

Respiratory syncytial virus infection is an underestimated cause of viral pneumoniae in adults

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Abstract

Respiratory syncytial virus (RSV) testing is generally available in most care centres, but it is rarely performed because clinicians' seldom suspect RSV to be the underlying pathogen in adults with respiratory disease. Here, we evaluate the impact of broad combined influenza/RSV testing on the clinical practice. Overall, 103 patients were tested positively for RSV. Our study indicates that positively tested patients were mostly of advanced age and suffered from chronic diseases. Mortality was significant in our cohort and higher in patients with advanced age. Further, we report a significant increase in detected RSV cases but also in detection rate. Together, these findings suggest that implementation of a combined influenza/RSV testing led to a significant increase in detection rate, supported clinicians establishing the correct diagnosis and allowed a safe and controlled handling of RSV patients.

Introduction

The respiratory syncytial virus (RSV), a single-stranded RNA virus, is primarily known as a major cause of lower respiratory tract infection in infants and young children ¹. In the recent past, numerous studies have demonstrated significant disease burden in adults, especially if immunocompromised, suffering from an oncological disease, chronic obstructive pulmonary disease, severe asthma or congestive heart failure ^{2,3}. Shi et al. estimated a global number of 336,000 hospitalized patients per year due to RSV in the group of older adults (≥ 65 years) ⁴.

Previously, an overwhelming amount of studies reported similar rates of hospitalization and mortality of influenza virus A and B compared to RSV ⁵⁻⁸. Similar clinical presentation of both viruses and comparable seasonal characteristics makes a differential diagnosis based on clinical or epidemiological characteristics nearly impossible without adequate diagnostics ⁹. Moreover, both viruses can be transmitted by aerosol droplets or direct contact to the virus, such as over fomites ^{10,11}. Hence, prevention protocols have to be implemented to protect health care workers (HCWs) and prevent disease transmission within health care facilities. Such prevention strategies mainly comprise two aspects. Firstly, clinicians must be aware of the virus and test for it. Despite overwhelming evidence that RSV is associated with a significant disease burden in adults, clinicians' awareness is still low ^{12,13}. At the Vienna General Hospital, 2,776 samples were tested for Influenza A and B, however only 387 samples were tested for RSV during season 2017/2018. Secondly, distinct infection control and prevention strategies have to be implemented to prevent nosocomial disease transmission and protect HCWs.

In autumn 2018, a combined flu/RSV test was introduced at the Vienna General Hospital. Hence, all patients with suspected respiratory tract infection tested for influenza were automatically tested for RSV. Furthermore, patients who tested positive for RSV were admitted to isolation wards if their clinical presentation warranted hospitalization. Here, we set out to describe RSV disease burden in hospitalized adults at a university hospital, highlight the impact on the clinical practice and elucidate pitfalls of misinterpretation with other respiratory viruses.

Results

Analysis of respiratory samples collected during season 2018 and 2019

A total 5393 respiratory samples were collected, 2857 samples during season 2018 and 2536 samples during season 2019. Performed tests and results are demonstrated in Fig. 1. Interestingly, there was a significant difference in detection rate between the seasons for all of the reported viruses. We detected a significant increase ($p < 0.001$) in influenza A in season 2019 (326 of 2388 [13.6%]) compared to season 2018 (215 of 2776 [7.7%]). Prevalence of influenza B was significantly lower ($p < 0.001$) in season 2019 (1 of 2388 [0.04%]) compared to 2018 (461 of 2776 [16.6%]). The newly implemented diagnostic strategy led to a significant increase ($p < 0.001$) in RSV infection rates in 2019 (111 of 2402 [4.6%]) compared to season 2018 (10 of 387 [2.6%]), and a higher proportion of patient tested received a specific diagnosis with combined influenza/RSV test.

Descriptive Analysis Of Rsv Patients

Within our observation period, from week 40 2017 to week 30 2019, a total of 121 respiratory samples were tested positive for RSV, corresponding to 103 patients (18 patients were tested more than once) with RSV infection. The median age of our cohort was 57 years (range 40–73), and female (49 of 103,[47.6%]) and male (54 of 103,[52.4%]) patients were equally affected. 31.3% (32 of 103) patients were smokers. 63.1% (65 out of 103) patients reported comorbidities, namely pre-existing cardiac disease (54 of 103 [52.4%]), pulmonary disease (33 of 103 [32%]), diabetes mellitus type II (20 of 103 [19.4%]), neoplasia (24 of 103 [23.3%]), terminal dialysis-dependent kidney insufficiency (13 of 103 [12.6%]) or were solid-organ transplant recipients (19 of 103 [18.4%]). 43.7 % (45 of 103) of the patients required in-hospital care. Of the patients admitted to in-hospital care 44.4% (20 of 45) of the patients reported complications. Respiratory complications were most frequently reported (14 of 45 [31.1%], COPD exacerbation accounted for the majority of them [11 of 14, 78.57%]), followed by bacterial or fungal superinfection (5 of 45, [11.1%]) and cardiac complications (2 of 45 [4.44%]). Most frequently describe pathogens were *Streptococcus pneumoniae* detected by rapid urine antigen testing (3 of 45, 6.67%), *Klebsiella pneumoniae* detected in blood culture (1 of 45, 2.2 %), *Enterococcus faecalis* detected in blood culture (1 out of 45, 2.2%) and *Aspergillus fumigatus* detected in a bronchoalveolar lavage culture (1 out of 45, 2.2%).

