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Original Article

Impact of multiplex polymerase chain reaction syndromic panel on antibiotic use among hospitalized children with respiratory tract illness during COVID-19 pandemic

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Abstract *Background/Purpose:* Precise detection of respiratory pathogens by molecular method potentially may shorten the time to diagnose and reduce unnecessary antibiotic use. *Methods:* Medical records of hospitalized children from January 2020 to June 2021 with acute respiratory illness who received a FilmArray RP for respiratory pathogens were reviewed and compared with data from diagnosis-matched patients without receiving the test. *Results:* In total, 283 patients and 150 diagnosis-matched controls were included. Single pathogen was detected in 84.3% (193/229) of the patients. The most common pathogen was human

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rhinovirus/enterovirus (31.6%, 84/266), followed by respiratory syncytial virus (18.8%, 50/266) and adenovirus (15%, 40/266). Although antimicrobial days of therapy (DOT) was significantly longer in FilmArray group than the control [7.1 ± 4.9 days vs 5.7 ± 2.7 days, $P = 0.002$], the former showed a higher intensive care unit (ICU) admission rate (3.9% vs 0%; $P = 0.010$). All ICU admissions were in FilmArray RP-positive group. There was no difference in antimicrobial DOT between FilmArray RP-positive and the negative groups, in all admissions, even after excluding ICU admissions. Antimicrobial DOT was shorter in the positive than negative group in patients with lower respiratory tract infections without admission to ICU [median (IQR): 6 (4–9) days vs 9 (4–12) days, $P = 0.047$].

Conclusions: Shorter antimicrobial DOTs were identified in children with lower respiratory tract infection admitted to general pediatric ward and with an identifiable respiratory pathogen, indicating a role of the multiplex PCR in reducing antimicrobial use for children with respiratory tract infection.

Introduction

Acute respiratory infections (ARIs) are the leading cause of childhood morbidity and mortality globally, with large proportion of disease burden occurred in low-income and middle-income countries (LMICs).[1,2] Although the causative pathogens can be due to bacteria, viruses are the most common causes of ARIs in children, among those less than five years of age.[3,4] However, signs and symptoms of ARIs caused by respiratory viruses are often overlaps with those of bacterial infections and, hence it is not possible to reliably predict and distinguish based on patients' clinical presentation. This has led to widespread use of empiric antimicrobial therapy due to uncertainty of causative pathogens, and may contribute further to antimicrobial resistance.

Inappropriate and excessive use of antimicrobial agents is a major contributor to antimicrobial resistance (AMR). In 2019, AMR was listed as one of the top ten threats to global health by World Health Organization (WHO).[5] The worrying phenomena of emerging multidrug-resistant organisms was pointed out in a study on the trends and drivers of antimicrobial consumption across 76 countries from 2000 to 2015 by Klein EY et al.[6] Over a period of 15 years, the antimicrobial consumption rate has increased by 39% from 11.3 to 15.7 defined daily doses (DDDs) per 1000 inhabitants per day, primarily driven by increased antimicrobial consumption in lower middle-income countries. Overall use per capita of Access antimicrobials (first-line or second-line therapies) and Watch antimicrobials (for use only with specific indications due to higher resistance potentials) according to WHO AWaRe classification Database[7] increased by 26.2% and 90.9% respectively. Antimicrobials are more frequently prescribed in children under 5 years of age compared with older children and adults due to greater burden of infectious diseases, hence efforts must be made to reduce usage of antibiotic in this age group.[8,9] Another important reasons to cut the use of antibiotics in young children were the association of early age antimicrobial exposure with increased risk of developing childhood asthma and increased risk of childhood obesity.[10–12]

Detection of respiratory pathogens using conventional methods such as antigen detection and viral culture are often limited and time consuming. In the recent years, development of multiplex polymerase chain reaction (PCR) syndromic panel, has shorten the time to detection and has the potential to reduce hospital or emergency department (ED) length of stay, optimize infection control practices and possibly has impact on antimicrobial use, thus improve antimicrobial stewardship.[13] However, results from few studies on impact on antimicrobial use were inconsistent.[14]

Furthermore, in COVID-19 pandemic, antimicrobial prescription has increased from pre-pandemic era, and inappropriate use of antimicrobials was high especially in elderly COVID-19 patients and those with severe disease,[15,16] while total outpatient antimicrobial prescription has decreased significantly.[17] The study aimed to examine the impact of multiplex PCR syndromic panel on antimicrobial use among hospitalized children with acute respiratory illness.

