Original Article

Pilot Study on the Current Management of Children with COVID-19 In Hospitals in Bangladesh; Findings and Implications

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Abstract

***Objective**: The focus on COVID-19 in children in low- and middle-income countries including Bangladesh has been on addressing key issues including poor vaccination rates as well as mental health issues, domestic violence and child labour. However, the focus on optimally managing children in hospitals is changing with new variants and concerns with the development of hyperinflammatory syndromes. There are also concerns with the overuse of antimicrobials to treat patients with COVID-19 in hospitals enhancing resistance rates. The Bangladesh Paediatric Association have developed guidelines to improve patient care building on national guidance. Consequently, there is a need to document the current management of children with COVID-19 in Bangladesh and use the findings for future guidance. **Methods**: Rapid analysis of the management of children with COVID-19 among eight private and public hospitals in Bangladesh with varying numbers of in-patient beds using purposely developed case report forms (CRFs). The CRFs were piloted before full roll-out. **Results**: Overall low numbers of children in hospital with COVID-19 (4.3% of in-patient beds). The majority were male (59.6%) and aged 5 years or under (63.5%). Reasons for admission included respiratory distress/ breathing difficulties with 94.2% of COVID-19 cases confirmed. All children were prescribed antibiotics empirically, typically those on the Watch list of antibiotics and administered parenterally, with only a small minority switched to oral therapy before discharge. There was appreciable prescribing of Vitamins (C and D) and zinc and encouragingly limited prescribing of other antimicrobials (antivirals, antimalarials and antiparasitic medicines). Length of stay was typically 5 to 10 days. **Conclusion**: Encouraging to see low hospitalisation rates and limited use of antimicrobials apart from antibiotics. Concerns with high empiric use of antibiotics and limited switching to oral formulations can be addressed by instigating antimicrobial stewardship programmes. We will be monitoring this.*

Keywords: Antimicrobials, Bangladesh, Children, COVID-19, Guidelines, Hospitals, Vitamins

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1. Introduction

COVID-19 was first identified in Wuhan, China, in December 2019[1,2], and towards the end of August 2021, there were already 213.7 million recorded cases worldwide with just under 4.5 million recorded deaths giving a case fatality ratio (CFR) of 2.09%[3]. This includes Bangladesh where 1.48 million cases had been recorded towards the end of August 2021 with over 25 thousand deaths giving a CFR of 1.73%[3].

Since COVID-19 is principally spread through physical contact and airborne transmission[4,5], the focus in the early stages of the pandemic was its prevention especially with an appreciable number of patients being asymptomatic[1,5]. Effective and cost-effective strategies included quarantining and lockdown measures incorporating the closure of borders as well as social distancing[4,6-8]. However, varying degrees of implementation resulted in appreciable differences in prevalence and mortality rates among different African and Asian countries as well as with Western European countries and the United States of America[9-11].

Various re-purposed medicines were also suggested to reduce morbidity and mortality in patients with COVID-19 including hydroxychloroquine, lopinavir/ritonavir and remdesivir. However, these three had little impact on patient outcomes when objectively trialled in an appreciable number of patients, with potential issues with hydroxychloroquine increasing morbidity, mortality and costs[4,12-17]. There is also ongoing controversy surrounding the potential use of ivermectin[18-21]. Concerns generally with the level of misinformation regarding potential approaches to prevention and treatment resulted in respected bodies including the British Medical Journal, European Centre for Disease Prevention and Control (ECDC) and the World Health Organisation (WHO) providing guidance from March 2020 onwards[22-26]. As a result, encouraging the implementation of evidence-based approaches[1,27]. This was helped in Bangladesh by the Ministry of Health and Family Welfare making national guidelines available from Spring 2020 onwards[28]. This included guidelines for managing patients in hospital depending on their severity, which were subsequently built upon as more data became available. In addition, guidance on how to run a COVID-19 Hospital in Bangladesh[29].

Similarly, separate guidelines have been developed for managing paediatric patients with COVID-19 in Bangladesh[30]. This is in addition to international guidelines developed to improve the management of children with COVID-19 in paediatric intensive care units (PICUs) in both high- and low-income countries[31]. This is important as adherence to trusted guidelines are seen to enhance the quality of care, with adherence increasingly seen as a robust marker of the quality of care to improve outcomes including patients in hospital with infectious diseases[32-36], with up-to-date and easy-to-use guidelines facilitating their use[37].