Risk Factor Analysis For A Severe Disease Progression

Risk factors for hospitalization in RSV patients were, advanced age ($> 65a$) ($p < 0.001$), smokers ($p < 0.001$), pre-existing cardiac diseases ($p = 0.001$), preexisting pulmonary disease ($p = 0.006$), diabetes mellitus type II ($p = 0.044$), clinical or radiological signs for pneumonia ($p = 0.009$). Antimicrobial

treatment was initiated in 29 of 103 (28.2%) patients. Decision for antimicrobial treatment was based on several factors as demonstrated in Fig. 2. Furthermore, C-reactive protein at admission did significantly correlate with hospitalization ($p < 0.001$) and administration of antimicrobial agents ($p < 0.001$). Of the patients admitted for in-patient care 15.56% (7 of 45%) needed further treatment and an ICU ward. Risk for ICU admission was higher in patient with preexisting pulmonary disease ($p = 0.03$), experience of complications ($p = 0.001$), evidence for pneumonia ($p = 0.002$) and bacterial superinfection ($p = 0.036$). 6.67% of hospitalized RSV patients died (3 of 45 patients, overall 2.9% [3 of 103]). Risk for death was higher in patients advanced age ($p = 0.048$). Table 1. demonstrates the odds-ratios of the risk factors depending on the outcome parameters risk for hospitalization, ICU admission and mortality.

Table 1

highlights odds-ratios for risk factors depending on outcome parameter hospitalization, ICU admission and mortality.

	Hospitalization		ICU admission		Mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age > 65 a	5.25 (2.2–12.5)	< 0.001	2.43 (0.51–11.51)	0.42	1.13 (1–12.74)	0.048
Smoking - yes	9.11 (3.4–24.38)	< 0.001	1.73 (0.36–8.24)	0.67	1.11 (0.1–12.74)	1
Cardiac disease	4.03 (1.75–9.28)	0.001	6 (0.7–51.74)	0.115	1.85 (0.16–21.02)	1
Pulmonary disease	3.35 (1.41–7.96)	0.006	6.07 (1.11–33.16)	0.033	4.45 (0.39–50.95)	0.24
DM type II	2.96 (1.07–8.21)	0.044	1.73 (0.31–9.66)	0.62	9.11 (0.78–106.01)	0.096
Dialysis	3.38 (0.97–11.79)	0.07	0.87 (0.8–0.94)	0.59	0.87 (0.81–0.94)	1
Neoplasia	2.17 (0.86–5.49)	0.108	2.68 (0.56–12.92)	0.349	7.09 (0.61–81.9)	0.135
SOT	1.82 (0.66–5.02)	0.31	0.68 (0.08–5.97)	1	0.8 (0.72–0.89)	1
Complications	-	-	21.43 (2.44–187.98)	0.001	6 (0.52–69.03)	0.167
Pneumonia	4.3 (1.4–13.21)	0.009	15.96 (2.8–91.02)	0.002	10.5 (0.9–122.81)	0.078
Superinfection	-	-	12.4 (1.67–91.87)	0.036	12 (0.89 – 161.65)	0.14

Assessment of the impact of clinicians' knowledge of RSV status on clinical practice

To evaluate the influence of the test on the clinical practice, we further reassessed all patients negatively tested for influenza virus A and B during the RSV peak during season 2018, corresponding to week 8 to 12. Indeed, we revealed 10 (of 191, 5.2%) additional RSV cases. We compared the handling of the patients with known RSV infection to the patients not tested for RSV on admission, but RSV positive in our analysis. We did not detect differences in rates of hospitalization (patients with known RSV infection = 43.7%, patients with unknown RSV infection = 40%, $p = 1$) or frequency of antimicrobial administration (patients with known RSV infection = 28.2%, patients with unknown RSV infection = 20%, $p = 0.725$). However, only patients diagnosed at admission got isolated.

