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A COMPARATIVE STUDY OF THE CLINICAL CHARACTERISTICS OF THE FIRST AND SECOND WAVES OF COVID-19 IN A TERTIARY CARE CENTRE OF NORTH INDIA

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Abstract:
Aims &Objectives : To compare the clinical characteristics/profiles of the patients in first and second waves of COVID-19 in India and correlate these characteristics with risk of in-hospital mortality.
Design: Observational analytical study with longitudinal follow-up. The clinico-epidemiological and laboratory profile of patients admitted in the second wave of COVID-19 will be noted at the time of admission, and they will be followed-up during their stay in the hospital to record their outcome status. Medical records will be used to record the data of COVID-19 patients admitted in the first wave.
Setting: A tertiary care centre in Bihar, India
Participants: All patients who are COVID-19 positive based on positive RT-PCR test of oropharyngeal or nasopharyngeal swab and admitted to AIIMS, Patna during the study period.
Outcome measures: The difference in clinic-epidemiological profile of patients admitted in AIIMS Patna during the first and second wave of COVID-19 and thus we attempted to discover the effects of multiple factors such as vaccination and mutant viruses on the profile of the 2nd wave.We could also correlate the outcome status of the patient with their clinic-epidemiological profile.
Results:Females were relatively more commonly affected in the second wave. Contact history was significantly higher in the second wave. Comorbidities and clinical features were mostly similar although generalized weakness and fatigue was more common in the second wave. ARDS and septic shock were less frequent in the second wave although overall mortality was slightly higher. Azithromycin, HCQ use was discontinued whereas pulse methylprednisolone started to be used frequently. Remdesevir and tocilizumab use was rationalized. HFNC and NIV were better utilized in the second wave. Mucormycosis outbreak complicated the second wave. Out of 42 individuals who were partly immunized (fourteen days after 1st dose to symptom onset), 28 patients survived.
Conclusion: The rapid upsurge of cases in the second wave led to COVID affecting previously less affected strata of the population as well as higher overall mortality, although the better training of healthcare workers and understanding of the disease helped offset some of these problems.
Keywords: second wave, covid-19, Mucormycosis, Covid vaccine

Introduction:

Over the last year and a half globally, there has been an outbreak of a novel coronavirus which started in Wuhan, China. It later progressed worldwide affecting over 16,00,74,267 persons as of May 13, 2020(1). It has led to over 33,25,260 deaths worldwide so far. It was declared a pandemic by the WHO on 11th March 2020.

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The virus responsible for the pandemic has been designated SARS-CoV-2(2) and it belongs to a group of RNA viruses known as coronaviruses. Bats are the primary source. Transmission is mainly via close range person-to-person contact apart from contact with contaminated surfaces which plays a minor role and airborne route which has been a cause for controversy(3).

Infection with the virus leads to a wide variety of clinical features, most prominently an ARDS-like picture with a cytokine storm, possibly leading to disastrous consequences such as respiratory failure, acute kidney injury and ultimately death(4). However, in a majority of cases it is usually asymptomatic or causes mild upper respiratory symptoms or constitutional symptoms.

Risk factors which predict severe course of the disease include older age, male sex, comorbidities like cardiovascular disease, diabetes mellitus, COPD, cancer, chronic kidney disease, solid organ/haematopoietic stem cell transplant recipients and obese individuals(5,6). Further, smoking was also found to increase the risk of severe disease(7).

Also, laboratory markers such as LDH, CRP, D-dimer, ferritin, IL-6 along with lymphopenia and thrombocytopenia were studied and correlated with worse outcomes(8).

Most of the above studies were conducted last year when the COVID pandemic had begun and rattled the world's healthcare systems, which were not adequately prepared to face the same. Also, very few mutant strains were detected by then(9). Further, the vaccination programmes rolled out worldwide currently had not yet been started then(10). Also, widely available drugs such as remdesevir, tocilizumab which were used then have been hit by a scarcity in India which has been facing a rapid upsurge of cases(11).