Other developments in Bangladesh to improve current and future management of patients with COVID-19 include assessing antibody kinetics in these patients as well as performing genomic sequencing of different SARS-CoV-2 strains detected among COVID-19 patients[38-40].

However, we are aware that children have a lower risk of infection with COVID-19 and milder clinical manifestations when they become infected compared with adults[41-46]. Typically, fever, cough, respiratory infections, nausea and diarrhoea are the most frequent clinical characteristics of children with COVID-19, with males typically more prone to COVID-19 than females[41,44-48]. In addition, an appreciable number of children are asymptomatic[44,48]. Overall, approximately 6% to 10% of infected children with COVID-19 experience severe disease as compared to as high as 26% of adults who progress to ICUs[44,45,49].

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The lower susceptibility of children to COVID-19 infection may be due to elevated antibodies compared with adults along with other factors[50].

Consequently, the focus in children in low- and middle-income countries (LMICs) including Bangladesh has typically been addressing key concerns including poor vaccination rates as a result of lockdown and other activities[51-53]. In Bangladesh, this includes organising immunisation outreach services, tracking children who had missed their vaccinations as well as increasing home visits by health workers[53,54]. In addition, addressing some of the mental health challenges arising from lockdown measures including increasing domestic violence and child labour[55-60].

However, the focus on the optimal management of children with COVID-19 in hospitals is increasing especially with new variants. Whilst a lower percentage of children with severe symptoms are admitted to intensive care units (ICUs) in LMICs versus high-income countries, deaths among hospitalised children are higher[45]. This may be because of manpower issues. For instance, Bangladesh has the second lowest doctor-to-patient ratio in South Asia making managing patients with COVID-19 in hospitals challenging[61]. Consequently, monitoring current management approaches as well as providing guidance should help improve the future care of these patients.

Having said this, we are aware of the high use of antimicrobials in hospitals including intensive care units in treating patients with COVID-19 despite only a limited number of patients have concomitant fungal or bacterial infections[62-69]. This includes hospitals in Bangladesh[70,71]. As a result, potentially increasing rates of antimicrobial resistance (AMR) with its associated increase in morbidity, mortality and costs[66,72-77]. The instigation of antimicrobial stewardship programmes (ASPs) should help to address key concerns as these programmes have reduced inappropriate antibiotic utilisation among a number of LMICs[72,73,78,79], with educational and other initiatives also reducing inappropriate antibiotic prescribing to prevent surgical site infections among LMICs[72,80].

We see though that children diagnosed with COVID-19 do develop Kawasaki Disease (KD)-like symptoms/ hyperinflammatory syndromes[41,81-83], which is reflected by higher C-reactive protein and erythrocyte sedimentation rates and children experiencing leucopoenia with marked lymphopenia, hypoalbuminemia, and hyponatremia along with gastrointestinal changes, abnormal electrocardiogram (ECG) and respiratory changes[81], which can result in the need for intensive care[81]. This is important as we know from research with adults with COVID-19 in ICUs in Bangladesh that over 50% died whilst in ICU[84].