Discussion

This study was conducted to assess the influence of a newly implemented combined flu/RSV test at the biggest tertiary care center in Austria. As expected, introduction of the test revealed that RSV is responsible for a substantial fraction of severe respiratory illnesses in adults during influenza season. Mortality in our cohort was high, and was even higher in patients with advanced age. Despite early and broad testing of our patients we were not able to safely discern any influence on admission rates to hospital or administration of antimicrobial agents.

When comparing RSV to influenza, overwhelming evidence showed similar rates of hospitalization, respiratory failure and mortality^{7,12}. RSV disease burden was particularly high in patients aged > 75years^{6,14}. Consistent with previous reports, our patients were mostly of advanced age and suffered from chronic diseases, such as oncological diseases, pulmonary diseases, diabetes mellitus type II and solid-organ transplant recipients. Previous reports have demonstrated rates of bacterial superinfections in up to 15% of RSV cases⁷. In our cohort 11.1% of the patients suffered from superinfection. Most frequently reported pathogens were *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Aspergillus fumigatus*. Bacterial superinfections were associated with increased need for hospitalization and need for ICU admission.

Despite an increasing number of reports highlighting the disease burden of RSV in adults, awareness of many health care providers to adults seems to be low^{12,13}. RSV is known to be transmitted by aerosol droplets or direct contact to the virus, such as over contaminated hands or surfaces^{15,16}. During winter months RSV and influenza have their epidemic peaks in Austria, RSV usually a bit later than influenza virus. As a result, clinicians in emergency rooms and ambulances had to separate patients with respiratory tract infections due to RSV and influenza quickly and reliably to prevent nosocomial transmission. To tackle this problem, the general diagnostic procedure for RSV was revised in early 2018 by implementing a combined diagnostic assay for influenza A, influenza B and RSV. We demonstrate that a combined test led to an expected increase in performed tests and detected cases, but also to an increase in detection rate from 2.6 to 4.6%. The clinical presentation of patients with RSV and influenza is non-specific and similar, which makes it almost impossible to differentiate between the viruses based on symptoms alone. We believe that the demonstrated increase in detection rate emphasizes these

diagnostic difficulties and supports the application of combined PCR tests in the clinical practice. At our center all positively tested patients were admitted to distinct wards and had to remain in quarantine for 5 days. Further, health care workers in contact with those patients had to wear personal protective equipment. Herewith we achieved a safe and controlled handling of RSV patients.

Apart from the implemented measures, the impact of the test on the clinical reasoning is difficult to quantify. In theory, detection of viral pathogens responsible for pneumonia should reduce administration of antimicrobial treatment. Coinciding data from previously published retrospective studies showed that increased viral testing only partially altered antimicrobial treatment^{17,18}. Here, we demonstrate that reasoning for antibiotic treatment depends on multiple factors such as an elevated CRP, clinical and radiological indication for pneumonia, as well as age of the patient rather than on the clinicians' knowledge about RSV/test result.

Due to increasing availability and potency of viral diagnostic tools, viruses are increasingly detected as a cause for pneumonia world-wide. Clinical influence of broad viral testing was often discussed controversially, mostly due to three factors. Firstly, apart from neuraminidase inhibitors for influenza virus infections no specific antiviral options exist¹⁹. Secondly, attempts to provide convincing evidence that broad antiviral testing reduces rates of antimicrobial treatment were unsuccessful^{17,18}. Thirdly, interpretation of naso-pharyngeal swabs poses a challenge of its own as the detected virus could be responsible for co-existing upper respiratory tract colonization or an actual pneumonia pathogen, making diagnosis difficult.¹⁹ The above points should not be interpreted in the sense that testing is unnecessary, but rather that further research is urgently necessary to improve diagnostic procedures and the availability of treatment options. Currently, however, the biggest argument for broad-based testing remains the prevention of the spread of disease and protection of HCWs.

We acknowledge several limitations. First, our control group of patients with unknown RSV status was relatively small, as we only detected 10 additional cases. Hence, we only compared 10 patients from season 2018 to 103 cases in season 2019 in terms of clinical practice and reasoning, which is a limiting factor of our study. However, it is plausible clinicians' select antimicrobial treatment based on multiple factors such as CRP, indication for pneumonia, age and not only on a test result. Furthermore, the assessed 191 samples corresponded to all samples during the suspected peak of RSV season in 2018, week 8 to 12. Hence, analysis of other periods would have been associated with increased efforts regarding costs and time. Secondly, we did not broadly test patients after the isolation period and cannot ultimately conclude if implemented strategies proved feasible in reducing risk of transmission after the isolation period. Finally, the present study was conducted retrospectively. Thus, the study design does not allow conclusions about the outcome of the patients besides the information documented in our system.

