



Antibiotic usage and sensitivity pattern in pulmonary medicine unit of a tertiary care teaching hospital in South India : A Prospective Study

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ABSTRACT

Antibiotic resistance is aggravated by multiple factors related to subjects, prescribers, manufacturing processes and environment. India has very little information on antibiotic resistance, patterns of prescription and consumption of antibiotics. The purpose of the study was to evaluate the antibiotics prescribing and sensitivity patterns of pathogens in pulmonary medicine unit of a tertiary care teaching hospital in South India. This prospective observational study was conducted in pulmonary medicine unit over a year. Of 725 subjects enrolled, 62.3% were males. 74.9% were prescribed with antibiotics, majority receiving oral antibiotics (44.9%). Average number of antibiotics per prescription was 1.82. Only 50% of prescribed antibiotics were from the World Health Organisation-Essential Drug List (WHO-EDL). Ceftriaxone (19.2%) was the most frequently prescribed antibiotic and the combination of cephalosporins with β -lactamase inhibitors was the most prescribed antibiotic class. DDD/100bed days was highest for Cefpodoxime-clavulanic acid (24.7). Bronchial Asthma (14.2%) was the most prevalent disorder. 62.6% of the total 364 cultured samples were gram positive cocci & gram negative bacilli. *Streptococcus pneumonia* (10.7%) and *Pseudomonas aeruginosa* (24.2%) were the most prevalent gram positive and gram negative organisms respectively, in the tested cultures. *Stenotrophomonas maltophilia*, MRSA ($n=10$) and Non-fermenting gram negative bacilli ($n=4$) were resistant to most of the widely prescribed broad spectrum antibiotics. Continuous surveillance of susceptibility testing is necessary for customization of empiric antibiotic therapy. Furthermore, reliable statistics on antibiotic resistance and policies should be made available.

INTRODUCTION

Inappropriate prescribing of antibiotics has been shown to be an important factor contributing to the development of antibiotic resistance [1-2]. It has been estimated that up to one third of all subjects receive at least one antibiotic during hospitalization. Hospital's drug expenditure attributed to antibiotics is more in developing nations when compared to developed (35%vs 11%) [3]. The data from developing countries about antibiotic usage is scarce despite a greater burden from infections, rapid transmission and poor sanitation [4]. The misuse of antibiotics has contributed to one of the world's most pressing problems of today i.e. Antibiotic resistance [5].

A resistant trait once evolved can spread and eventually lead to 'super bugs'; or multi-drug resistant microbial species. Dumping of unused antibiotics in the soil, antibiotics in veterinary and agriculture, untreated effluents from manufacturing plants also contribute towards emergence of resistant strains over a period of time, particularly in India [6]. Illiteracy and low educational levels among subjects coupled with the unrestricted dispensing of antibiotics by pharmacists without prescription (virtually as over-the-counter drugs) are also major factors contributing to antibiotic resistance in some countries including India [7]. Other patient-related factors include under use (failure to complete the full course), improper timing, non-compliance and self-

Table 1. Subject's Demographics, Literacy level, Socio-economic status and Days of Hospitalization

<i>Patient demographics</i>	<i>Demographic group</i>		<i>Number of patients (%)</i>			
Gender	Male		452(62.3)			
Age (years)	51-70		328 (45.2)			
	31-50		231(31.9)			
	>70		88(12.1)			
	<=30		78(10.8)			
Literacy Level	Illiterate		257(35.4)			
	Less than tenth grade		223(30.8)			
	Tenth grade		134(18.5)			
	Twelfth grade		58(8.0)			
	Under graduates		46(6.3)			
	Post graduates and above		7(1.0)			
Occupation	Homemakers		252(34.8)			
	Farmers		176(24.3)			
	Daily wage labours		99(13.7)			
	Retired		72(9.9)			
	Office going staff		61(8.4)			
	Businessman		39(5.4)			
	students		25(3.4)			
	Health Care Professionals		1(0.1)			
Economic Status	<100,000 INR		334(46)			
	>100,000 INR		284(39.2)			
	Not willing to disclose		107(14.8)			
Days of Hospitalization			<i>Number of patients (%)</i>			
			1-7days	8-16 days	>16 days	Total
	Gender	Male	223(63.3)	195(60)	34(70.8)	452
		Female	129(36.7)	130(40)	14(29.2)	273
		Total	352(100)	325(100)	48(100)	725
	Age (years)	<30	52	26	0	78
		31-50	122	93	16	231
		51-70	145	158	25	328
		>70	33	48	7	88
		Total	352	325	48	725

