COVID-19 Pandemic Preparedness in a United Kingdom Tertiary and Quaternary Children's Hospital: Tales of the Unexpected

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Brief Description: We describe a heterogeneous group of 57 paediatric patients admitted to a tertiary and quaternary care children's hospital and the preparedness required to adapt to managing such a diverse population. Lessons learned at the beginning of the COVID-19 pandemic are described and how this knowledge can be translated into further preparation for an expected second wave of paediatric SARS-CoV-2 infections.

Abstract

We describe the adaptive coping strategies required in the management of a heterogeneous group of SARS-CoV-2 paediatric patients. The diverse range of presentations, presenting in distinct phenotypic waves, exemplified the importance of preparedness for the unknown. Lessons learned will be essential in planning for a likely second wave of SARS-CoV-2.

Key Words: Epidemiology, Virology, Health Services Research

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus causing severe respiratory symptoms (coronavirus disease 2019 [COVID-19]) was first identified in China. COVID-19 cases in the United Kingdom (UK) emerged on 29th January 2020. Data from England suggests that 1.7% and 0.8% of COVID-19 cases affected people <20 and 10 years of age respectively, with increasing rates in children first noted in March 2020 (1).

The paucity of data describing SARS-CoV-2 in the paediatric population mandated a broad-arching approach to pandemic planning with preparations designed to manage a heterogeneous population of patients presenting with a range of single and multi-organ pathology of varying severity. We describe a diverse, paediatric SARS-CoV-2 cohort treated at Great Ormond Street Hospital (GOSH), a tertiary/quaternary paediatrics hospital that exemplified the importance of preparedness for the paediatric COVID-19 unknown. We further illustrate four distinct temporal waves of SARS-CoV-2 clinical phenotypes at our centre and lessons learned throughout the preparatory process.

Methods

All patients aged ≤ 18 years with positive respiratory/nasal SARS-CoV-2 RT-PCR and/or serum IgG (Epitope Diagnostics Inc.™) up to 19th May 2020 were included. This time interval was chosen as it corresponds to the first two months of local cases when preparation measures remained in flux. It also represents the onset of the local epidemic when community sero-prevalence remained low, thus, both diagnostic methods likely represented recent infection. Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS; similarly defined as

Multisystem Inflammatory Syndrome in Children [MIS-C]) and paediatric COVID-19 related phenotypes were defined using the Royal College of Paediatrics and Child Health case definition (2).

Results

Fifty-seven patients were included in the final analysis (n=28 RT-PCR, n=27 serology, n=10 both).

Table 1 summarises the cohort characteristics. The median age was 9.3 years (IQR 5.16-13.48), 70% were of non-Caucasian or mixed ethnicity. Four distinct clinical groups were identified: PIMS-TS (54%), primary respiratory (18%), incidental (7%), and non-specific febrile/viral illness with or without single organ dysfunction (21%).

These groups presented in distinct chronological blocks (*Figure 1*). Respiratory and other febrile illnesses predominated during the three weeks after the first positive case was admitted. This was followed almost exclusively by PIMS-TS cases in the latter third of the study period. Compared to the primary respiratory phenotype, PIMS-TS patients were generally older, (median 10.1 [8.7-13.9] vs. 3.4 years [0.1-8.2]), healthier at baseline (supplementary *Table 2*), and of non-Caucasian ethnicity (n=26 [84%] vs n=5 [50%]). 61% had no known COVID-19 contacts. Lab investigations and adaptations in treatment modalities are presented in supplementary *Tables 3&4.* 36 (63%) required PICU admission with a median length of stay of three days (IQR 1-7). PICU admissions included all phenotypic groups except those with incidental positive tests. All children survived discharge from PICU.

Discussion

Our cohort illustrates four distinct SARS-CoV-2 infected groups, with clear demographic differences requiring varied management approaches. As such, dissimilarities in presentation, management, and follow-up of paediatric versus adult cohorts must be considered in anticipation of a second COVID-19 wave and for future pandemic planning.