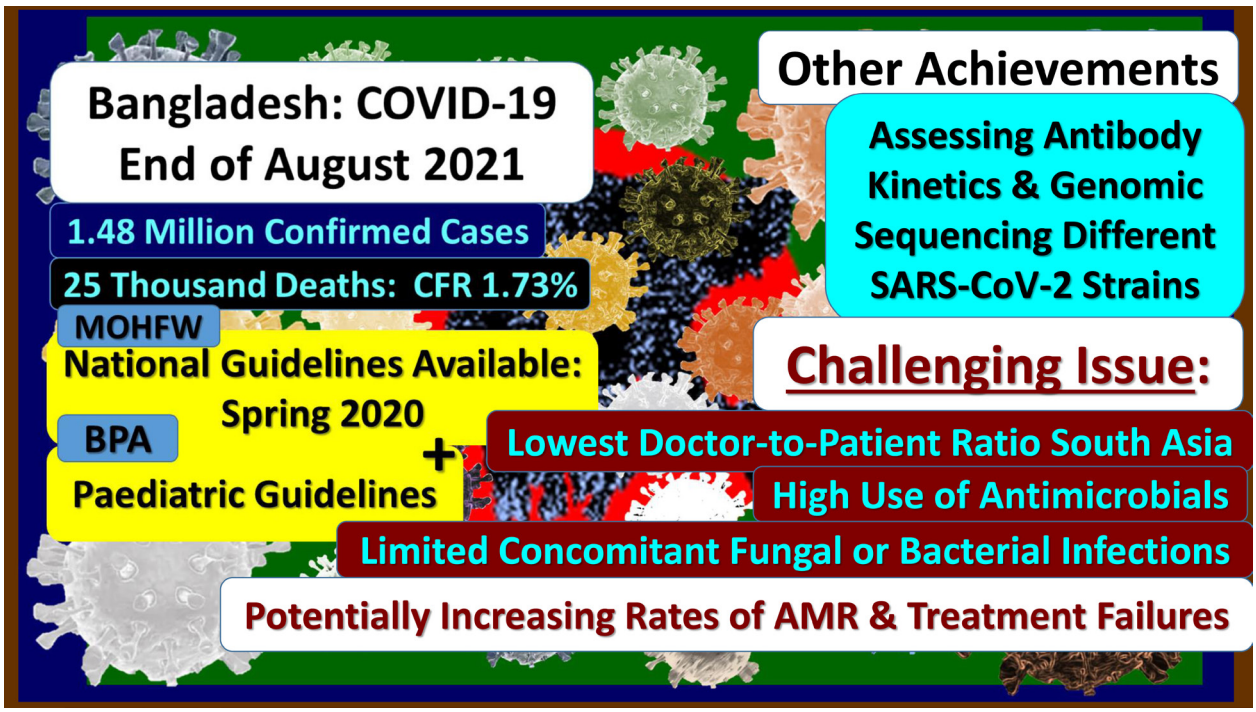

Figure 1: Rationale for The Pilot Study

As a result of growing concerns with the number of children with COVID-19 in Bangladesh especially those with symptoms, coupled with concerns with the overuse of antimicrobials, we believed it was important to document the current situation among paediatric patients hospitalized in Bangladesh as a result of COVID-19[61] (Figure 1).

The findings can be utilised to improve future management building on the earlier study of Hussain *et al.* (2020) and the recent guidelines[30,53]. This was the objective of this pilot study. We believed this was important given the current higher mortality rates in children with COVID-19 in LMICs versus high-income countries[45].

2. Methodology

A rapid analysis was undertaken among eight public and private hospitals in Bangladesh with an appreciable range of in-patient paediatric beds treating children with COVID-19. Case report forms were purposely developed for this study based on the published literature as well as the experience of the co-authors[30,44,45,53,85]. These were piloted before roll-out between Mid July 2021 and Mid August 2021.

Key data sets based on the past ten days was included (10 days was chosen due to potentially low numbers of children with COVID-19, especially in general hospitals):

- Number of paediatric patients typically being treated in the hospital
- % of children with COVID-19 in the hospital
- Patient's ages in years (3 bands: 0 – 5 years; 6 – 10 years; 11 – 18 years) and Gender
- Principal reasons for admittance (3 principal reasons – drop-down menu of breathing difficulties/respiratory distress; prolonged fever; cough; diarrhoea; and feeding difficulty/vomiting
- Comorbidities (mention top 3)
- % of these patients admitted to PICU and the reasons – taken from severe respiratory distress/ low O_2 saturation; shock; coagulation disorders/ thromboembolic manifestations; and extensive lung involvement in high-resolution CT scan (HRCT)
- % of prescribed antimicrobials (which ones – ATC Grouping) and % empiric
- Route of administration, when prescribing re-assessed and total length of prescription
- Whether any antivirals (e.g., remdesivir), antimalarials (e.g., hydroxychloroquine), anti-inflammatories (e.g., dexamethasone) or supplements/ immune boosters such as Vitamins C or D or zinc administered
- Recovery – mortality, morbidity or recovery
- Possible costs

We also assessed antibiotic prescribing against the WHO Access, Watch, or Reserve (AWaRe) list, which is increasingly being used to assess the quality of antimicrobial prescribing[86,87]. In addition, where documented, against key guidance contained with the recent guidance from the Bangladesh Paediatric Association (Box 1)[30].

