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Original research article

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Pathogen spectra in hospitalised and non-hospitalised children with community acquired pneumonia

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"Take home" message

Our prospective multicenter study analyses outpatients and hospitalised children with CAP. Clinical phenotype, pathogen spectra, and outcome were compared. A high rate of viral pathogens in young children questions the use of antibiotics in this group.

Introduction

Paediatric community-acquired pneumonia (pedCAP) is one of the leading causes of childhood morbidity and mortality worldwide. Even in high income countries, it causes up to 20% of paediatric hospital admissions (1). In Germany, annual hospitalisation rates of children below the age of 5 years with pedCAP are estimated to be around 90/10,000 (2). However, a critical gap in the knowledge on etiology and management of pedCAP exists. Most pedCAP-studies thus far focused on hospitalised pedCAP, and longitudinal data on non-severe courses is scarce (3-5). Detailed etiologic data in young age groups is particularly rare (4,6,7). Diagnostic and predictive value of clinical pedCAP symptoms such as fever and tachypnea, especially in infants, are under debate (8-11), and validated severity scores for pedCAP are pending. In recent years, implementation of anti-Pneumococcal and anti-Haemophilus-influenzae B vaccines and novel diagnostic nucleic acid amplification techniques led to a significant shift in pathogens identified in children with pedCAP (12-16). However, even with updated diagnostic tools, clear differentiation between viral and bacterial pedCAP remains challenging (4,5,17-19). Although viral infections are assumed to be responsible for a high proportion of pedCAP, particularly in infants, antibiotic therapy in pedCAP is still recommended in a large proportion of cases (11,20-22). To contribute to current knowledge on etiology, phenotype, and treatment regimens and improve pedCAP management, we initiated the prospective, multi-center pedCAPNETZ study (23). Here, we present first data from this cohort with a particular focus on pathogen spectra in hospitalised and non-hospitalised pedCAP.

Methods

Study cohort

Setup and protocol of the pedCAPNETZ cohort is described in detail elsewhere (23). The here presented analysis includes data obtained between December 2014 and August 2020. In brief, patients were recruited in nine clinical centers in in- or outpatient settings as a convenience sample not following an established protocol to identify eligible patients. Inclusion criteria were age <18 years and diagnosis of pedCAP confirmed by lung ultrasound (LUS) or chest radiography. Proof of lung consolidation with air bronchograms by LUS was classified as pneumonia (24,25). If pleural effusion was present in LUS, extent and morphology were determined. Chest radiographs were reviewed by two independent, certified paediatric radiologists in accordance with WHO guidelines (26,27). Exclusion criteria were hospitalisation for any reason or cytostatic therapy 28 days prior to inclusion, neutropenia (<1000/µl), other relevant immunosuppressive treatment, congenital or acquired immunodeficiency, concomitant respiratory disease with impaired mucociliary clearance, or tuberculosis. Respiratory insufficiency (demand for O2 supplementation) was defined as SpO2 <92%.

Data collection

Demographic data and information on clinical symptoms, comorbidities, previous medical antibiotic treatment, inflammation parameters, diagnostic data, radiological findings, and treatment were recorded in pseudonymised fashion in a central online database at study inclusion. Follow-up visits by phone interview or chart reviews were performed on day 14 and 90 upon enrollment, follow up on day 28 was performed when clinical symptoms persisted until day 14 after inclusion.