In the following study we are attempting to assess the effects of the above factors on the pandemic, especially due to the rapid and devastating effects of the so-called second wave of the pandemic in India. Also, we intend to confirm or refute many anecdotal reports and preliminary studies which have suggested that younger population, females and other such previously less affected subgroups have been affected more in the current wave of COVID-19.We do so by recording and then comparing the data from the current patients with the data recorded previously from 01/06/20 to 31/8/20.

Materials and Methods:

Definitions of Mild, moderate and severe COVID-19-

Mild: No evidence of breathlessness or Hypoxia (normal saturation)

Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), Respiratory Rate of 24 or more and no features of severe disease

Severe: Any of the following – Severe respiratory distress, oxygen saturation < 90% on room air, respiratory rate > 30, shock or evidence of a life-threatening organ dysfunction

All patients admitted in the COVID wards of All India Institute of Medical Sciences, Patna during the study period (15/5/21-30/6/21) with a COVID-19 RT-PCR positive report wereincluded in the study. Once the patients provided written informed consent, their baseline characteristics as mentioned below were notedat the time of admission.

Epidemiological features including age, sex, contact history, travel history, smoking history, any negative RT-PCR report before subsequent positive report, time from symptom onset to admission(in days), vaccination status and its details were noted. Also, clinical features including presenting complaints, oxygen requirement and severity at the time of admission, comorbidities (if any) were assessed. Laboratory parameters including N/L ratio, TLC, LDH, Ferritin, D-dimer, IL-6, CRP and procalcitonin (if available) were recorded at the time of admission.

During the course of hospital stay, the following parameters were noted - Final outcome i.e. in-hospital mortality or discharge, progression of disease severity. Need for HFNC (high flow nasal cannula), NIV (non-invasive ventilation), IMV (invasive mechanical ventilation) were also recorded.

We also followed up to see whether remdesevir, steroids, tocilizumab amongst others were given or not. Apart from this, we notedany complications such as septic shock – defined as - documented or suspected infection plus vasopressors needed to maintain MAP>65 mm of Hg and serum lactate >2 mmol/L despite adequate fluid resuscitation. Also, Acute Kidney Injury (AKI) – defined as increase in serum creatinine >0.3 mg/dL within 48 hours or 50% higher than baseline within 1 week, or a reduction in urine output to <0.5 ml/kg/hour for longer than 6 hours.

After recording the above parameters, the same were compared with characteristics of patients admitted last year between 01/06/20 to 31/08/20 in the same study setting. This was considered to represent the first wave of COVID in India. Also, the baseline characteristics of each wave were correlated with mortality and complications during hospital stay as well as severity of disease during hospital stay and need for HFNC, NIV, IMV.

Outcome measures:

With this study, we attempted to find the difference in clinic-epidemiological profile of patients admitted in AIIMS Patna during the first and second wave of COVID-19 and thus try to discover the effects of multiple factors such as vaccination and mutant viruses on the profile of the 2nd wave.We could also correlate the outcome status of the patient with their clinic-epidemiological profile.

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Statistical analysis:

Statistical analysis was done using IBM SPSS (Chicago, USA) software, version 22. All descriptive data were expressed as mean (SD) and frequency (percentage) using student's t test. Chi-square test and Fischer's exact test were performed to assess difference in the primary and secondary outcome measures between the two groups. The clinical parameters were noted on alternate days over a time period of stay of the patients in the hospital. The data thus recorded was utilized to calculate two-way repeated measure anova. A p value < 0.05 was considered to be statistically significant. Data analysis was done using SPSS.20 and STATA.12.

Ethical clearance:

Ethical clearance was obtained from the institutional ethics committee, AIIMS Patna.

Results:

Comparison between the two waves:

As per our study, the mean age of the admitted patients was almost the same in the first (53.8) and second (51.5) waves of COVID-19. There was a male preponderance in both waves but the second wave had significantly higher proportion of females being affected (31% vs 23%). Significantly higher patients had an exposure history and travel history in the second wave as compared to the first wave (table 1).

Fever, cough and dyspnoea were the predominant symptoms in both the waves but significantly higher patients in the first wave complained of fever, cough, headache and sore throat as compared to those affected in the second wave (table 1). Whereas fatigue and myalgias were much more common in the second wave.