prescribing for viral infections. Infections by resistant bacteria prolong hospital stay, increase mortality and medical costs [4]. Optimization of antibiotic use and judicious use of reserved antibiotics are important to counteract the emerging resistance. A remarkable study published in Lancet around 40 years back by Price and Sleigh showed complete disappearance of multiple drug resistant *Klebsiella* strains as well as reduced rate of infection with other organisms, upon complete withdrawal of all antibiotics in a specific medicine ward [8].

Respiratory tract infections (RTIs) constitute a major disease segment requiring antibiotic prescription and the leading cause of death after Ischemic heart disease and cerebrovascular diseases [9]. Apart from viral infections, majority of the RTIs such as throat infections, cold, cough etc. are self-limiting, and do not require antibiotic therapy.

Antibiotic use varies greatly across nations and depends upon various factors including patient-related factors, ethnic factors, socio-economic factors, physicians' or prescribers' expertise and beliefs [10,11]. Very few studies predict the usage patterns of antibiotics and resistance patterns of microbes in India. Global Antibiotic Resistance Partnership (GARP) was established in order to develop actionable policy regarding the utilization of antibiotics, especially in developing nations like India [12]. GARP aims to (1) lower the need for antibiotics, (2) improve antibiotic targeting to reduce resistance-enhancing drug pressure, (3) facilitate nationwide surveys of antibiotic consumption and drug resistance, and (4) restrict the use of antibiotics for agriculture or non-therapeutic purposes.

Infections are among the major causes of death over the world [13]. Increasing antibiotic resistance coupled with a simultaneous decline in introduction of newer antibiotics, make infections particularly difficult to treat, increasing both cost of therapy and public health burden. Implementing hospital practices that limit the spread of resistant bacteria and investigating outbreaks add to

the cost of healthcare. India has been indiscreet about the emergence of hyper-virulent organisms such as NDM-1 (New Delhi Metallo- β lactamases-1) [14].

Defined daily doses (DDD) helps us to compare drugs of different potency and to keep a control on nationwide consumption of drugs. DDD reflects the antibiotic exposure of a society [15]. World Health Organization (WHO) defines DDD as the assumed average maintenance dose per day for a drug used for its main indication in adults" [16].

Antibiotic consumption calculator (ABC calculator) transforms the data provided by pharmacies into antibiotic utilization rates, as per recommendation of WHO and reports hospital antibiotic consumption as number of defined daily doses (DDD) per 100 bed days [17]. Our study aims to evaluate the prescribing patterns of antibiotics, survey the prevailing respiratory disorders, apply the ATC classification to the commonly used antibiotics, calculate their DDD/100 bed-days, identify the common organisms isolated during culture-sensitivity testing and obtain the sensitivity patterns of bacteria prevailing in pulmonary medicine ward of a tertiary care teaching hospital..

METHODOLOGY

The study was conducted in the Pulmonary Medicine ward of Kasturba Hospital, Manipal from Sept 2012 to August 2013. All adult subjects (≥ 18 years) admitted to the pulmonary ward, with complete records were included in the study. Ethical Clearance was obtained from the Hospital Ethics Committee, Manipal. Subject demographics (age, sex, literacy level, and socioeconomic status), diagnosis, duration of hospitalization, antibiotic information (name, frequency, dose and dosage form) and results of culture and sensitivity testing of cultured samples were entered in the Case Record Forms (CRF).