Pathogen detection and determination of biomarkers

Extended description can be found elsewhere (23), in brief study inclusion and biomaterial collection were performed within 24 hours after radiologic or sonographic proof of pneumonia. Bacterial cultures (BC) were performed in all available blood, pleural-fluid (PF), deep throat swab, sputum (Spu, with or without previous hypertonic saline inhalation), and bronchoalveolar-lavage fluid (BALF) specimens upon study inclusion. Diagnostically valuable sputum was obtained in children >6 years of age. Polymerase chain reaction (PCR) assays were performed in nasopharyngeal swabs (NPS) or nasopharyngeal aspirates (NPA) to detect Mycoplasma (M.) pneumonia, Chlamydia (C.) pneumoniae, Legionella, Bordetella pertussis and a panel of respiratory viruses (adenovirus (AdV), coronavirus (CoV) 229E/HKU1/NL63/OC43 (not SARS-CoV-2), human metapneumo virus (HMPV), human rhinovirus (HR), influenza A and B (Flu), parainfluenza virus (PIV) types 1-4, bocavirus (BV), enterovirus (EV), parechovirus (PV), and respiratory syncytial virus (RSV) at study inclusion. Available blood samples were tested for differential blood cell counting, C-reactive protein (CrP), creatinine, sodium, urea, blood gas, and C. pneumoniae and M. pneumoniae immunoglobulins (Ig) in routine clinical testing. At the time of study inclusion the results of NPS or NPA–PCR, BC, and sputum as well as serology results of C.pneumoniae and M.pneumoniae were not available for the attending physicians according to daily clinical practice and analysis duration. Results of differential blood cell counting, CrP value, creatinine, sodium, urea and blood gas analysis were available for the treating physicians at the time of study inclusion.

The gained biomaterials were either directly measured at the participating centers (differential blood cell counting, CrP value, creatinine, sodium, urea, blood gas analysis, blood culture, sputum, BAL, PF, serology for M.pneumoniae and C.pneumoniae) or immediately stored at -80°C and send to the study center (NPA, NPS).

Statistical analysis

All statistical analyses were performed employing Statistical Software Package for Social Sciences (SPSS; 24, IBM, Armonk, New York (USA)), Excel, or GraphPad Prism V9 (San Diego, California (USA)). Descriptive data were calculated as mean with standard deviation (SD) or interquartile range (IQR). Categorical data were reported as frequencies and percentages. Differences between groups were analyzed by T- or Man-Whitney-U testing and Chi-quadrat or Fisher's exact testing for nominally distributed data. P values <0.05 were considered statistically significant.

Ethical approval

The pedCAPNETZ study was approved by ethical review boards of all participating centers (e.g. lead study center approval number MHH#2356–2014). All patients and their legal guardians provided written informed consent.

Results

A total of n=486 children were screened for study participation. N=41 (8.4%) of these did not meet radiographic or sonographic inclusion criteria, and in n=8 cases (1.6%) thoracic imaging was missing. Accordingly, n=437 patients were included into the analysis (Fig.1). For demographic data see table 1. N=92 (21.1 %) were treated as outpatients, whereas n=345 patients (78.9%) required hospitalisation (Table 1). The mean duration from symptom onset until study inclusion was seven days (IQR: 3-9 days, 7.5 days in outpatients and 6.8 days in hospitalised cases, p=0.36).

Amongst the n=426 cases with pedCAP confirmation by chest radiographs, alveolar infiltrates were the most prevalent pathological finding occurring in n=399 of patients (93.6%). Detailed radiographic differences of in-and outpatient treated children are given in table 2. In n=11 CAP was diagnosed by LUS showing lung consolidation with air bronchograms.

Overall, the most prevalent symptom at study inclusion was cough, occurring in 91.8% of patients (95.6% of outpatients, 91.0% of hospitalised cases, p=0.14), followed by fever (89.2% of all and 91.3% of outpatients vs. 88.7% of hospitalised cases, p=0.57), tachypnea (62.0% of all, 54.3% of outpatients vs. 64.1% of hospitalised cases, p=0.09), and chest retractions (55.5% of all and 21.3% of outpatients vs. 65.7% of hospitalised cases, p<0.0001). Fluid intake reduction also occurred more often in hospitalised cases than their outpatient counterparts (49.8% vs. 1.03% p<0.001). Auscultation abnormalities occurred in 91.1% of patients (91.3% of outpatients and 90.7% of hospitalised cases, p=1.0), with wheezing and/or extended expiration in 27.0% of all and 13.0% of outpatients vs. 30.7% of hospitalised cases (p<0.001, table 2).