Most comorbidities like diabetes, hypertension, chronic kidney disease were more prevalent in the first wave but only chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) were statistically significant in terms of being more prevalent in the first wave as compared to the second (table 1).

When we compared the inflammatory markers of patients in both the waves at admission, ferritin and C reactive protein (CRP) were significantly higher in those admitted in the first wave. The white blood cell (WBC) counts and neutrophil to lymphocyte ratio were higher in those admitted in the second wave as compared to the first (table 1).

Table 1:

mparison of various aspects of COVID- 19 presentation and outcome in 1st and 2nd wave			
haracteristics	t Wave [N= 283] (%)	nd Wave [N= 296] (%)	value
ean Age	3.8 (15.8)	1.5 (16.1)	0734
ender			
ale	17 (76.7)	03 (68.2)	054
emale	5 (23.3)	3 (31.4)	
noking History			
ever	79 (63.2)	97 (66.5)	154
ccasional	3 (27.6)	4 (28.4)	
noker	5 (9.2)	5 (5.1)	
story of Travel	4 (1.4)	2 (4.0)	053
story of Exposure within 14 days	3 (11.7)	02 (68.2)	.00
inical Features			
ever	31 (81.6)	17 (73.3)	017
ough	16 (76.6)	37 (63.2)	.00
ortness of Breath	03 (72.0)	98 (66.9)	184
eadache	2 (32.5)	3 (6.1)	.00
re throat	5 (12.4)	3 (2.7)	.00
eakness/ Fatigue	) (17.7)	06 (35.8)	.00
yalgia	7 (2.5)	3 (6.1)	033
I symptoms	5 (5.3)	4 (8.1)	178
o- morbidity			
ype 2 DM	2 (43.1)	24 (41.9)	767
TN	12 (39.6)	01 (34.1)	174
KD	4 (8.5)	) (3.4)	009
OPD	7 (6.0)	4 (1.3)	003
sthma	7 (6.0)	) (3.0)	085
ancer	1 (0.3)	4 (1.3)	373
/pothyroidism	3 (8.1)	1 (10.5)	332
AD/IHD	1 (7.4)	3 (4.4)	121
nflammatory Markers (mean + SD)			

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erritin	25.5 (644.7)	56.2(330.9)	0008
RP	9.6 (89.3)	3.5 (76.1)	042
dimer	0 (4.6)	0 (4.6)	9823
BC	1.28 (7.4)	3.66 (13.9)	
eutrophil	9.44 (13.1)	3.99 (15.0)	
mphocyte	5.5 (11.0)	1.7 (11.3)	
reatment			
emdesevir	41 (49.8)	19 (40.2)	02
cilizumab	9 (20.8)	4 (4.7)	0.00
IV	7 (16.2)	09 (36.8)	0.00
MV	9 (20.9)	9 (23.3)	475
omplications			
KI	7 (6.0)	5 (2.0)	014
RDS	1 (21.5)	9 (6.4)	0.00
eptic shock	4 (15.5)	4 (4.7)	0.00
utcome			
eath	5 (23.0)	3 (28.1)	167
urvivor	18 (77.0)	00 (71.9)	

As we followed up the patients and studied the outcomes, there was a significantly higher proportion of patients having findings suggestive of acute respiratory distress syndrome (ARDS) and septic shock, which developed as COVID complications in the first wave more than in the second. Paradoxically though, the mortality rate in the second wave was higher as compared to the first, although the difference was not statistically significant (table 1). Apart from this, mucormycosis was an outbreak noticed in the second wave and it affected 7% of the patients in our study during this period.

With regards to the treatment received, azithromycin (67%) and hydroxychloroquine (39%) were very common modalities of treatment in the first wave whereas they were barely used in the second wave. Similarly, plasma therapy was very commonly used in the first wave (56%) but not used in the patients treated in the second wave. The use of remdesevir and tocilizumab was much more frequent in the first wave (50%, 21%) as compared to the second wave (40%, 5%). Methylprednisolone therapy and its use as a short-term pulse gained traction in the second wave (28%, 13%) whereas it wasn't in use in the first wave.