Box 1: Key recommendations from Bangladesh Paediatric Association on the management of children with COVID-19 in hospital [Adapted from[30]]

- Ideally PCR test to confirm the diagnosis and subsequent management on a designated COVID-19 ward or treatment area.
- Comorbid conditions can include bronchial asthma, chronic kidney or liver disease and rheumatological conditions including Kawasaki disease.
- General treatment incudes supportive care, electrolyte balancing and providing oxygen when necessary.
- Children transferred to ICU if experiencing severe/ critical symptoms, respiratory failure requiring mechanical ventilation, shock and organ failure. Treatment includes vasoactive drugs if required as well as balanced/ buffered crystalloids.
- Medicines:
    - Antivirals – potentially reserved for children with severe acute respiratory syndrome. If remdesivir – then ideally part of ongoing clinical trials. Conflicting evidence regarding lopinavir/ ritonavir.
    - Antibiotics – specific cases only avoiding excessive use. 1st line – ampicillin plus gentamicin; 2nd line ceftriaxone.
    - Corticosteroids – not used routinely. Low dose dexamethasone may be beneficial in children with severe disease.
    - Vitamins – may be beneficial.
- For suspected Kawasaki Disease/ MIS-C – typically admit to PICU with supportive care including antibiotics for suspected infections as well as steroids and other immune modifying therapies.

The co-authors orchestrated ethical approval for their hospitals and others involved in the study. The reference numbers were: ibh/mirpur/2020/01.

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3. Results

Overall, there were low numbers of children with COVID-19 among the eight hospitals taking part in the pilot study at 4.3% of paediatric in patients (Table 1). The majority were male (59.6%) and aged between 0 to 5 years (63.5%). The principal reasons for admission for actual or suspected COVID-19 included respiratory distress/ breathing difficulties, prolonged fever, cough and feeding difficulties. Overall, 94.2% of cases were confirmed.

Table 1: Key Characteristics of The Children Among the Eight Hospitals

Hospital	Date Survey Conducted	Total Patients Childrens' Wards	Total with COVID-19	% with COVID-19	Number confirmed (tests) and %	Male	Female	0 to 5 years	6 to 10 years	11 to 18 years
Hosp 1	11.08.2021	65	3	4.6%	3 (100%)	2	1	3	0	0
Hosp 2	31.08.2021	125	5	4.0%	5 (100%)	4	1	2	3	0
Hosp 3	30.07.2021	19	2	10.5%	1 (one suspected)	1	1	1	1	0
Hosp 4	31.07.2021	210	26	12.4%	26 (100%)	15	11	13	6	7
Hosp 5	16.07.2021	32	2	6.3%	0 (two suspected)	1	1	2	0	0
Hosp 6	25.07.2021	18	1	5.6%	1 (100%)	1	0	0	1	0
Hosp 7	17.07.2021	654	9	1.4%	9 (100%)	5	4	9	0	0
Hosp 8	10.08.2021	85	4	4.7%	4 (100%)	2	2	3	1	0
Total		**1208**	**52**	**4.3%**	**49 (94.2%) -3 suspected**	**31**	**21**	**33**	**12**	**7**

Only a minority of those with COVID-19 were admitted to PICU (17.3%), with the principal reasons being severe respiratory distress/ low O2 saturation and shock.

All of children with COVID-19 received antibiotics, which was typically empiric and principally parenterally (Table 2), for typically 5 to 10 days, with children generally reviewed after 3 to 5 days. However, only a small minority of children were switched to oral therapy before discharge (2%). There was also appreciable prescribing of Vitamins (C and D) and zinc with limited prescribing of antimalarials, antivirals and antiparasitic medicines (Table 2). Steroids were also administered to children in three of the hospitals.

Typically, the antibiotics prescribed were on the Watch as opposed to the Reserve list of antibiotics (Table 2). Encouragingly, mortality rates were low (under 2% of children) with the vast majority of children (88.5%) making a full recovery from COVID-19. Where measured, 4 out of the 5 hospitals surveyed stated that they adhered to the Bangladesh Paediatric Guidelines when managing their patients. Having said this, there was appreciable empiric use of antibiotics in all hospitals (Table 2). In addition, where antibiotics were administered there was limited use of ampicillin although greater use of aminoglycosides including gentamicin (Table 2).

Length of stay in hospitals was typically 5 to 10 days (range 5 to 15 days), with total costs when available ranging between 3,000 and 20,000 BDT.