Sputum samples collected on the date of admission prior to the

Table 2. Pattern of ten most commonly prescribed antibiotics with ATC codes and DDD/100 bed-days

Name of Antibiotic	Number of prescriptions (%)	ATC Code	DDD/100bed days (*WHO)	DDD (calculated)
Ceftriaxone	190(19.2)	J01DD04	2g	9.53
Azithromycin	165(16.7)	J01FA10	0.3g	9.79
Cefoperazone-Sulbactam	117(11.8%)	J01DD62	4g	15.23
Cefpodoxime	113(11.4%)	J01DD13	0.4g	9.42
Cefpodoxime-clavulanic acid	84(8.5%)	J01DD13	0.4g	24.74
Amoxicillin-Clavulanicacid acid	59(6.0%)	J01CR02	1g	15.46
Amikacin	46(4.6%)	J01GB06	1g	1.82
Cefuroxime-clavulanicacid	37(3.7%)	J01RA03	0.5g	4.49
Cefuroxime	27(2.7%)	J01DC02	0.5g	4.22
Levofloxacin	25(2.5%)	J01DC02	0.5g	4.22

Table 3. Antibiotics sensitivity pattern to organisms

Antibiotics	Gram positive Organism (%)							Gram negative Organism (%)								
	Strept .pneu monia	S.aure us (MRS A)	β- haemol ytic strepto cocci	MSSA	Strept pyogen es	Enteroc occus.s ps	Nocardia a.sps	P.aerugin osa	K.Pneum onia	Acinetob acter	Haemop hilusinfl u	Moraxell a catarrhal is	E.coli (ESBL)	Nonferm enting gram-ve bacilli	Enteroba cter sp. nasmalt ophila	
Prevalence (%)	10.75	5.38	1.61	1.075	1.075	0.54	0.54	24.19	16.13	9.14	6.99	5.91	4.30	2.15	1.61	1.075
Amikacin	--	60	--	--	--	--	100	93.03	90.91	62.5	--	--	100	0	100	50
Amoxi-Clav	--	7.69	--	--	--	--	100	100	51.85	17.65	72.73	100	0	--	0	0
Ampicillin/amoxicillin	0	8.33	100	100	100	100	0	100	3.571	13.34	53.85	40	14.28	--	0	0
Aztreonam	--	--	--	--	--	--	--	0	0	0	--	--	0	0	--	0
Cefazolin/Cefadroxil	--	--	--	--	--	--	--	100	51.61	6.25	--	30	0	0	0	0
Cefepime/Cefpirome	--	--	--	100	--	--	--	0	17.65	50	50	100	14.28	33.33	--	0
Cefoperazone/Sulbactam	--	--	--	--	--	--	--	100	84.62	100	--	--	100	66.67	100	0
Cefotaxime/Ceftriaxone	100	--	--	--	100	--	100	--	62.5	18.75	100	100	25	--	66.67	0
Ceftazidime	--	--	--	--	--	--	--	97.62	--	--	--	--	--	50	--	0
Cefuroxime	--	--	--	--	--	--	--	100	58.06	6.25	--	100	12.5	--	66.67	0
Chloramphenicol	100	--	--	--	--	--	--	--	--	--	--	--	--	--	--	100
Cipro/Oflo/Levofloxacin	84.21	15.38	100	100	50	0	--	93.34	62.07	58.83	30.77	100	42.86	66.67	66.67	100
Clindamycin	100	46.15	--	100	--	--	--	--	--	--	--	--	--	--	--	--
Cloxacillin/Oxacillin	--	7.69	--	100	--	--	--	--	--	0	--	0	--	--	--	--
Collistin	--	--	--	--	--	--	--	--	100	100	--	--	--	--	--	--
Cotrimoxazole	40	93.33	0	100	50	--	100	100	64.52	53.34	--	45.45	44.45	--	100	0

[illegible]

Figure 2: Most commonly prevailing organisms in pulmonary medicine ward

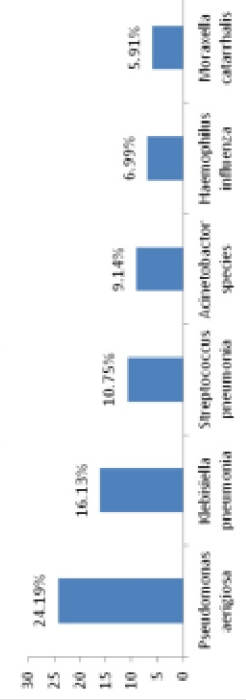
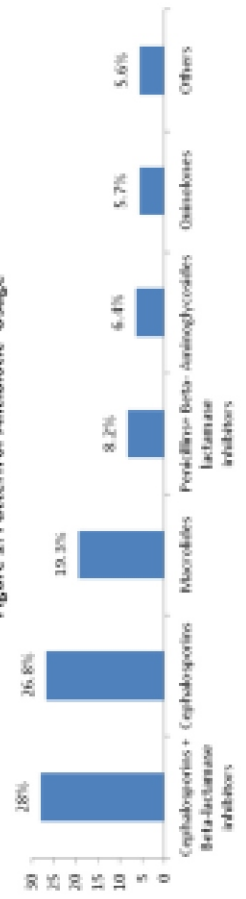