Methods

Study design and case enrollment

Chang Gung Memorial Hospital (CGMH) is a university-affiliated medical referral center located in northern Taiwan, catering medical care for cities namely New Taipei, Taipei and Taoyuan. Total population in these cities is approximately 8.9 million.

We conducted a retrospective observational study at CGMH, Taoyuan, Taiwan. From January 2020 till June 2021, we recruited hospitalized children less than 18 years old who presented with or without fever and at least one of the following documented symptoms of respiratory tract illness upon admission: cough, rhinorrhea/nasal congestion, sore throat or rapid breathing. Neonates within the first 28 days of age and children with hospital acquired pneumonia were excluded. All enrolled cases were separated into three groups: FilmArray RP-positive (RP-positive), FilmArray RP-negative (RP-negative), and the control group. FilmArray RP-positive and negative group consisted of patients who had a positive or a negative result of the FilmArray respiratory panel during the hospitalization, respectively. Enrolled children who didn't receive a FilmArray test during hospitalization were in the control group. The study was

ethically approved by the Institutional Review Board of CGMH (20211576B0).

Etiology survey for each patient, mostly used nasopharyngeal swab specimens as target samples, was performed according to the clinical judgement of clinical physicians.

The multiplex PCR syndromic panel was utilized by the FilmArray® Respiratory Panel (FilmArray RP) (BioFire® Diagnostic, Utah, USA) in the ward. Targets of respiratory pathogens included in the panel include adenovirus, Coronaviruses (HKU1, NL63, 229E, and OC43), human metapneumovirus, human rhinovirus/enterovirus, influenza A viruses (Influenza A, A/H1, A/H3, A/H1-2009), influenza B, parainfluenza virus type 1—4, respiratory syncytial virus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Bordetella pertussis*.

Electronic medical records of eligible patients were retrieved and reviewed. Basic demographic data, clinical data, laboratory data and antimicrobial data such as regimens and duration of each antimicrobial agent were collected and analyzed.

Definitions

To access standardized evaluation of antimicrobial use for each individual, antimicrobial days of therapy (DOT) defines a day of therapy as any calendar day in which at least a single dose of antimicrobial is received. DOTs are counted separately for each antimicrobial agent (i.e. a patient on two different antimicrobials simultaneously would be counted as 2 DOT on a single calendar day).[18]

Statistical analysis

Data was analyzed using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp). Data were expressed in percentage, mean ± SD and median (IQR) when appropriate. Categorical data was compared using Chi-squared test or Fisher's exact test. Continuous variables were compared using student's *t*-test or Mann Whitney U test. A two-sided *P* value of <0.05 was considered clinically significant.

Results

During the study period from January 2020 till June 2021, a total of 283 eligible patients who had FilmArray RP test done, matched to 150 patients in control group, were included in the analysis. All children in the FilmArray RP group had only one FilmArray RP test done during hospitalization, among which 80.9% (229/283) were tested positive with at least one pathogen identified, and the other 54 children had negative FilmArray results.

The mean age of children was similar between control and FilmArray RP group (2.9 ± 2.0 years versus 3.0 ± 2.6 years, $P = 0.754$), while children in RP-positive group were younger (2.8 ± 2.2 years) than RP-negaitve group (3.8 ± 3.9 years), but this difference was not statistically significant ($P = 0.064$). The proportion of male gender, prematurity and mean body weight were of no significant difference between control and FilmArray RP group, as well as between RP-positive and RP-negative group (Table 1).

Children in RP-positive group had higher mean heart rate (138.6 ± 20.9 bpm versus 132 ± 20.5 bpm, $P = 0.036$) and higher mean respiratory rate (28.9 ± 6.5 versus 26.5 ± 6.8 breath per minute, $P = 0.016$) on admission than those in RP-negative group. There was no significant difference in vital signs on admission (body temperature, heart rate, respiratory rate and oxygen saturation) between control and FilmArray RP group. Mean body temperature and the proportion of children with oxygen saturation were similar between the RP-positive and RP-negative group. All eleven admissions to intensive care unit (ICU) during the study period were children from RP-positive group and none in control group and RP-negative group. More children in the

Table 1 Basic demographic and clinical data of patients in control and FilmArray group, and FilmArray-negative and -positive groups.