4. Discussion

We believe this is the first study conducted in Bangladesh among a number of both private and public hospitals regarding the management of hospitalised children with COVID-19. This builds on the earlier study of Hussain *et al.* (2020) who found a higher mortality rate (13.3%) among children in the early stages of the pandemic[53]. This may reflect improved management as more knowledge is gained regarding the aetiology of COVID-19 and optimal treatment approaches. In addition, only a low number of paediatric patients in hospital had COVID-19 (Table 1). This is important when looking to increase services such as elective paediatric surgery which was put on hold in the early stages of the pandemic[88].

Table 2: Management of Children With COVID-19 Among the Eight Hospitals

Hospital	Number and % Rx antimicrobials	Empiric or CST	Antibiotic Rx	Antiviral	Anti-parastitic	Anti-inflammatory (steroid)	Supplements, etc
Hosp 1	3 (100%)	All empiric	Ceftriaxone	No	No	No	Vit C, D, Zinc
Hosp 2	5 (100%)	All empiric	Aminoglycosides, carbapenems, cephalosorins	No	No	No	No
Hosp 3	2 (100%)	All empiric	Ceftriaxone, ciprofloxacin	No	No	No	Vit C, D, Zinc
Hosp 4	100%	All empiric	Ceftriaxone, ceftazidim, meropenem, vancomycin, flucloxacillin, amikacin	No	No	Steroids	Vit C, D, Zinc
Hosp 5	2 (100%)	All empiric	Ampicillin, aminoglycoside, cephalosporin	No	No	No	No
Hosp 6	1 (100%)	All empiric	Ceftriaxone	No	No	No	Vit C, D, Zinc
Hosp 7	9 (100%)	All empiric	Aminoglycosides, carbapenem, macrolides	No	No	Dexamethasone	Vit C, D, Zinc
Hosp 8	4 (100%)	All empiric	Aminoglycosides, carbapenems, cephalosorins	No	Ivermectin	Steroids	Vit C, D, Zinc

Overall, it was encouraging to see low hospitalisation rates for children with COVID-19 (Table 1) reflecting other recent publications[44,46,48]. Alongside this, similar to other published studies, fever and cough as well as respiratory diseases were the most frequent clinical characteristics of children admitted with COVID-19, with again boys accounting for more cases of COVID-19 in hospital than girls[41,44-48].

Encouragingly there was limited use of antimalarials, antivirals and anti-parasitic medicines (Table 2) given concerns with their lack of effectiveness in treating patients with COVID-19 despite the hype[12-15,20,89]. In addition, the high use of vitamins and zinc is in line with current national guidelines in Bangladesh (Box 1). However, there were concerns with the high empiric use of antibiotics (Table 2) despite, as mentioned, only a limited number of patients across ages have concomitant fungal or bacterial infections[62-69]. In addition, concerns with overuse are documented in the current national guidelines (Box 1). This is similar to the high use of antibiotics among adults admitted to hospital with COVID-19 in Bangladesh[70,71]. This is despite clinicians in most of the surveyed hospitals stating they follow the current national guidelines.

Potential ways forward to improve antimicrobial use include the instigation of ASPs, which have been successful across countries to enhance the appropriate use of antibiotics in hospitals including LMICs[72,73,78,79,90]. Future activities should also include encouraging prescribing where pertinent according to local antibiograms to improve empiric use along with the instigation of ASPs[91,92]. These combined activities should also reduce the prescribing of 'Watch antibiotics in favour of increased prescribing of Access antibiotics[93,94]. In addition, encourage earlier switching from parental to oral antibiotics to hasten earlier discharge from hospital and conserve resources[95-97]. We will be following these activities in the future.

Limitations

We are aware of a number of limitations with this study. This included the fact that this was only a pilot study. In addition, the study involved a retrospective review of notes without the ability to check with physicians regarding the rationale for their treatment approaches and all cases of COVID-19 could not be confirmed by rt-PCR. Despite these limitations, we believe the findings are robust providing direction for the future.

5. Conclusions

It was encouraging to see low hospitalisation rates for children with COVID-19 among the pilot hospitals in Bangladesh, which mirrors findings in other countries. It was also encouraging to see limited use of antimicrobials apart from antibiotics given the hype that has surrounded some of these. However, there are concerns with the high empiric use of antibiotics and limited switching to oral formulations. This needs to be addressed to reduce the potential for increasing antimicrobial resistance and costs. This can be addressed by instigating or enhancing antimicrobial stewardship programmes in hospitals. We will be monitoring this in the future.

Conflicts of interest

The authors declare they have no conflicts of interest

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