Figure 1: Pattern of Antibiotic Usage



initiation of antibiotic therapy are considered to process culture sensitivity testing. Antibiotics which belong to Anti Tubercular Therapy (ATT) regimen in tuberculosis (TB) patients are excluded from the study. Contaminated samples or polymicrobial growth samples were considered as rejected for culture sensitivity testing. We calculated the percentage of antibiotics prescribed from Hospital Formulary, National Essential drug list of India and WHO list of essential drugs. DDD/100bed days for ten most commonly prescribed antibiotics in the pulmonary medicine ward was also calculated. All the data were entered in Statistical Package Social Sciences (SPSS) data sheet and results were analyzed using the SPSS version 20.0, for descriptive statistical analysis.

RESULTS

The study was carried out for a period of one year, the number of beds in the Pulmonary Medicine ward was 35 and the average occupancy index during the study period was 0.85. Out of the 725 subjects enrolled in the study, males (452; 62%) constituted the majority. Males outnumbered females in all age groups and represented all kinds of occupations (excluding homemakers). Majority of subjects belonging to age group 51-70years (45%). Most of them were homemakers (35%), illiterates (35%) and economically backward (46%; annual family income less than 100,000 INR (1619 USD)). Literacy level was higher in males. Most subjects were farmers, homemakers and daily wage earners. On the other hand, students (3%) and health care professionals (0.1%) were very few. 48.6% subjects were hospitalized between one to seven days. Table 1 shows Subject's Demographics, Literacy level, Socio-economic status and Days of Hospitalization in detail.

Five hundred and forty three (75%) of the 725 subjects admitted to the Pulmonary Medicine ward were prescribed with antibiotics. Of all the prescriptions containing antibiotics, 284(52.3%) prescriptions contained a single antibiotic, followed by 136(25.0%), 78(14.4%), 30(5.52%), 11 (2.0%) 3(0.5%) and 1(0.2%), prescriptions had 2, 3,4,5,6 and 7 antibiotics respectively but not necessarily administered simultaneously. Majority of the subjects received antibiotics orally (44.9%), parenterally (18.4%) or both ways (36.3%). Cephalosporins in combination with β -lactamase inhibitors were the most prescribed class of antibiotic (28%). Figure 1 shows the six most commonly prescribed classes of antibiotics. DDD/100bed days was highest for Cefpodoxime-clavulanic acid (24.74g). Table 2 shows the ATC codes and the DDDs/100 bed days of the ten most commonly used antibiotics in the Pulmonary Medicine ward.

Majority of subjects (68.3%) admitted to pulmonary medicine ward had comorbidities such as Type2 diabetes mellitus, hypertension and anaemia, either singly or in combination. Only a small number of subjects (3.8%) had non-pulmonary diseases (example: anxiety induced breathlessness). The most prevalent disorder was bronchial asthma (14.2%), followed by chronic obstructive pulmonary disease (COPD) (11%), bronchial asthma with allergic rhino sinusitis (10.3%), pulmonary tuberculosis (10.2%), acute exacerbation of COPD (9.2%) and others (45.1%). Out of all subjects with COPD / acute exacerbation of COPD, 48.6% were illiterates.

Gram staining was done in 364 subjects (50.2%). Growth of gram positive cocci along with gram negative bacilli was most prevalent in cultured samples(31.4%), followed by gram positive cocci in 10.5% cultures, gram negative bacilli in 6.1% and others in minor proportions. Culture and sensitivity testing was

performed in 597 Subject's specimens (sputum, bronchoalveolar lavage fluid, blood, pleural fluid, wound swab and Endotracheal aspirate). Among the tested specimens, 124 subject specimens were rejected either because the sample was not "adequate" or not considered representative of conditions in the lower respiratory tract. From the remaining specimens, 186 organisms were isolated, out of which 178 were bacteria and the remaining were fungi (*Candida* species and *Aspergillus* species). Gram negative organisms were more frequently detected than gram positive (73.66% vs 22.04 %). *Pseudomonas aeruginosa* (24.2%) and *Streptococcus pneumonia* (10.7%) were the most prevalent gram negative and gram positive organisms respectively. Figure 2 shows the most prevalent organisms in pulmonary medicine ward.