For n=425 children (97%), data on antibiotic management was available. In 31.4% of these cases (33.4% of outpatients vs. 22.8% of hospitalised cases, p=0.06), antibiotic treatment for pedCAP

had already been initiated prior to study inclusion. Upon study inclusion, antibiotic treatment was changed or initiated in 87.4% (92.4% of outpatients vs. 86.1% of hospitalised cases, p=0.11). Aminopenicillins were the most common initial antibiotic treatment (71.2% in all, 74.4% in inpatients, 60.0% in outpatients, p=0.01), followed by macrolides which were prescribed in 19.6% of all cases. Macrolides were prescribed significantly more frequent in outpatients (31.8%) than in hospitalized patients (14.8%, p=0.001).

At day 14 after enrollment (d14FU), n=251 cases (65.4%) reported to be healthy. Outpatients were more frequently symptom-free (83.1%) than hospitalised cases (57.7%, p<0.001, table2). In line with this, 90 days after inclusion (d90FU), 91.0% of all patients were symptom-free, with a significantly higher rate in outpatients (98.8%) than in those with hospital treatment (88.8% , p=0.002, table 2). At study inclusion, normal CrP values (<10mg/l) were observed in 27% of cases. Mean CrP value of all patients was 65.4mg/l (IQR: 8.9-84.5) with significantly higher levels in hospitalised cases than outpatients (mean of 30.5mg/l (IQR 4.9-52) vs. 74.9mg/l (IQR 10-107), p<0.001).

When we analysed pathogen occurrence within our cohort, at least one pathogen was detected in 90% of all cases. PCR-testing of NPA or NPS was performed in 91.7% yielding positive results in 80.3% (Fig. 2A). The most commonly detected viral pathogens in PCR analyses were RV (24.2%), RSV (20.3%), bocavirus (11.3%), PIV (8.5%), HMPV (7.5%), coronavirus (not SARS-CoV-2, 7.2%), flu (6.9%), adenovirus (5.9%), enterovirus (5.1%), and parechovirus (1.0%, Fig. 2A). In children <6 years of age (preschoolers), detection of viruses was significantly more common than in older children (82.1% vs. 34.2%, p<0.001). RSV was the most common virus amongst preschoolers with pedCAP with a significantly higher incidence in cases >6 years of age than in older patients (28.4% vs. 0.9%, p<0.0001, Fig. 2B). A similar pattern was observed for

HMPV, which was detected in 10.5% of preschoolers, but in none of the older children in our cohort ($p<0.001$), for bocavirus (14.9% vs. 2.6%, $p<0.001$), and for RV (25.8% vs. 20.2%, $p=0.3$, Fig. 2B). There was no statistical difference in the prevalence of flu between preschoolers and older children (6.5% and 7.9% , $p=0.66$), Fig. 2 B).

Virus pathogen detection was performed in 97.8% of outpatients and 86.7% of inpatients. When we compared detection rates of viral pathogens via NPA or NPS-PCR in outpatients vs. hospitalised children, again, a higher rate of virus detection was observed for both patient groups in patients younger than 6 years of age (86.0% for outpatients and 82.2% for inpatients, $p=0.6768$, and 28.6% for outpatients and 26.5% for inpatients aged >6 years, $p=0.31$, Fig. 3B/C). For the entire cohort, M. pneumoniae and PIV occurred significantly more frequently in outpatients (31.1% vs. 13.0% in hospitalised cases; $p<0.01$ and 13.3% vs. 6.4% in hospitalised cases; $p<0.05$, respectively, Fig. 3A). RSV was the leading viral pathogen in both hospitalised and non-hospitalised preschoolers (27.4% for outpatients and 29% for inpatients vs. 0% in outpatients and 1% inpatients aged >6 years; $p=0.0003$ and $p<0.0001$ respectively), whereas RV was the most prevalent virus in in- and outpatients older than 6 years (15.8% and 25.0% vs. 20.0% and 28.5% in out-and inpatients aged <6 years, $p=0.29$ and $p=0.3$, Fig. 3B). Most virus detection rates were not significantly different between patients with or without hospital treatment, but PIV was detected significantly more frequent in non-hospitalised preschoolers (20.0% vs. 7.0% of hospitalised preschoolers, $p=0.04$, Fig 3B).

