ORIGINAL ARTICLE

Assessing treatment Patterns of acute Exacerbation of Chronic Bronchitis (AECB) in Outpatient Settings- Bangladesh

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Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) is a heterogeneous group of disorder that is broadly defined and encompasses several clinical and pathologic entities, primarily emphysema and chronic bronchitis. Being a lifelong disease, COPD patients require constant care and special care is needed for acute exacerbation of their condition along with the proper assessment of their treatment pattern and medications. Though a global guideline for management of COPD (GOLD) along with other management protocols are available in different countries, but in Bangladesh there is no local guideline and little data regarding the treatment pattern and medications including the use of antibiotic during the exacerbation phase of COPD. Therefore, this study has been designed to assess the use of antibiotic during acute exacerbation of chronic bronchitis (AECB) in outpatient settings- Bangladesh.*

Methods: *This was a multicenter, observational, prospective study. A total of 525 patients were planned to be enrolled in outpatient (Male & Female) > 18 years and presenting with suspected acute exacerbation of chronic bronchitis (AECB) where the physician intend to treat with antibiotic as well as signed informed consent to meet the inclusion criteria in this observational study from 20 centers. The physicians were selected randomly from a list of physicians who have post graduations in Respiratory Medicine and General practitioner with special training on Respiratory Medicine. Clinical diagnosis was based on sign, symptoms, radiological evidence and laboratory results as per routine practices. Patient data were collected by the investigators during baseline (Visit 1), intermediate (Visit 2) (if decided by the physicians) and at the end of antibiotic therapy. At visit 2 the effectiveness of the therapy in terms of therapeutic response and patients' compliance as per physicians' choice were assessed. Therapeutic response were evaluated in terms of Cure, Improvement, failure and relapse by the investigators.*

Results: *Among the enrolled patients there were 435 (83%) male with age varied from 20~91 years (57.9±13.5). More than 80% of the patients were 50 years and older and only 55 (10.47%) was below 40 years old. The rural resident patients were larger than urban and semi urban (48.8% vs. 36.4% and 14.9%). 34.5% were employed, 34.9% were previously employed, 15.4% were retired person and 15.2% were house wife. There were 26.5% of current smoker, 51% of former smoker, and 22.5% of never smoker. Abnormal breath*

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sound was found in 91% of patients. Radiologically, 61% of patients had bronchitis, 23.8% had pneumonia, only 3.1% had tuberculosis and 12% had other provisional diagnosis such as pleural effusion and pulmonary fibrosis. Out of 525 only 11.4% patients have had spirometry report available including 4 patients had mild (FEV e"80% predicted), 38 had moderate (50% d"FEV1 <80% predicted), 15 had severe (30%d" FEV1 <50% predicted), and 3 patients had very Severe (FEV1< 30% predicted). Age of the patient, severity of disease, suspected organisms, local trend of antibiotic resistance, culture and sensitivity report, and patient's compliance were considered to choose antibiotic. Most commonly prescribed antibiotic was co-amoxiclav (45.2%) followed by cefuroxime (12.95%), cefixime (10.85%), ceftriaxone (10.28%), levofloxacin (8.76%) and azithromycin (7.6%).

Conclusion: *Patients with chronic bronchitis frequently develop AECB, a devastating illness if not appropriately managed. Not all patients with AECB need antibiotic therapy, but this intervention is valuable. It could be mentioned that in the AECB study while patients were treated at outdoor setting the physicians advised almost three fourth of the patients the chest x ray and more than 9 patients out of 10 were prescribed Co-amoxiclav, cefuroxime, cefixime, ceftriaxone, levofloxacin or azithromycin.*

Introduction:

COPD is a heterogeneous group of disorder that is broadly defined and encompasses several clinical and pathologic entities, primarily emphysema and chronic bronchitis.[1] The global scenario of diseases is shifting from infectious diseases to non-communicable diseases, with chronic conditions such as heart disease, stroke and chronic obstructive pulmonary disease (COPD) now being the chief causes of death globally.[2] It is estimated that more than 64 million people have COPD worldwide. More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year. Almost 90% of COPD deaths occur in low- and middle-income countries, where effective strategies for prevention and control are not always implemented or accessible.[3-5]