Sensitivity study of antibiotics revealed that Amikacin was 100 % sensitive to *Nocardia.sps*, *E .coli* and *Enterobacter sp*. *Cefotaxime /ceftriaxone* was 100% sensitive to *Strept.pneumonia*, *Strept pyogenes*, *Nocardia.sps*, *Haemophilus influenza*, *Moraxella catarrhalis* and *K.oxytoca*. Details of antibiotics sensitivity pattern is given in Table 3.

DISCUSSION

Studies have proved that misuse, overuse and underuse (including non-compliance) of antibiotics are major clinical factors for the development of resistant strains [18]. Antibiotics are the most commonly used drugs in hospitals [1]. In developed countries 30% of hospitalized subjects will be treated with antibiotics [19].

Males were dominant in our study (62.3%). Out of them 38.9% were farmers, 21.9% were daily wage earners with annual income less than 100,000 INR (1619 USD). Since subjects belonging to lower income groups are unable to earn when they are ill, they expect aggressive treatments that help them to recover quickly and return to work. Majority of the subjects included in our study was from lower socio-economic strata and were hospitalized for one to seven days, whereas in another study by Khavane K et al maximum hospitalization ranged from four to eighteen days [20]. Long hospital stay could be a reason for adopting aggressive treatment strategy. Poverty and lack of education were correlated (56% of the lower educated group had an income of less than 100,000 INR per annum), with higher disease burden. This might also be a result of associated problems such as unemployment, poor hygiene, work-related stress etc. Economic burden of disease is further exaggerated because lower income groups are rarely covered by health insurance.

Majority of the subjects were in the 51-70 years age group, who also received the maximum antibiotics per prescription. Previous studies from developing countries have also demonstrated that older populations are more likely to be prescribed with antibiotics [21]. 75% of the study population received at least one antibiotic during their hospital stay. This number is much higher than what is reported by others. Khavane K et al (29%) [22], Shankar PR (29.5%) [21], Shankar PR (50.2%) [23], *Takahiro Higashi* (60%) [24] and S KI (69.4%) [25]. However, the above studies have been carried out in internal medicine wards and intensive care units over relatively shorter intervals. On the other hand, a few studies by Kumar R (India) [26], Badar V A (India) [18] which were carried out in intensive care or internal medicine units, demonstrated more frequent antibiotic prescriptions per subjects (81.3%, 81.8% and 83% respectively).

The data from developed nations cannot be compared with ours because most studies from abroad focus on diseases individually rather than a department. Warren et al (Canada) reported 58.4% LRTI subjects being prescribed with antibiotics [19], whereas Michael et al (Scottsdale, Arizona) demonstrated 69% of ARTIs prescribed with antibiotics [27]. This difference in prescribing might be due to differences in the specialty unit selected, varying diseases, different prescribers, and health care policies. Many of the respiratory diseases turn out to be complicated despite aggressive therapy.

Out of 543 subjects prescribed with antibiotics, 284 subjects received monotherapy and the rest received poly-therapy. Of the 990 antibiotics prescribed, 50 % were from the WHO-EDL [28], 61.9% from the National list of essential medicines of India [29] and 100% from the hospital formulary. Being a tertiary care hospital, the high infection rates sometimes entails extensive therapy with reserved antibiotics not listed in WHO-EDL.

The most commonly prescribed class of antibiotics were cephalosporins, followed by macrolides, penicillins with β -lactamase inhibitors, aminoglycosides and quinolones. Few studies from South India [25], Nepal [21] has reported a high proportion of Penicillin containing prescriptions. A Malaysia study reported high percentage of Penicillins in combination with β -lactamase inhibitors [30]. However, these studies have been carried out in different specialties. Studies in developed countries show a higher percentage of macrolide prescriptions (Canadian Study; Warren J et al [19] US Study; Michael L et al [27]) and a European study by Wood J et al [31] shows tetracycline or amoxicillin being prescribed most often.