In total, in 18.7% of all cases, bacterial pathogens were detected by airway specimen cultures or Ig-screening. NPA or NPS-PCR for M. pneumoniae was positive in 17.5% of the total study cohort (13.0% of hospitalised cases and 31.1% of outpatients, $p<0.001$), with a significantly higher incidence in children ≥6 years of age than in preschoolers (47.4% vs. 5.0%, $p<0.001$, Fig.

3A) and the highest incidence in children ≥12 years of age (50.0%). In line with this, M. pneumoniae was also the leading pathogen in both in- and outpatients in the age group ≥6 years, where it was detected significantly more frequent in outpatients than in hospital treated cases (63.9% vs. 39.5%, $p<0.05$, Fig. 3C). For further bacterial diagnostics, in total n=116 blood cultures were performed (98.3% of them in hospitalised patients), which were positive for bacterial pathogens in 5.1% (all hospitalised cases). Here, Streptococcus (S) pneumoniae was the most common strain (50% of positive cultures). With regard to lower respiratory tract analyses, n=30 sputum (n=9 in outpatients) and n=13 BALF specimens were obtained. Overall, 54.5% of positive sputum cultures resulted from growth of Staphylococcus (Staph.) aureus, S. pneumoniae and Haemophilus (H) influenzae (50.0% in outpatients and 57.1% hospitalised children). In 39% of patients with BALF sampling, bacterial pathogens were detected with H. influenzae as the leading pathogen (40%). In those cases where pleural fluid was collected (n=24, all hospitalised patients), S. pyogenes and Staph. aureus were most commonly detected (22% each). In 4.5% of patients, both viral and bacterial pathogens were detected (4.6% in hospitalised children and 2.2 in outpatients).

Discussion

Our study is one of the first to address the full spectrum of radiographically confirmed pedCAP based on a cohort consisting of both non-hospitalised and hospitalised patients. The rates of clinical symptoms such as cough (91.8%), fever (89.2%), and chest retractions (55.5%) observed in our cohort were in accordance with those observed in a previous hallmark study on hospitalised pedCAP which found cough in 95.6%, fever in 91%, and chest retractions in 45% of cases (5). In accordance with previous studies (5,28), pedCAP-related hospitalisation rates in our cohort were highest in infants and toddlers. As expected, hospitalised children were significantly younger and presented with significantly lower SpO2 and higher rates of cyanosis, pulmonary obstruction, chest retractions, impaired liquid intake, and CrP levels than outpatients.

The analyses of pathogen spectra within our cohort confirmed previous findings on the relevance of viral pathogens in pedCAP (4,5). In both in- and outpatients, viral pathogens were highly prevalent. Compared to previous studies, the incidence of viral pathogens observed in our analysis (68.1% of all patients, 82.1% of children <6 years of age) is within the range described in previous large pedCAP cohorts (4,5), although a broad range of 18.7% to 91.0% detection rates of viral pathogens in pedCAP has been described (12). In our examinations, RV and RSV were the most commonly detected viruses with around 25% detection rate each. This is in line with previous reports on the high prevalence of these pathogens in the airways of pedCAP patients (4,5) and fits to previous reports on the relevance of RSV particularly in young children with pedCAP (5,28). Interestingly, we show that RSV belongs to the most frequent pathogens also in pedCAP outpatients, particularly in those <6 years of age. Our analyses also confirm previous reports on the high rate of M. pneumoniae positive pedCAP patients, particularly in older children and adolescents. In children ≥12 years of age, bacterial pathogens were more

prevalent with a 42.8% overall detection rate. The increasing relevance of bacterial pathogens, particularly of M. pneumoniae in older children and adolescents is in accordance with previous publications on the high rate of M.pneumoniae pedCAP in this age group (5,28). Furthermore, our data illustrates that this pathogen is significantly more prevalent in mild pedCAP, as a striking 63.9% of children ≥6 years of age with outpatient treatment in our cohort displayed a positive NPA or NPS-PCR for M. pneumoniae.