Paediatric SARS-CoV-2 data remains limited compared to adults, even at the conclusion of the initial wave. As a result of reassuring findings at the start of the pandemic, initial planned patient pathways included transfer of SARS-CoV-2 patients to regional High Consequence Infectious Diseases Units. As cases surged in the UK, regional paediatric secondary care services were consolidated at our centre to facilitate expansion of adult inpatient capacity. Initial adaptations for severe cases of COVID-19 requiring intensive care were minimal as, based on Chinese and Italian data, it was assumed more would be unnecessary. However, crucially, protocols were primed to enable rapid expansion if activated. At the onset of the unexpected paediatric surge, a separate dedicated 16-bed COVID-19 PICU was created within 48 hours to accommodate increasing cases.

Consolidation of paediatric patients at our centre allowed for the utilisation of established specialist pathways in the management of complex cases, with rapid expansion of these operational processes to accommodate general paediatrics. This capitalised on the scalability of existing resources and specialist knowledge. Importantly, the early recognition of emergent paediatric-specific phenotypes (e.g. PIMS-TS) was partly achieved because our centre is exclusively paediatric. Thus, cases were not mixed with, and perhaps obscured by, severe adult COVID-19 patients.

Treatment guidelines for all evolving paediatric SARS-CoV-2 phenotypes, based on available evidence, were drafted prior to admission of the first patients, and were given expedited approval by the hospital drug and therapeutics committee. A system for rapid approval of investigational drugs was implemented in partnership with our bioethics committee. Decision-making support was provided by an established multidisciplinary team (MDT), inclusive of external specialists for impartiality. In light of the lack of treatment data for this patient group, pooling expertise in the MDT provided a foundation for the development of a standardised treatment protocol, upon which an evidenced-based approach could be built. The MDT embraced videoconferencing technology to uphold infection-prevention-and-control (IPC) precautions. It could be convened urgently by any member ad hoc (sometimes within minutes) to discuss critical cases or when rapid approval of investigational treatments was necessary.

As a research centre, continuity of translational research activity was a top priority. Whilst aligning with national research prioritisation guidance, resources were rapidly and efficiently redeployed to COVID-19 studies. Our well-established PICU research team diversified to recruiting non-PICU COVID-19 patients into relevant studies. The MDT's inclusion of members of the research team allowed for streamlining of screening and consent procedures. At all times we were mindful to not overburden families with too many options for study involvement. Studies were encouraged nationally to collate data collection and analysis to avoid duplicate reporting. After recognition of PIMS-TS, GOSH clinical/academic staff were included in the paediatric RECOVERY study working group. In collaboration with colleagues nationwide, we were able to rapidly feedback and modify protocols to allow inclusion of PIMS-TS patients and potential therapies based on the outcome of the Delphi process (3).

Improvement in paediatric-specific protocols, collaborative research capacity, and pandemic capabilities will serve to better prepare for an imminent second wave. Further pooling of expert MDT expertise and expansion and inclusion of paediatric patients in specific treatment trials will help mitigate the uncertainties associated with a novel virus having multiple presentations in an innately heterogeneous and complex population ranging from neonates to adolescents.

The complexity of paediatric pandemic preparedness in our centre and the associated lessons learned can be summarised in four distinct ways:

(i) *Changing Disease Phenotypes: Evolving presentations with chronologically heterogeneous groupings of childhood disease.* Preparedness for changing pathology required different levels of care, the creation of an MDT, and the construction of separate COVID-19 and non-COVID-19 PICUs with a specific COVID-19 general paediatric step-down ward.

(ii) *Unforeseen Disease Pathology: The emergence of PIMS-TS not previously described in the initial Asian epidemic.* Timely collaborative efforts with other paediatric centres capitalising on intra- and inter-institutional multidisciplinary input was essential in the early recognition and management of this novel paediatric phenomenon. As long-term effects remain unknown, the MDT approach will equally be essential in patient follow-up.