There is a global guideline for management of COPD-'Global Initiative for Chronic Obstructive Lung Disease (GOLD)[5]. In addition there are other management protocols developed according to local context in different countries.[6-8] But in Bangladesh there is no local guideline. Various institutions follow separate protocolos.[9-10] But being a lifelong disease[2], COPD patients require constant care and special care is needed for acute exacerbation of their condition. Moreover there is little data about how they are treated, what drugs are administered most

commonly and for how long. It is also unclear what protocols are followed for management of acute exacerbation of COPD. So to explore the situation and find out this information, an observational study may be the best tool.

Method:

This is a multicenter, observational, prospective study. A total of 525 patients were planned to be enrolled in this observational disease registry study from 20 different centers from greater Dhaka and Comilla to see the current real life management patterns of acute exacerbation of chronic bronchitis (AECB) with various antibiotics at outdoor settings. The physicians were selected randomly from a list of physicians who have post graduations in Respiratory Medicine and General practitioner with special training on Respiratory Medicine. Clinical diagnosis was based on sign, symptoms, radiological evidence and laboratory results as per routine practices. Management of AECB and selection of antibiotics were as per the physician's discretion.

Data on participating physicians were collected on a self-questionnaire during the selection of the investigators. Patient data were collected at visit 1, visit 2 and any visit in between done as per the need of the physicians. Data on demography, clinical problems, diseases history, vaccination history, method of diagnosis,

concomitant diseases, treatment prescribed were collected in the data collection form (CRF) at visit 1 (Day 1). Patients were advised to come back at visit 2 (as per physician's decision) to assess the effectiveness of the therapy in terms of therapeutic response and patients' compliance as per physicians choice. During this Follow up visits patient's overall assessment to the therapy and occurrence of adverse events during treatment were also evaluated. Patients who completed follow-up visit at the end of antibiotic therapy were considered for analysis. Statistical analysis was mainly descriptive and was summarized as mean, median, standard deviation, minimum, maximum and percentages for continuous parameters and frequency and percentages for categorical parameters. Statistical analysis was done using SPSS 17.0.

The primary endpoint was the relative proportion of AECB patients treated with various antibiotics at outdoor settings. Secondary endpoints were profile of the patients, center specificities that may determine some therapeutic decisions: type of center, laboratory tests, traditions following local/international guidelines, treatment costs, COPD diagnosis method used by physicians, treatments prescribed for AECB, dose & duration of treatment with antibiotic, vaccination history against influenza and pneumonia and therapeutic response to different treatment modalities according to patients and physicians assessment. Clinical outcome (success) was categorized into 4 headings: a) Cure: disappearance of all pre-treatment signs and symptoms of infection, b) Improvement: improvement in, or partial disappearance of signs and symptoms without requiring further antibacterial therapy. c) Failure: no change in, or worsening of baseline signs and symptoms requiring modification of treatment, i.e., addition of or switch to another antibacterial therapy, and d) Relapse: initial amelioration in the clinical picture, a favorable response to therapy, followed by worsening or reappearance of some signs or symptoms either later during treatment or once off therapy.

Safety analysis:
There were 4 death cases and the investigators confirmed that the reason of death was aging and cardiorespiratory failure. As the investigators confirmed that the patients were

not on Sanofi brand, death was not considered as reportable serious adverse event from sanofi end. Use of non-Sanofi brand was identified in 5 patients and was not eligible for AE reporting. Among the 43 patients, uses of non-Sanofi brand were confirmed by the investigators in 12 patients and were non-eligible for AE reporting. Use of Sanofi brand was confirmed in 26 patients of whom 3 were not considered for reporting AE due to identification of non-reportable event on Pharmacovigilance reevaluation. There were 5 patients for whom use of Sanofi brand was unknown to the investigators was also considered for AE reporting considering possibility of Sanofi Brand use. Finally 28 (5.3%) patients were considered for reporting non-serious AEs and the event was lack of efficacy or no improvement in sign and symptoms. There were no SAEs reported for Sanofi INN.