The particular strength of our cohort lies in the broad inclusion of pedCAP patients with and without hospitalisation. Only around one fourth of CAP cases in Western Europe are hospitalised and the majority of pedCAP cases are treated as outpatients (5,28). Almost all recent studies in the field of pedCAP focused on hospitalised patients (4,5,16,28-30), but this is insufficient to understand the full spectrum of pedCAP etiology. Therefore, we also included outpatients in our study. As we did not focus on an epidemiological study and therefore did not perform systematic screening for pedCAP, outpatients are outnumbered. We systematically compare the occurrence of viral and bacterial infections in hospitalised and non-hospitalised pedCAP and show that also in outpatients, viral pathogens are highly prevalent with pathogen spectra similar to hospitalised pedCAP cases. In fact, our age specific comparative analyses of pathogen spectra in in- vs. outpatients yielded little differences in the prevalence of specific pathogens. In spite of the high rate of virus infections, overall, 87.4% of children in our cohort received antibiotic treatment, aminopenicillins and macrolides were the most prevalent anti-infective agents administered to our patients. This is similar to observations of other groups, although prescription behavior of antibiotics varies strongly and is impacted by regional and economic differences (4,5,16,28). Particularly in the youngest group of our cohort (<2 years of age), with the highest detection rate of viral pathogens, a strikingly high rate of 83% with antibiotic treatment occurred (data not

shown). This discrepancy of high virus detection rates and frequent use of antibiotic therapy in pedCAP supports the notion of an assumingly high rate of unjustified or ineffective antibiotic treatments in mild pedCAP and emphasizes the need for updated management guidelines and advocate for stringent antibiotic stewardship in this disease (31).

Our study has certain limitations. Firstly, although our study design aims at a well-balanced patient recruitment with regard to hospitalised and non-hospitalised cases, only around one fifth of patients were outpatient cases. As such, numbers in age and pathogen specific subgroups of this subgroup were low in some analyses. Also, due to the high rate of patients recruited upon hospital admission, a high proportion of young children (75% <6 years of age) were enrolled, impeding statistical power in older age groups. Although our recruiting pattern somewhat reflects the previously described age distribution of pedCAP with high disease burden in infants (4,5), it may have biased our analyses, particularly with regard to mild cases and older children. Altough pedCAPNETZ study group has partnered with paediatric outpatient practices to increase recruitment of patients with mild disease course, most cases have been recruited in tertiary care centers. Moreover, recruitment did not follow a stringent screening routine, but were collected as a convenience sample. Both factors may lead to a patient selection with a more severe phenotype and also explain why the pathogen detection is at the higher end of the range compared to previous studies (4,5,7,12,18).

Another limitation of our work may be the fact that pedCAPNETZ is a case-only study without recruitment of control probands. However, a plethora of case-control or healthy-only studies analysing airway pathogens in children exist and were taken into account in our work (4,5,7,12,18,32-38).

Paediatric community acquired pneumonia still poses diagnostic, etiologic, and therapeutic challenges. In future, improved viral diagnostic approaches will become increasingly available and may help to limit the overuse of antibiotics in children. Future analyses of the pedCAPNETZ study group will aim on the correlation of upper and lower airway tract pathogens, appropriateness and effectiveness of microbial treatment and pathogen specific pedCAP outcomes.

Conclusion

The pedCAPNETZ study addresses the full spectrum of pedCAP. Here, we firstly present data of a cohort with hospitalised and non-hospitalised children. Despite significant clinical and CrP value differences, both groups show comparable viral pathogen distributions. Independently from hospitalisation status and pathogen detection, the majority of children in both groups received antibiotic treatment. Particularly in young patients with mild disease, viruses are the leading pedCAP cause. This should be taken in account by clinicans when considering the use of antibiotics in the care of a child with pneumonia.