Variables	Control group n = 150	FilmArray RP group n = 283	*P*	FilmArray RP NEG n = 54	FilmArray RP POS n = 229	*P*
Age, years*	2.9 (2.0)	3.0 (2.6)	0.754	3.8 (3.9)	2.8 (2.2)	0.064
Male, n (%)	92 (61.3)	152 (53.7)	0.128	30 (55.6)	122 (53.3)	0.762
Prematurity, n (%)	27 (18)	39 (13.8)	0.245	6 (11.1)	33 (14.4)	0.527
Body weight, Kg*	13.9 (5.9)	14.0 (7.8)	0.853	16.4 (11.5)	13.4 (6.5)	0.079
Vital signs on admission						
Body temperature, °C*	37.8 (1.1)	37.9 (1.2)	0.625	37.8 (1.2)	37.9 (1.2)	0.455
Heart rate, bpm*	140.0 (18.8)	137.5 (20.9)	0.192	132.0 (20.5)	138.6 (20.9)	0.036
Respiratory rate, bpm*	27.4 (6.1)	28.5 (6.6)	0.102	26.5 (6.8)	28.9 (6.5)	0.016
SpO2, %*	95.3 (2.3)	95.7 (2.1)	0.139	96.3 (1.8)	95.5 (2.1)	0.050
ICU admission, n (%)	0 (0)	11 (3.9)	0.010	0 (0)	11 (4.8)	0.132
Oxygen supplementation, n (%)	44 (29.3)	56 (19.8)	0.025	3 (5.6)	53 (23.1)	0.004
Inotropes, n (%)	0 (0)	1 (0.4)	>0.99	0 (0)	1 (0.4)	>0.99
Length of hospital stay, days*	3.9 (1.5)	4.4 (2.0)	0.003	4.1 (1.9)	4.7 (2.3)	0.113

*Data presented as mean (standard deviation); n, number; NEG, negative; POS, positive; *P*, *P* value.

Table 2 Antimicrobial profile of patients in control and FilmArray group.

Variables	Control group	FilmArray RP group	*P*
All admissions	n = 150	n = 283	
Antimicrobial use, n (%)	98 (65.3)	179 (63.3)	0.668
Days of therapy, days*	5.7 (2.7)	7.1 (4.9)	0.002
All admissions (excluding ICU)	n = 150	n = 272	
Antimicrobial use, n (%)	98 (65.3)	168 (61.8)	0.467
Days of therapy, days*	5.7 (2.7)	6.5 (3.7)	0.047

*Data presented as mean (standard deviation); n, number; *P*, *P* value.

Table 3 Antimicrobial profile for patients in FilmArray-negative and FilmArray-positive group.

Variables	FilmArray RP NEG	FilmArray RP POS	*P*
All admissions	n = 54	n = 229	
Antimicrobial use, n (%)	34 (63.0)	145 (63.3)	0.961
Days of therapy, days*	7 (4–10)	6 (4–9)	0.734
All admissions (excluding ICU)	n = 54	n = 218	
Antimicrobial use, n (%)	34 (63.0)	134 (61.5)	0.840
Days of therapy, days*	7 (4–10)	6 (4–9)	0.384
Lower Respiratory Tract Infections (including ICU admissions)	n = 22	n = 156	
Antimicrobial use, n (%)	19 (86.4)	119 (76.3)	0.415
Days of therapy, days*	9 (4–12)	6 (4–9)	0.443
Lower respiratory tract infections (excluding ICU)	n = 22	n = 145	
Antimicrobial use, n (%)	19 (86.4)	108 (74.5)	0.290
Days of therapy, days*	9 (4–12)	6 (4–8)	0.047
Upper respiratory tract infections	n = 32	n = 55	
Antimicrobial use, n (%)	15 (46.9)	20 (36.4)	0.335
Days of therapy, days*	5 (3–7)	5 (3–8)	0.711

*Data presented as median (Interquartile range, IQR); n, number; NEG, negative; POS, positive; *P*, *P* value.

RP-positive group needed oxygen supplementation than the RP-negative group. This might be explained by RP-positive group had more children with bronchopneumonia (50.7% versus 24.1%, P ≤ 0.001) while more children in RP-negative group had more cases with diagnosis of acute tonsillitis (29.6% versus 10.0%, *P* ≤ 0.001) and upper respiratory infection (24.1% versus 8.3%, *P* = 0.001) (Supplementary Table 1).

Impact on antimicrobial use

Children in the FilmArray RP group had received significantly longer mean antimicrobial DOT than the control group (7.1 ± 4.9 days versus 5.7 ± 2.7 days, P = 0.002), and the result remained significant even after ICU admissions were excluded from analysis (Table 2). There was no significant difference in median antimicrobial DOT whether or not the child was tested positive for FilmArray with or without ICU admission (Table 3). Subgroup analysis was performed, among children with lower respiratory tract infections (LRTIs) with no ICU admissions, RP-positive group had significantly shorter antimicrobial DOT [median (IQR): 6 (4–9) days versus 9 (4–12) days, *P* = 0.047] compared to RP-negative group.