Results:
A total of 525 patients who were attended to the physicians with clinical features of AECB were enrolled in this study, however, four of them died due to complication of other comorbidity and another two patients were lost to follow up before their visit 2. Patients were recruted in 20 different sites in two districs of Bangladesh. 20 physicians who were specialized in the respiratory medicine and or experienced in this area participated in this study as investigators and recruited eligible patients from 20 centers (private hospital or chamber). Among the enrolled patients, there were 83% male and 17% female patients with age from 20~91 years (57.98±13.54). More than 80% of the patients were 50 years and older and only 10.47% was below 40 years old that might be cause of alpha 1- antitrypsin deficiency or any other gnetically transmitted diseases. The majority of the patients were (48.8%) were residing in rural areas than semi urban (14.9%) and urban (36.4%) areas. About 34.5% were employed, 34.9% were previously employed, 15.4% were retired person and 15.2% were house wife. There were 26.5% of current smoker, 51% of former smoker, and 22.5% of never smoker. The demographic characteristics of the patients at baseline are presented in Table 1

During the baseline visit 478 (91%) patients had abnormal breath sound and most common were wheezes and crackles. Two common laboratory

tests that the patients presented to their physicians during visit 1 were sputum culture and X-ray chest along with other routine blood tests. Radiologically 177 (61%) patients had bronchitis, 69 (23.8%) had pneumonia, only 9 (3.1%) had TB and 20 (12%) had other provisional diagnosis such as pleural effusion and pulmonary fibrosis were common. Out of 525 only 60 (11.4%) patients have had spirometry report available during their visit 1. 4 patients had mild (FEV e"80% predicted), 38 had moderate (50% d"FEV1 <80% predicted), 15 had severe (30%d" FEV1 <50% predicted), and 3 patients had very Severe (FEV1< 30% predicted). Table 2 showed clinical characteristics of the patients at baseline.

All the 525 patients were prescribed antibiotics either single or in with another one. Choice of antibiotics and their dosage and duration were determined by the physicians. Age of the patient, severity of disease, suspected organisms, local trend of antibiotic resistance, culture and sensitivity report, and patient's compliance were considered to choose antibiotic. Most commonly prescribed antibiotic was co-amoxiclav (45.2%) followed by cefuroxime (12.95%), cefixime (10.85%), ceftriaxone (10.28%), levofloxacin (8.76%) and azithromycin (7.6%). Table 3 indicated antibiotics and their dosage and duration.

Other antibiotics prescribed were doxycycline, moxifloxacin, clarithromycin, amikacin, ceftazidime, ciprofloxacin, linezolid, gentamycin, gemifloxacin. Most of the cases physicians' first choice was oral antibiotic (74.2%) and dosage, frequency of dosages and duration were as per physicians' discretion. Table 4 Prescribed antibiotics responses at final visit at baseline.

Most common concomitant diseases were cardiovascular (20.4%), diabetes mellitus (14.9%), hypertension (44.8% within 67 patients), anxiety and depression (9.8%). Table 5 below shown all concomitant diseases reported by the physician.