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Table 1

Item	n (%)	Item	n (%)
total cohort (mean age 4.5/ IQR 1.6-6.6 yrs)	437	cough	426 (98)
Female	207 (47)	fever (>38,0°C)	380 (89)
hospitalisation rate	336 (79)	tachypnea	271 (62)
intensive care unit admission	35 (8)	auscultation abnormalities	369 (91)
mechanical ventilation	12 (2)	wheeze, prolonged exspirium	157 (37)
Death	0	thoracal retractions	188 (56)
CrP <10 mg/l	115 (27)	oxygen demand (SpO2 <92)	106 (25)
CrP >100 mg/l	93 (22)	reduced liquid intake	179 (42)

Table 2

Item	Inpatients n (%)	Outpatients n (%)	p-value
proportion of total study group	345 (79)	92 (21)	
mean age (yrs/IQR)	4.3 /1.5-5.7	5.5 /2.6-7.4	<0.001
CrP (mg/l/IQR)	30.5/ 4.9-52	74.9/ 10-107	<0.001
x-ray images	340 (99)	86 (93)	
alveolar infiltrates	322 (95)	77 (90)	0.08
consolidations	213 (63)	26 (30)	<0.001
Atelectasis	65 (19)	8 (9)	0.01
hyperinflation	84 (25)	7 (8)	<0.001
interstitial infiltrates	68 (20)	7 (8)	0.01
pleural effusion	98 (29)	20 (23)	0.35
Symptoms			
Cough	313 (91)	88 (96)	0.14
fever (>38.0°C)	306 (93)	84 (97)	0.572
Tachypnea	221 (64)	50 (54)	0.092
thoracal retractions	199 (66) [1]	19 (21)	<0.0001
pulmonary obstruction	106 (31)	12 (13)	<0.001
abdominal pain	82 (27) [2]	15 (17)	0.052
reduced liquid intake	167 (50) [3]	12 (13)	<0.001
clinical course			
healthy d14FU	177 (58) [2]	74 (83) [5]	<0.001
healthy d90FU	270 (89) [4]	84 (99) [6]	0.002
re-diagnosis pedCAP d90FU	20 (6.6) [4]	7 (8.3) [6]	0.63

Legends

Figure 1: Study flowchart.

Abbreviations: d = day; FU = follow up

Figure 2: Pathogen detection within the cohort. A: Results of pathogen detection by PCR analysis of nasopharyngeal specimens of the entire cohort. B: Age dependent subgroup analysis of results. Bars display cumulative percent with the darker/lower part of each bar representing singular pathogen and the lighter/upper part of each bar representing co-occurrence in mixed pathogen detection.

Abbreviations: Rhino = rhinovirus, RSV = respiratory syncytial virus, Parainfl = parainfluenza virus, HMPV = human metapneumovirus, Adeno = adenovirus, Corona = coronavirus, Flu = influenza, Boca = bocavirus, M. pneum = Mycoplasma pneumoniae, Entero = enterovirus, Parecho = parechovirus.

Figure 3: Pathogen detection in outpatient treated vs. hospitalized pedCAP cases. A: Detection rates of pathogens in all outpatients (blue) versus hospital treated cases (red). B/C: Detection rates of pathogens in probands aged <6 years (B) and 6-18 years (C) with outpatient (blue) and hospital treatment (red). Bars display cumulative percent.

Abbreviations: Rhino = rhinovirus, RSV = respiratory syncytial virus, Parainfl = parainfluenza virus, HMPV = human metapneumovirus, Adeno = adenovirus, Corona = coronavirus, Flu = influenza, Boca = bocavirus, M. pneum = Mycoplasma pneumoniae, Entero = enterovirus, Parecho = parechovirus. *p<0.05, **p<0.01, ***p<0.001.

Table 1: Cohort characteristics.

Abbreviations: IQR = interquartile range, CrP = C reactive protein, °C = degree Celsius, SpO2 = partial oxygen saturation

Table 2: Cohort characteristics for hospitalized and non-hospitalized children.

Abbreviations: IQR = interquartile range, yrs = years, °C = degree Celsius, d= day, FU = follow. Data were available in [1]n=336, [2]n=81, [3]n=303, [4]n=307, [5]n=335, [6] n=304, [7]n=89, [8]n=85.