Respiratory pathogens detection using multiplex PCR and its distribution

By using multiplex PCR, single pathogen was detected in 193/229 (84.3%) of tests, while mixed infections of two pathogens were detected in 35/229 (15.2%) and only one child with mixed infections of three pathogens (adenovirus, human rhino/adenovirus and human metapneumovirus), giving total of 266 pathogens detected from 229 tests. Respiratory pathogens detected with FilmArray RP panel were human rhino/enterovirus (84/266, 31.6%), followed by respiratory syncytial virus (50/266, 18.8%) adenovirus (40/266, 15.0%), human metapneumovirus (39/266, 14.7%), parainfluenza viruses 1–4 (32/266, 12.0%), *M. pneumoniae* (14/266, 5.3%), human coronaviruses (6/266, 2.3%) and *B. pertussis* (1/2966, 0.4%). No influenza A or B virus was found during this study period. The most common combination of mixed infections of two pathogens were Rhino/enterovirus plus parainfluenza (7/35, 20.0%) followed by adenovirus plus rhinovirus/enterovirus (6/35, 17.1%) and human metapneumovirus plus rhinovirus/enterovirus (5/35, 14.3%). Distribution of respiratory pathogens detected according to the epidemiologic calendar of study were shown in Fig. 1.

Laboratory investigations

Complete blood count, serum creatinine, liver enzymes and inflammatory markers such as C-reactive protein and procalcitonin were comparable between control group and FilmArray RP group, as well as between RP-positive and RP-negative group (Supplementary Table 2).

Discussion

We studied the impact of rapid molecular testing on antimicrobial DOT on hospitalized children with non-SARS-CoV-2 acute respiratory tract infections during COVID-19 pandemic. Our study showed that median antimicrobial DOT was significantly shorter among patients with LRTIs and a positive multiplex PCR result, excluding ICU admissions. This could be explained by the belief that the upper respiratory tract microbiome is generally thought to be the source of LRTIs in childhood. This concept is supported by the findings from a research conducted by Man WH et al.[19] He investigated the link between the composition of nasal microbiome and LRTIs in children and found high intra-

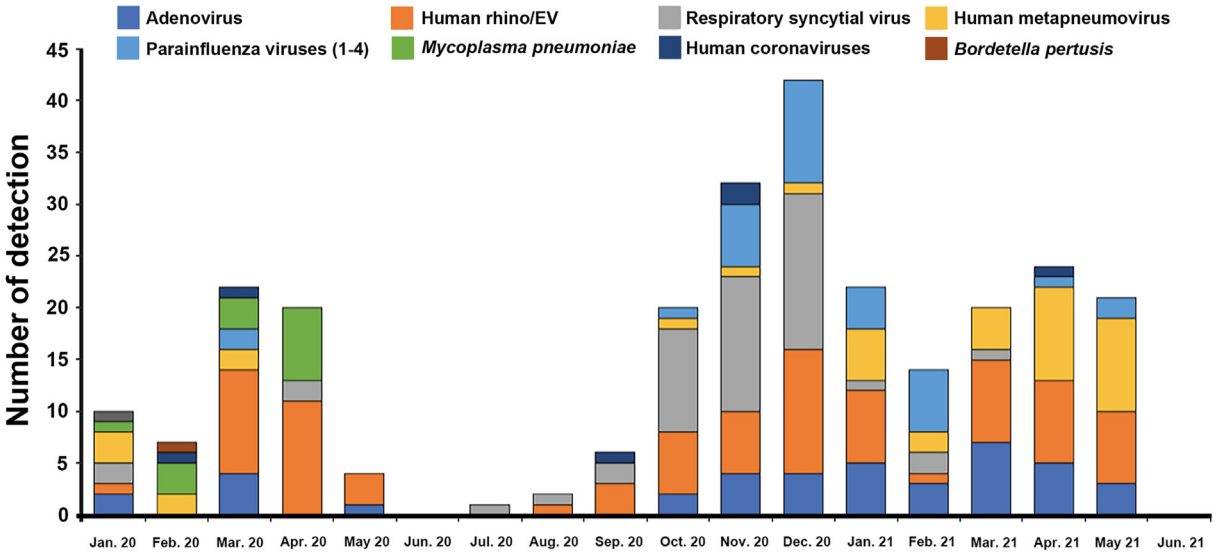

Figure 1. Distribution of respiratory pathogens detected using multiplex PCR panel according to month, January 2020 to June 2021.