Antibiotics frequently prescribed in combination were Cephalosporins with β -lactamase inhibitors. Majority of the subjects were treated empirically with third generation cephalosporins namely Ceftriaxone or Cefoperazone/Sulbactam. Severity of clinical symptoms and the delay in culture sensitivity reports were the most common reasons for empirical prescription of antibiotics. Most of the subjects were prescribed with broad spectrum antibiotics as an initial empirical therapy irrespective of the disease, which was later changed in 153 subjects, after the culture sensitivity reports were obtained. This is a common practice in India.

DDD/100bed days was highest for Cefpodoxime-clavulanic acid (24.74) followed by amoxicillin-clavulanic acid (15.46), Cefoperazone/Sulbactam (15.23), Azithromycin (9.79) and Ceftriaxone (9.73). DDD/100 bed days for amoxicillin-clavulanic acid (15.46 vs. 7.87) and Ceftriaxone (9.73 vs. 4.56) were higher in our study than what was reported by Shankar et al [21]. DDD/100 bed days for amoxicillin-clavulanic acid was 15.46 in our study whereas the study conducted by Mikic et al [32] DDD/100 bed days for amino penicillin was 5.1.

Our study demonstrates the high rate of parenteral use of antibiotics (55%) in the pulmonary medicine ward, which is much higher than what was reported by Srishlya et al [20] (36%) and by Shankar RP [21] (51%) in internal medicine ward of a tertiary hospital. The study conducted by Shankar PR in the intensive treatment unit of teaching hospital reported 61.9% of antibiotics being prescribed by parenteral route which is much higher than our study [23]. It is difficult to compare the results obtained from studies carried out in different departments. However, the higher DDD values in our results validate the choice of the pulmonary ward for studying antibiotic prescriptions.

Prescription audit monitors the average number of drugs per prescription, which helps to minimize number of drugs per prescription, risk of drug interactions, bacterial resistance and hospital costs [33]. The number of drugs per prescription was 11 ± 4.93 drugs as against 7.5 reported by Badar V A et al [18]. On the other hand, average number of antibiotics per prescription during the hospital stay was found to be 1.82, slightly higher than Shankar et al [21] and Sharma D et al [33] and more or less equal to Seikh Farid Uddin Akter et al study (1.8 ± 0.9) [30].

The majority of respiratory infections are caused by *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Streptococcus pneumonia*, *Acinetobacter* sps and *Haemophilus influenza*. Many of these are resistant to penicillins, cephalosporins and fluoroquinolones (Table 3). The resistance is also evident from our hospital's antibiotic policy 2013 and GARP- India working group [12]. The high prevalence of MRSA, *Enterobacter* sps and *S. maltophilia* resistant to penicillins (amoxicillin and ampicillin) and fluoroquinolones could be a reason for widespread use of broad spectrum antibiotics. Study by Khavane K et al (2010) showed that *K. pneumonia* was 100% sensitive to Piperacillin/Tazobactam and ciprofloxacin [22]. However, we observed that only 62% were sensitive to ciprofloxacin and 69.4% sensitive to Piperacillin/Tazobactam. While it is difficult to compare results from different studies separated temporally and geographically, the overall picture suggests an emergence of resistance.

CONCLUSION

Three-fourth of the total subjects was prescribed with antibiotics during the study period. The overuse of broad spectrum antibiotics could have accelerated the evolution of resistant strains of microbes, especially MRSA, *S. pneumonia* evolving as multi drug resistant strain. Resistance can be aggravated due to inappropriate use of antibiotics. Bronchial Asthma was the most common reason for admission into the pulmonary medicine ward. Empirical use of ceftriaxone and azithromycin were most frequently encountered. Cephalosporins in combination with β -lactamase inhibitors were the most commonly prescribed antibiotics followed by cephalosporins alone, macrolides, penicillin with β -lactamase inhibitors and amino glycosides. Parenteral use of antibiotics was observed to be significant, increasing the cost of therapy. Most commonly prevalent gram negative organism was *Pseudomonas aeruginosa* and gram positive organism was *Streptococcus pneumonia*. *Stenotrophomonas maltophilia*, MRSA, Non fermenting gram negative bacilli were highly resistant to most of the widely prescribed antibiotics such as Ceftriaxone, Amikacin, Amoxicillin-clavulanic acid etc.

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