Table-I

Patients demographic characteristics at baseline

	Total (n=525)
Age (years)	
Mean ±SD	57.98±13.54
Gender	
Male/Female	435/90
Locality [n (%)]	
Urban	191 (36.4%)
Sub-urban	78 (14.9%)
Rural	256 (48.8%)
Occupational status	
Employed	181 (34.5%)
previously employed	183 (34.9%)
Retired person	81 (15.4%)
Office based staff	130 (24.8%)
Labour	118 (22.5%)
Industrial staff	81 (15.4%)
Engaged in agriculture	70 (13.3%)
Businessmen	41 (7.8%)
House wife	80 (15.2%)
Others (student, painter, singer, ward boy, self-employed)	5 (1%)
Smoking	
Former smoker	268 (51%)
Current smoker	139 (26.5%)
Never smoker	118 (22.5%)

Table-II

Patients clinical characteristics at baseline

		Total (n=525)
Vital Signs	Range	M±SD
Pulse Rate	62-120	87.85±11.17
Systolic	80-200	125.71±18.97
Diastolic	50-120	78.99±9.97
Respiratory Rate	14-40	22.57±4.49
Sign & Symptom	(n, %)	
Increased Dyspnea	468 (89.14%)	
Increased Sputum Volume	388 (73.90%)	
Chronic Cough	495 (94.28%)	
Fever	282 (53.71%)	
Abnormal Breath Sound	478 (91.04%)	
Clinical diagnosis:		
AECB with previous hospitalization	162 (31%)	
AECB patients advised hospitalized	79 (15%)	
AECB treated as out-patient	446 (85%)	
Investigations		
Sputum culture	35 (6.66%)	
X-ray chest	243 (46.3%)	
Bronchitis	177 (61%)	
Pneumonia	69 (23.8%)	
TB	09 (3.1%)	
Other provisional diagnosis	20 (12%)	
Normal radiological findings	15 (2.85%)	
Chest X-ray advised at the visit 1	391 (74.5%)	
Spirometry	60 (11.4%)	
Mild (FEV ≥80% predicted)	04 (0.76%)	
Moderate (50% ≤ FEV1 <80% predicted)	38 (7.23%)	
Severe (30% ≤ FEV1 <50% predicted)	15 (2.85%)	
Very Severe (FEV1< 30% predicted)	03 (0.57%)	
Spirometry at the visit 1	245 (46.7%)	
Vaccination history		
Influenza	33 (6.28%)	
Pneumonia	30 (5.71%)	
Both influenza and pneumonia.	25 (4.76%)	
Patients had never vaccinated	453 (86.28%)	
(on either influenza or pneumonia)		
Unknown	79 (15.04%)	

Table-III

Antibiotics and their dosage and duration. (Visit 1)

ANTIBIOTIC	Total Number	mg	Times daily No. of Patient	Duration No. of Patient
DOXYCYCLINE	6	100	1 (3)	14 (3)
			2 (2)	7 (2)
		200	2 (1)	7 (1)
AZITHROMYCIN	40	500	1 (30)	5 (4)
				7 (18)
				10 (4)
				14 (4)
			2 (10)	7 (5)
				10 (1)
				14 (4)
CO-AMOXICLAV	239	250	2 (2)	10 (2)
		375	3 (15)	7 (5)
				10 (10)
		500	2 (2)	7 (2)
		625	2 (30)	10 (4)
				14 (26)
			3 (141)	7 (78)
				10 (46)
				14 (17)
		1000	2 (14)	7 (5)
				10 (9)
		1200	3 (35)	5 (2)
				7 (28)
				10 (5)
CEFUROXIME	68	250	2 (11)	7 (3)
				10 (5)
				14 (3)
		500	2 (41)	7 (28)
				10 (6)
				14 (7)
			3 (4)	7 (3)
				14 (1)
		750	2 (3)	5 (3)
			3 (2)	7 (2)
		1500	2 (2)	5 (2)
			3 (5)	7 (5)
CEFIXIME	57	200	2 (53)	7 (41)
				10 (12)
		400	2 (4)	7 (2)
				10 (1)
				14 (1)