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Conflict of interests

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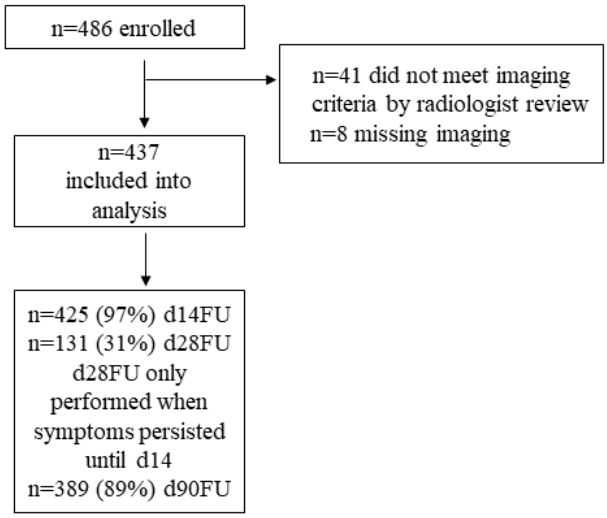
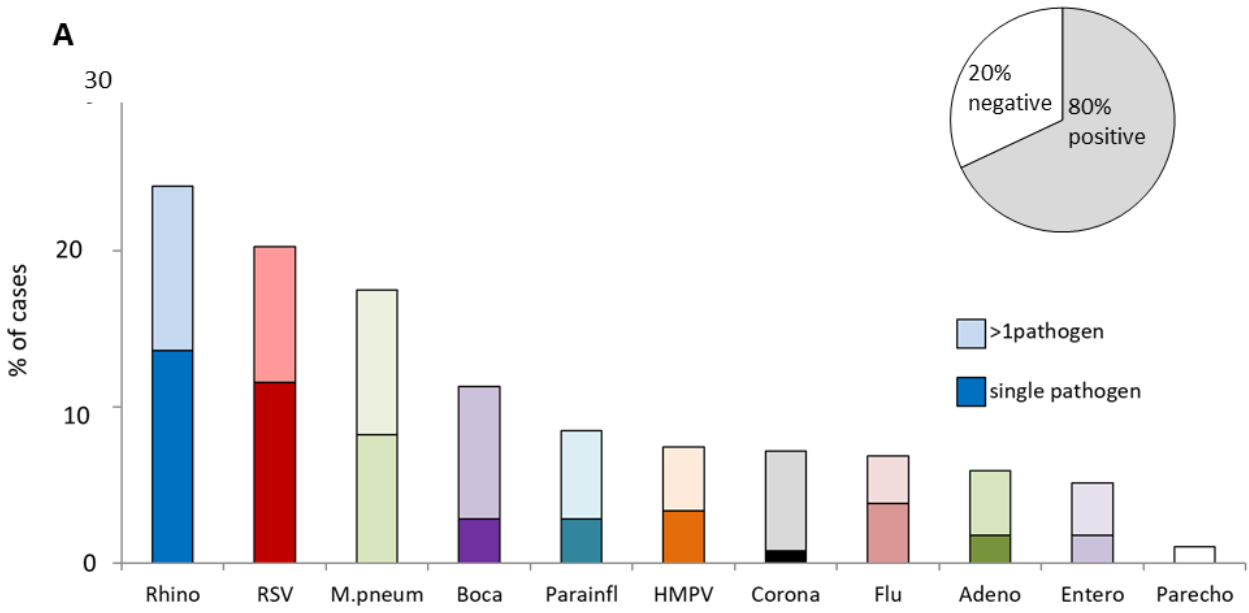