High-flow nasal cannula (HFNC) was a modality extensively used in the second wave (7%), which wasn't available at the time of the first wave. Non-invasive ventilation (NIV) was extensively used in the second wave (37%) as compared to the first (16%). Invasive mechanical ventilation (IMV) was required more in cases affected in the second wave (23%) versus those in the first wave (21%).

Predictors of mortality:

In the first wave of COVID-19, the neutrophil to lymphocyte ratio at admission was an independent predictor of mortality ($p<0.05$). So was a raised WBC count. Other inflammatory markers or comorbidities did not significantly increase the risk of mortality.

With regards to the second wave, the neutrophil to lymphocyte ratio at admission was found to be an important predictor of mortality with those having a higher ratio more at risk for morbidity and mortality. Also, overweight and obesity was an important comorbidity which predicted mortality in those affected by the second wave.

Vaccination and outcomes in the second wave:

In the second wave of COVID-19, when vaccines were available and had started to get rolled out, we could assess the impact vaccination had on clinical outcomes. 42 patients out of 296 admitted in the second wave were partly immunized (more than 14 days after the first dose to onset of symptoms). 28 of these patients survived whereas 14 expired. Compared to overall mortality (28%), this was slightly higher (33%) but the difference was statistically not significant ($p=0.391$).

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able 2: Difference in Treatment modalities and Complications reported in 1st and 2nd ave

reatment modality in 1st wave		**reatment modality in 2nd wave**	
zithromycin	)0 (67.1)	ıoxaparin	;4 (85.8)
CQ	.0 (38.9)	ılse methyl prednisolone	. (13.8)
lasma Therapy	;8 (55.8)	ethyl Prednisolone	3 (28.0)
teroids	:6 (79.9)	examethasone	36 (62.8)
emdesivir	H1 (49.8)	ısopressor	! (10.8)
cilizumab	) (20.8)	emdesivir	.9 (40.2)
IV	' (16.2)	cilizumab	ł (4.7)
1V	) (20.9)	IV	)9 (36.8)
		1V	) (23.3)
		:NC	) (6.8)
)mplications in 1st wave		**)mplications in 2nd wave**	
KI	' (6.0)	KI	; (2.0)
RDS	. (21.5)	RDS	) (6.4)
:ptic shock	ł (15.5)	:ptic shock	ł (4.7)
neumonia	1 (26.1)	econdary Infection on C/S	) (3.4)
		ucor mycosis	. (7.1)

able 3: Predictors of mortality among COVID- 19 patients in 1st wave

	djusted Odd's ratio (95% CI)	**value**
'BC Count	17	0.027
eutrophil- Lymphocyte Ratio	11	0.018

able 4: Predictors of mortality among COVID- 19 patients in 2nd wave

	djusted Odd's ratio (95% CI)	**value**
besity		
verweight	28	0.564
bese	59	0.000
orbid Obese	'.4	0.001
eutrophil- Lymphocyte Ratio	04	0.001

Discussion:

The COVID-19 pandemic, which has wreaked havoc worldwide, has placed a heavy stress on the healthcare system in the country and led to extensive mortality and morbidity(12). Initially, when it exploded in 2020 in India, the healthcare set-up was ill-prepared to deal with the pandemic and there were a wide variety of drugs being used in an attempt to mitigate the disastrous effects of the pandemic(13). As clinical trials and their data was subsequently released, these clinical practices have evolved drastically over the past year.

Further, the delta variant of the COVID-19 virus, which originated in India was found to cause more severe disease as compared to the original(14). Also, the delta plus variant was discovered. Both of these were thought to play a major role in the second wave of the COVID-19 outbreak in the country.

A major boost in the fight against COVID-19 was the discovery of multiple vaccines against the virus which were also effective against most variants of the virus as well(15). These were made widely available in 2021. As a result, it was expected that a significant proportion of those exposed to the virus after vaccination would have a milder variety of the disease as compared to that in 2020.

