in high-risk paediatric patients with CHD, prophylactic hygiene measures should be considered (isolation for possible incubation periods, medical face mask obligation of all contact persons).

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**Conflicts of interest.** None.

**Ethical standards.** This retrospective study was approved by the responsible ethics committee (No: 21-1179) of University Hospital of Cologne, Cologne, Germany (Chairperson Prof. Dr R. Voltz). The ethics committee waived the requirement to obtain informed consent from parents to review the data. The authors assert that all procedures to this work comply with the ethical standards in accordance with the Helsinki Declaration on Patient Safety in Anaesthesiology.<sup>14</sup>

**Preliminary data presentation.** Parts of the data were shown as an abstract presentation at the annual congress of the German Society for Interdisciplinary Intensive Care Medicine (DIVI/01-03 December 2021) in German.

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