(iii) *Changing Treatment Modalities: The evolution of COVID-19 treatment evidence extrapolated from adult data at the height of our local epidemic.* There was a timely need to adapt paediatric management pathways in our cohort according to the latest research. However, alterations in

treatment were carried out cautiously given the distinct clinical differences in children versus adults. Moving forward, our cohort re-enforces the need for: paediatric-specific clinical trials, inclusion of paediatric patients in large intervention and observational studies, and paediatric-specific pharmacokinetic data for novel therapeutics.

(iv) *Changing Patient Demographics: A high proportion of paediatric pathology in adolescent ethnic minority populations.* This must be considered during the development of prevention strategies, tailored medical management, supportive care, and targeted follow-up plans implemented in a culturally appropriate manner, acknowledging SARS-CoV-2 impacts on both physical and mental health (4).

From a laboratory perspective, rapid upscaling of microbiology and immunology capacity was reliant on the ability to adapt at a fast pace. The on-site laboratory promptly developed validated RT-PCR and antibody testing. Provision of validated serology testing early in the pandemic, something not yet widely available at other centres, was fundamental for the identification of SARS-CoV-2 as the likely trigger for PIMS-TS. In addition, RT-PCR was performed but not completely validated on: cerebrospinal fluid, stool, blood, urine, and saliva samples. This allowed for testing in patients with atypical presentations potentially triggered by SARS-CoV-2. Our immunology laboratory scale-up also allowed for widespread and timely assessment of the immunological effects of SARS-CoV-2 in the paediatric population.

Conclusions

Supported by an ability to respond quickly in all phases of the pandemic, our SARS-CoV-2 paediatric outcomes were reassuringly good. Our centre needed to adapt throughout the pandemic including when previously undescribed phenotypes manifested and new at-risk populations were identified. An adaptive, MDT approach was paramount. Expanded laboratory capacity and incorporation of technology platforms to facilitate remote collaboration in response to strict IPC were both indispensable. Paediatric-specific planning must not be static and the evolution of preparedness endeavours must continue, particularly when facing a second wave of SARS-CoV-2. Of utmost importance, the distinction between paediatric and adult populations must not be overlooked.

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Figure Legend

Figure 1: Local phenotypic presentations of paediatric SARS-CoV-2 cases over time compared to daily cases in England (page 4)