Apart from these differences, anecdotal reports suggested extensive demographic differences between patients admitted in the first and second waves of COVID-19(16). Younger age of affected patients, females and obese

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patients were very commonly affected according to some preliminary studies in the second wave. Besides, most reports suggested maximum over-burdening of the healthcare facilities during the second wave, which might have affected outcomes(17). There was also an outbreak of mucormycosis during the second wave of COVID-19(18).
To assess the effects of all of these factors, we conducted a study where we collected epidemiological, clinical, therapeutic and outcome data of patients admitted to a tertiary care centre in Patna, India during the second wave of the COVID-19 pandemic, and then compared this with data we had procured during the first wave of the pandemic in July to September of 2020.
When we assessed the demographic data, we found almost identical mean age amongst affected patients, 53.8 years in the first wave and 51.8 years in the second wave. This was contrary to some preliminary reports suggesting younger patients being affected more in the second wave. There was a higher proportion of females affected in the second wave (31.4%) as compared to the first (23.3%), and it was borderline significant statistically (p=0.054). According to a preliminary study by Vijay Kumar Jain et al(19), younger population was thought to be more affected. Sandeep Budhiraja et al (20) found that in their study, which was a large scale multi-hospital study, no significant difference in age distribution was found, but a similar increase in the number of females affected in the second wave was seen, as in our study. This could be due to higher infectivity of the virus and rapid upsurge in cases in the second wave. As in a developing country like ours, more males are involved in outdoor work and come in contact with more people, they were affected more in both waves, but especially the first wave. In the second wave, as there was a rapid upsurge of cases and as almost 68% of patients had a contact history, most of which were relatives at home, the difference in sexes affected might have been relatively less.
Crucially, we found that almost 68.2 % of patients in the second wave had a history of exposure in the past 14 days to someone who was diagnosed with COVID-19, either already or soon after exposure. This was opposed to just 11.7 % in patients in the first wave. The sudden and rapid upsurge of cases in the second wave was largely attributed to non-adherence of people to the lockdown norms as they were eased gradually in the country(21). Our findings correlated with these suspicions as gross breach of COVID-19 protocols was seen in those later affected by the disease.
With regards to the clinical features, fever, cough and dyspnoea were the commonest clinical features in both the waves of COVID-19 as per our study. Cough was much more common as a presenting complaint in the first wave (76.6%) as compared to the second wave (63.2%). Headache and sore throat were also much more common in the first wave (32.5%, 12.4%) compared to the second wave (6.1%, 2.7%). Fatigue (35.8%) and myalgias (6.1%) were common complaints in the second wave which were relatively less noticed in the first wave (17.7%, 2.5%).Gastrointestinal complaints were not too common in the second wave either (8%) as expected according to preliminary observations by Vijay Kumar Jain et al(19).

Diabetes mellitus and hypertension are known to be two of the commonest comorbidities in patients affected by COVID-19. These were the most prevalent comorbidities in both the first (43.1%, 39.6%) and second (41.9%, 34.1%) waves of COVID-19. Chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) were more common in patients in the first wave (8.5%, 6%) than those affected in the second wave (3.4%, 1.3%). Asthma, hypothyroidism, ischemic heart disease and any form of cancer were the other most prevalent comorbidities across the two waves. Similar observations were seen in the study by Budhiraja et al (21) but they found that significantly more persons with diabetes mellitus, hypertension and CKD were admitted during the second wave. In a study by Shiv Lal Soni et al(22), done during the second wave of COVID-19, there was a relatively high proportion of patients who were not affected by any comorbidity, almost $4/5^{th}$ of patients. Our study too had a slightly lower prevalence of comorbidities in COVID-19 patients in the second wave, although it did not reach statistical significance. Study settings, i.e. government versus private set up, sample size and different timings of the studies with respect to the peak of the pandemic might have accounted for the above differences.
A major point of research was the use of various inflammatory markers to best represent and hence prognosticate the course of the disease in COVID-19. A variety of expensive markers were used to help towards this end. Ferritin, C reactive protein, D-dimer, N/L ratio were some of the common ones used apart from procalcitonin and IL-6 levels.At admission, ferritin and C reactive protein (CRP) were significantly higher in those admitted in the first wave as compared to the second wave. The white blood cell (WBC) counts and neutrophil to lymphocyte ratio were higher in those admitted in the second wave as compared to the first. More importantly, the N/L ratio was the only marker in our study which predicted mortality in the second wave. Other markers like interleukin-6 (IL-6), C reactive protein (CRP) and ferritin all predicted mortality in a meta-analysis by Furong Zeng et al(8). Our study, due to a small sample size might not have yielded a similar result with regards to these markers.
COVID-19 ultimately leads to death via a variety of complications including septic shock, ARDS, secondary sepsis amongst others. Our study showed a significantly lower incidence of septic shock and ARDS in the second wave (6.4%, 4.7%) as compared to the first (21.5%, 15.5%). Yet, the overall mortality rate was much higher in the second wave as compared to the first (28.1% versus 23%), although the difference was not statistically significant. A similar pattern was seen in the study by Buddhiraja et al (20) where the mortality was significantly higher in the second wave ($p<0.001$). Purkayastha et al(23) and Ranjan et al (24) found a lower case fatality rate in the second