individual concordance of viral microbiota agreement (96% agreement [95% CI: 93—99]) and bacterial microbiota between nasopharyngeal and endotracheal aspirates, among children between 4 weeks and 5 years with lower respiratory tract infection requiring mechanical ventilation. His study suggested that the nasopharyngeal microbiota can serve as a valid proxy for lower respiratory tract microbiota in childhood LRTIs and that clinical LRTIs in children result from the interplay between microbiota and host characteristics.

The impact of the molecular testing on antimicrobial usage for patients in different clinical settings would need further evaluation. We found a positive multiplex PCR result would be more useful in general ward settings when used together with antimicrobial stewardship. Manatrey-Lancaster and colleagues found no influence of rapid molecular testing on antimicrobial DOTs among hospitalized adult patients,[20] but among patients discharged from the ED, average DOTs would have been 2.3 DOTs shorter than patients with negative rapid test if influenza was detected. While Rao S et al. conducted a randomized control trial among pediatric patients visiting ED for influenza-like illness,[21] and found no significant difference in antimicrobial prescribing (relative risk, RR 1.1; 95% CI, 0.9—1.4), but more antiviral prescriptions and hospitalizations among children with test results known.

Our study showed that antimicrobial DOTs differed among children with LRTIs whom were tested positive and those who were not, after excluding all eleven patients admitted to ICU, indicating more antimicrobials were used in ICU setting, likely contributed by more severe clinical course. Among the eleven patients, two patients had bronchopneumonia/bronchiolitis with encephalitis, one patient with bronchopneumonia and myocarditis, two had empyema thoracis, two with lobar pneumonia and four patients were in ICU for close monitoring of clinical deterioration. Both Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommended the use of rapid molecular testing (nucleic acid testing) for hospitalized patients and hospitalized immunocompromised patients to improve detection of responsible respiratory pathogens and to aid in reduce use of inappropriate antimicrobials.[22,23] In the ICU setting, Yoshida K et al. found no reduction in antimicrobial use (84% vs 75%; $P = 0.14$) in children with respiratory infections in the Pediatric intensive care unit between the pre- and post-multiplex PCR periods.[24] There is a need to address some concerns among intensivists including unfamiliarity with the molecular diagnostic test capabilities, uncertainties on the significance of respiratory pathogens detected leading to either over-treatment or under-treatment, and concern of patient deterioration while awaiting molecular diagnostic results.[25]

Similar with findings on trends of circulating respiratory viruses from other countries,[26,27] we observed a generally low numbers of cases with identifiable respiratory pathogens, especially from May 2020 till August 2020 and June 2021 with the implementation of non-pharmaceutical interventions (NPIs) such as universal masking and social and physical distancing to combat COVID-19 pandemic. No influenza virus was detected using multiplex PCR in our study cohort. Non-enveloped respiratory virus, human rhinovirus/enteroviruses was the most common respiratory virus detected.

The limitation of our study was firstly, the reduced numbers of respiratory illness related hospital admissions (including ICU) and the "disappearance" of certain respiratory viruses due the implementation of NPIs from the start of COVID-19 pandemic, such as universal masking, social distancing, and Level 3 alert "soft lockdown" policy in May 2021. Secondly, we could not compare antimicrobial DOTs before and after COVID-19 pandemic as the multiplex PCR for respiratory pathogens detection test only available in our center at the end of year 2019. Thirdly, as we only include in-hospital antimicrobial use in our study and the tendency to discharge patients as soon as they were ready during the pandemic, probably had some impact on the pattern of antimicrobial use and prescription if compared with pre-pandemic era, for which we did not explore in this

study. Fourthly, as this was a retrospective study, the clinical severity as well as the distribution of upper and lower respiratory tract infections might be inconsistent in the RP group and control group, which could interfere with the antimicrobial DOTs.

In conclusion, during the COVID-19 pandemic, with the implementation of NPIs, diseases caused by circulating respiratory viruses were generally less. The shorter antimicrobial DOTs among pediatric patients with LRTIs admitted to general pediatric ward and with an identifiable respiratory pathogen, indicating an important role of rapid molecular testing in reducing antimicrobial use when use in combination with antimicrobial stewardship program.

Declaration of competing interest

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.01.009.