n=486 enrolled
n=41 did not meet imaging criteria by radiologist review
n=8 missing imaging
n=437 included into analysis
n=425 (97%) d14FU
n=131 (31%) d28FU
d28FU only performed when symptoms persisted until d14
n=389 (89%) d90FU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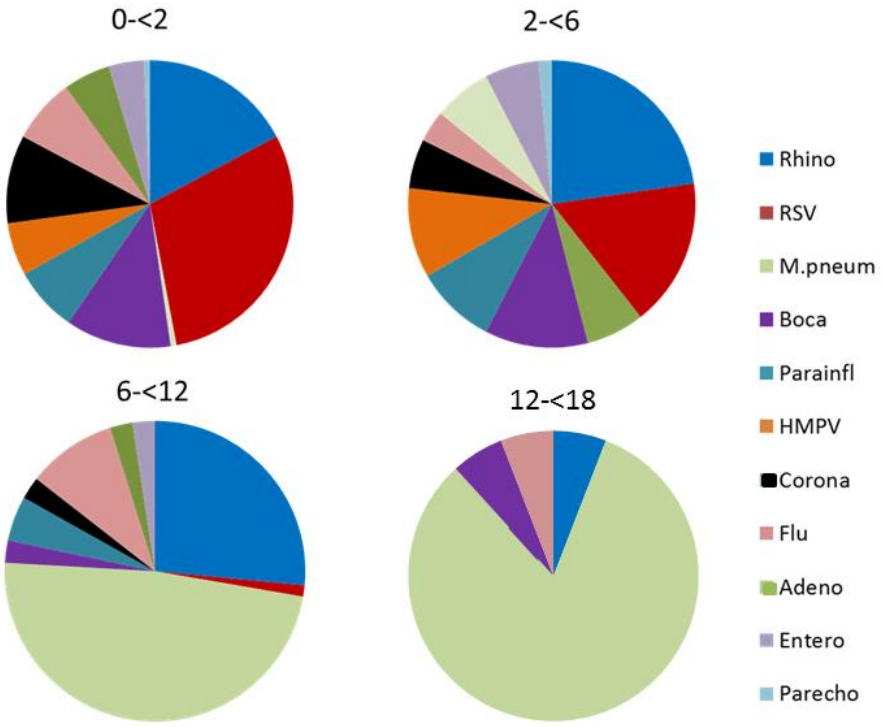
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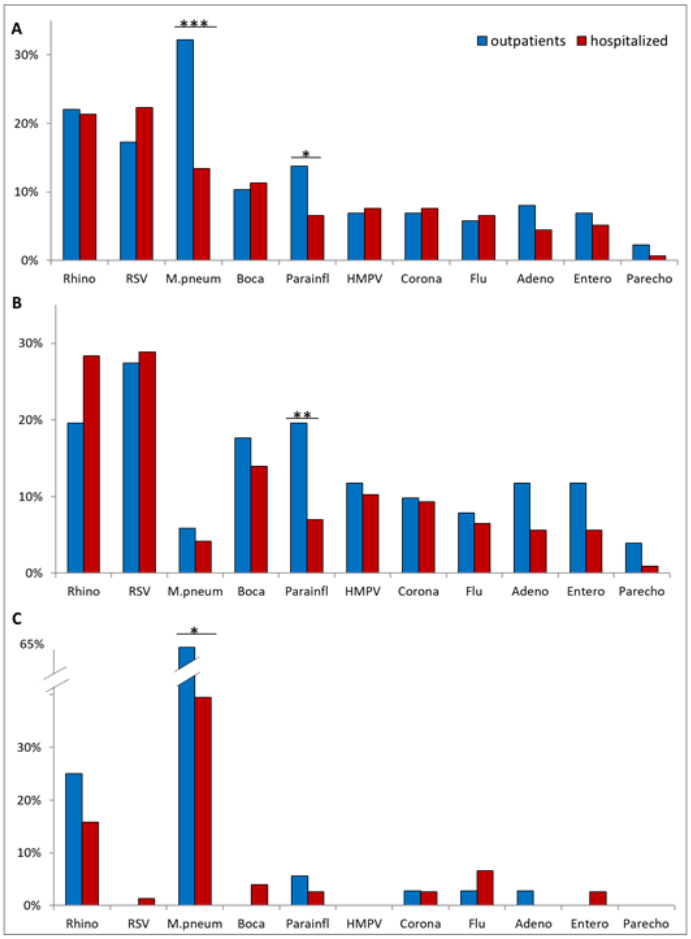
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