Table 1: Cohort demographics

	All (n=57)	PIMS-TS (n=31)	Respiratory (n=10)	Incidental (n=4)	Other (n=12)
Male, n (%)	36 (63)	21 (68)	5 (50)	0 (0)	10 (83)
Age, years, median (IQR)	9.3 (5.2-13.5)	10.1 (8.7-13.9)	3.4 (0.1-8.2)	3.7 (1.2-7.9)	7.4 (0.9-12.7)
	n=50	n=31	n=10	n=4	n=12
Admission duration*, days, median (IQR)	9 (6.0-15.5)	9 (7-15)	16.5 (9.5-18.8)	0 (-)	4.5 (2.3-10.8)
	n=57	n=31	n=10	n=4	n=12
Ethnicity,** n (%)	-	-	-	-	-
White	11 (19)	4 (13)	4 (40)	1 (25)	2 (17)
Black African/Caribbean	19 (33)	14 (45)	2 (20)	1 (25)	2 (17)
Asian	12 (21)	9 (29)	1 (10)	1 (25)	1 (8)
Mixed	5 (9)	3 (10)	2 (20)	0 (0)	0 (0)
Other	4 (7)	0 (0)	0 (0)	1 (25))	3 (25)
Unknown	6 (11)	1 (3)	1 (10)	0 (0)	4 (33)
Weight-for-age (kg) percentile, n (%)	-	-	-	-	-
<5	7 (12)	2 (6)	4 (40)	0 (0)	1 (8)
5-84.9	26 (46)	16 (52)	1 (10)	2 (50)	7 (59)
85-95	9 (16)	4 (13)	2 (20)	2 (50)	1 (8)
95-98.9	9 (16)	5 (16)	1 (10)	0 (0)	3 (25)
>99	6 (11)	4 (13)	2 (20)	0 (0)	0 (0)
BMI- for-age (kg/m^2) percentile, n (%)	-	-	-	-	-
<5	4 (7)	3 (10)	0 (0)	0 (0)	0 (0)
5-84.9	14 (25)	9 (29)	4 (40)	0 (0)	4 (33)
85-95	8 (14)	5 (16)	1 (10)	1 (25)	1 (8)
95-98.9	8 (14)	5 (16)	1 (10)	0 (0)	1 (8)
>99	5 (9)	2 (6)	0 (0)	1 (25)	0 (0)
Not available (no height)	18 (32)	7 (23)	4 (40)	2 (50)	6 (50)
COVID-19 contact†, n (%)	-	-	-	-	-
No known contact	35 (61)	22 (71)	5 (50)	0 (0)	8 (67)
Household	20 (35)	9 (29)	3 (30)	4 (100)	4 (33)
Hospital	1 (2)	0 (0)	1 (10)	0 (0)	0 (0)
Household and hospital	1 (2)	0 (0)	1 (10)	0 (0)	0 (0)
SARS-CoV-2 Testing, n (%)	-	-	-	-	-
Respiratory sample RT-PCR	-	-	-	-	-
Positive	34 (60)	20 (65)	8 (80)	4 (100)	11 (92)
Negative	23 (40)	11 (35)	2 (20)	0 (0)	1 (8)
Serology	-	-	-	-	-
Positive	33 (58)	28 (90)	2 (20)	0 (0)	3 (25)
Negative	2 (4)	2 (6)	0 (0)	0 (0)	0 (0)
Not available	22 (33)	1 (3)	8 (80)	4 (100)	9 (75)
RT-PCR + & Serology positive	10 (18)	8 (26)	0 (0)	0 (0)	2 (17)
Symptoms, n (%)	n=53	n=31	n=10	-	n=12
Fever	50 (94)	31 (100)	8 (80)	-	11 (92)
Vomiting	38 (72)	23 (74)	6 (60)	-	9 (75)
Abdominal pain	34 (64)	26 (84)	4 (40)	-	4 (33)
Diarrhoea	28 (53)	22 (71)	5 (50)	-	1 (8)
Rash	26 (49)	24 (77)	1 (10)	-	1 (8)
Cough	21 (40)	9 (29)	8 (80)	-	4 (33)
Dyspnoea	21 (40)	12 (39)	7 (70)	-	2 (17)
Headache	20 (38)	15 (48)	2 (20)	-	3 (25)
Encephalopathy	18 (32)	14 (45)	1 (10)	-	3 (25)
Conjunctivitis	18 (34)	18 (58)	0 (0)	-	0 (0)
URTI symptoms‡	16 (30)	7 (29)	5 (50)	-	3 (25)
Oedema	13 (25)	11 (35)	1 (10)	-	1 (8)
Generalised Weakness	13 (25)	13 (42)	0 (0)	-	0 (0)
Lymphadenopathy	11 (21)	11 (35)	0 (0)	-	0 (0)
Meningitis	5 (9)	4 (13)	0 (0)	-	1 (8)
Thrombotic event	4 (8)	2 (6)	2 (20)	-	2 (20)
Anosmia	2 (4)	1 (3)	1 (10)	-	0 (0)

*patients admitted long term to Great Ormond Street hospital testing positive during admission and those asymptomatic whom were already admitted were not included in the calculation of length of stay

** Self-identified ethnicity as extracted from paediatric electronic medical records

†contact with household member with COVID-19 compatible symptoms or proven SARS-CoV-2 infection, hospital contact with laboratory proven SARS-CoV-2 infection

‡ pharyngitis, coryza

BMI: Body mass index, COVID-19: Coronavirus disease 2019; RT-PCR: real time polymerase chain reaction; PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, URTI: Upper respiratory tract infection

Figure 1