In conclusion, we demonstrated that although RSV disease is a well described cause for pneumonia in adults. Implementation of a combined influenza/RSV test led to a significant increase in detection rate, supported clinicians establishing the correct diagnosis and allowed a safe and controlled handling of RSV patients.

Methods

This retrospective cohort analysis assesses the influence of a newly implemented combined influenza/RSV RT-PCR test on the clinical practice at a university hospital. The study protocol was approved by the Ethics Committee of the Medical University of Vienna, Austria (ECS 1523/2019) and all study-related procedures were conducted according to the declaration of Helsinki.

Setting Of The Study

The Vienna General Hospital is the largest tertiary care center in Austria, and contributes significantly to the medical care of patients with respiratory tract infections during influenza virus and RSV epidemics. Here we describe the impact of the combined influenza/RSV test, newly implemented in week 40 of 2018, to complement pre-existing infection control and prevention strategies. Thus, treatment of RSV patients was compared between the season 2018 (period before combined influenza/RSV testing), defined as week 40 of 2017 to week 30 of 2018, and the season 2019 (period with influenza/RSV testing in place), defined as week 40 of 2018 to week 30 of 2019. The general infection control and prevention strategies comprise (1) all patients reporting respiratory symptoms and admitted to the hospital, within the influenza and RSV season, were tested for influenza virus A, B and RSV, (2) all RSV positively tested patients in need for in-hospital care were admitted to distinct wards to maintain isolation for 5 days, (3) all HCWs at the center were offered free influenza vaccination and (4) all HCWs in direct contact with influenza A, B or RSV patients were trained for the use of appropriate PPE (filtering facepiece (FFP) 2 mask, goggles or face shield, long-sleeved water-resistant gown and at minimum one pair of gloves at contact with influenza virus A,B or RSV patient).

Diagnostic Assays Performed

Tests were performed differently depending on the season. In season 2018 testing for influenza virus A and B was performed by RT-PCR (in-house protocol established after Ward et al or Xpert® Xpress Flu, Cepheid) and testing for RSV was performed by (MagNA Pure 96 system, TaqMan-based RT-PCR using the LightCycler Multiplex RNA Virus Master [Roche Diagnostics, Rotkreuz, Switzerland] on a Roche Lightcycler 480II thermocycler [Roche Diagnostics, Rotkreuz, Switzerland]²⁰. RT-PCR was performed using the routine test for respiratory viruses in-house established after Fry et al, but not always in parallel²¹. In season 2019 RSV infection was diagnosed by a combined Flu/RSV RT-PCR (Xpert® Xpress Flu/RSV XC, Cepheid). Finally, all samples (n = 191), not tested for RSV but tested negative for influenza, from the encompassed peak of 2018 RSV season in Vienna (week 8 to 12) were reassessed for RSV by RT-PCR with the above mentioned routine protocol.

Data Collection

Adult patients diagnosed with RSV between October 2017 and April 2019 were included in this study. Demographic parameters, outcome parameters (outpatient/inpatient care, need for ICU admission and mortality) treatment procedures and laboratory parameters were retrospectively extracted from the Vienna General Hospital Information System (AKIM). To assess the implemented measures, patients were divided into two groups depending on clinicians' knowledge of the RSV status. Then handling of the patients, assessed by rates of hospitalization and antimicrobial treatment, were compared between those groups.

Statistical analysis

Statistical analysis was performed using commercially available computer software SPSS Statistics 20 (IBM, USA) and figures were produced in R (R Core Team, 2014) using the package ggplot2 (Wickham, 2009)^{22,23}. The hypothesis testing was performed by Chi-Square test for categorical variables and Student's t tests or Mann-Whitney tests for metric data. Furthermore, the RSV collective from the season 2018 was compared to the collective from previous season 2019. To illustrate correlations between categorical variables, a Pearson-correlation is performed for normally distributed variables, as well as Spearman's Rho for non-parametric variables.

Declarations

Author contributions statements

Lorenz Schubert and Christoph Steininger wrote the main text, Johanna Steininger and Lorenz Schubert contributed for data acquisition, Anna Nele Herdina and Robert Strassl performed the diagnostic assays, Lorenz Schubert and Felix Lötsch prepared figures 1-2 and Selma Tobudic, Michael Kundi and Monika Redlberger-Fritz contributed for statistical analysis and interpretation of the data. All authors reviewed the manuscript.

Competing interest

The author(s) declare no competing interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics declaration

The study protocol of this retrospective analysis was approved by the Ethics Committee of the Medical University of Vienna, Austria (ECS 1523/2019) and all study-related procedures were conducted

according to the declaration of Helsinki. Due to the retrospective study design, informed consent was waived by the Ethics Committee of the Medical University Vienna.

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