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wave as compared to the first. The latter two were statistical estimates based on overall data available as opposed to the first two, which were direct comparisons in a similar setting. The explosive nature of the second wave, which surpassed some of the early predictions in the second wave, might have accounted for the differences observed in this case. Unavailability of hospital beds, patients needing ICU care being treated in the wards and lack of the number of healthcare workers needed to manage the wards and ICU'S was a common sighting throughout the country in the second wave. Although better adjustment of the healthcare workers in treating COVID-19 patients was seen in the second wave, the peak of the wave noticed massive over-burdening of the facilities, which might have accounted for the higher mortality.

Another major player during the second wave of the COVID-19 pandemic was the mucormycosis epidemic which arose in a background of COVID-19, improper steroid use and raised blood glucose. 7.1% of patients in our study developed mucormycosis during hospitalization for COVID-19 or were admitted with a COVID-19 diagnosis along with mucormycosis. In a study by Seralka et al (18), 1.8% of patients in three tertiary centres across India treating COVID-19 patients had mucormycosis.

A point of major interest was the evolution of practices involved in treating COVID-19 patients after there has been extensive ground breaking RCT'S and meta-analysis with regards to COVID-19 treatment. Drugs like azithromycin and hydroxychloroquine which were commonly used in the first wave (67.1%, 38.9%) were barely used in the second wave. This follows multiple RCT's (25), which did not show any benefit by HCQ use. The use of remdesevir and tocilizumab which were used without exact guidelines on their use early on, were used relatively more specifically in the second wave (40.2%, 4.7%) as compared to the first (49.8%, 20.8%) after large-scale RCT's had provided more information regarding their utility(26,27). Another factor in this difference might be the unavailability of these drugs during the second wave, as India faced a gross shortage of a lot of anti-COVID-19 drugs. Use of plasma therapy was common in the first wave but after evidence against its usefulness(28), it was not utilized in the second wave. Use of methylprednisolone, especially as a pulse dose was seen in our study in the second wave. Multiple recent RCT'S have supported use of the same(29).

It was observed that the use of HFNC (7%) and NIV (37%) was very common during the second wave. This is thought to have resulted due to increased familiarity and knowledge of the healthcare personnel in treating COVID-19 patients. This follows multiple studies (32) which had shown promising results, especially with the use of HFNC.

When it came to predicting mortality, the neutrophil to lymphocyte ratio was the only marker which predicted mortality across both waves. Similar results were seen in multiple other studies(30). Other inflammatory markers did not show such correlation although there have been positive results in other studies(8). This could be mainly due to a limited sample size. In the second COVID wave, overweight and obesity were found to predict mortality and it was statistically significant. This has also been observed in multiple prior studies(31).

A major additional outcome of the current study was that it was performed when vaccines were introduced in India, both covaxin and covishield were provided, especially for healthcare workers and the elderly by this time. 42 of the patients in our study had taken some form of vaccination at least 14 days prior to admission(32). 28 of these patients survived whereas 14 expired. This corresponds to 33% mortality whereas overall mortality during this wave was 28%. Reasons for such a discrepancy include older age of vaccinated individuals, small sample size and inability to recall exact date of onset of symptoms.

Authors contribution :

All authors have contributed equally in the study and preparation of the manuscript.

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