ANTIBIOTIC	Total Number	mg	Times daily No. of Patient	Duration No. of Patient
AMIKACIN	14	500	2 (14)	5 (5)
				7 (6)
				10 (2)
CEFTAZIDIME	12	1000	3 (12)	5 (4)
				7 (7)
				10 (1)
CEFTRIAXONE	54	1000	1 (3)	7 (1)
				14 (2)
			2 (51)	5 (6)
				7 (30)
				10 (15)
CIPROFLOXACIN	3	500	2 (3)	7 (3)
CLARITHROMYCIN	14	250	2 (1)	7 (1)
		500	2 (13)	7 (10)
				10 (3)
CLAVULANIC ACID	5	250	2 (5)	7 (2)
				10 (2)
				14 (1)
GEMIFLOXACIN	4	320	1 (4)	7 (4)
LEVOFLOXACIN	46	500	1 (40)	5 (3)
				7 (15)
				10 (17)
				14 (5)
		750	1 (4)	7 (1)
				10 (2)
				14 (1)
		1000	2 (2)	10 (2)
LINEZOLID	5	400	2 (5)	7 (5)
MOXIFLOXACIN	14	400	1 (14)	7 (11)
				14 (3)

Table-IV

Prescribed antibiotics responses at final visit at baseline

Antibiotic (Multiple responses)	Physicians assessment				Total (n=590)
	Cure (n=187, %)	Improvement (n=371, %)	Failure (n=20, %)	Relapse (n=12, %)	
Azithromycin	10, 25%	28, 70%	0, 0%	2, 5%	40
Co-amoxiclav	80 (33.5%)	149 (62.3%)	6 (2.5%)	4 (1.7%)	239
Cefuroxime	27 (40%)	39 (57%)	1 (1.5%)	1 (1.5%)	68
Cefixime	10 (17.5%)	43 (75%)	4 (7.5%)	0 (0%)	57
Ceftriaxone	17 (31.5%)	30 (55.5%)	3 (5.5%)	4 (7.5%)	54
Levofloxacin	24 (52.17%)	19 (41.30%)	2 (4.35%)	1 (2.17%)	46
Others	19 (22%)	63 (73.3%)	4 (4.7%)	0 (0%)	86

Table-V

Below shown all concomitant diseases reported by the physician

Concomitant Disease	N (%)
Diabetes	96 (14.9)
Infections	33 (5.1)
Cardiovascular	131 (20.4)
Osteoporosis	20 (3.1)
Lung Cancer	2 (0.3)
Anxiety and depression	63 (9.8)
None	218 (33.9)
Unknown	13 (2.0)
Others (Multiple)	67 (10.4)
Hypertension (HTN)	30 (44.8)
BEP	1 (1.5)
Bladder cancer	1 (1.5)
PUD	5 (7.5)
IHD (Ischemic Heart Disease)	5 (7.5)
Chronic kidney disease (CKD)	4 (6.0)
Cor pulmonale	3 (4.5)
Chronic liver disease (CLD)	1 (1.5)
Hypothyroidism	2 (3.0)

Others (Laryngeal carcinoma, TB, Thyroid disease, Pneumonia, Neurological, Bronchitis, Urinary Tract Infections, Senile tremor, Osteochondritis, Non Ulcer Dyspepsia, Respiratory Failure, Prostate Infection, Irritable bowel syndrome, Pneumothorax, Lumbar Spondylosis)   15, 22.4

Out of 525 patients 114 (21.7%) had a family history of AECB. With a range of 0-40 years 70% of the patients (365) had a history of AECB for 9 years or less. 25% (133) patients had history of AECB between 10-19 years and only 5% (27) had 20 years or more. Number of exacerbation per year was 0-12 times. 31% (162) had previous history of hospitalization due to AECB. During visit 1 after the examination physician advised only 79 (15%) AECB patients to be hospitalized for better management of their acute condition. The rest of 85% (446) was treated as out-patient.

Discussion:

This study was conducted to see the relative proportion of AECB patients treated with various antibiotics at outdoor settings. It was also intended to describe the profile of the patients, different diagnostic methods and different treatment options for AECB in real life practice in Bangladesh. 20 physicians who were specialized in the respiratory medicine and experienced in this area participated in this study as investigators and recruited eligible patients from 20 centers (private hospital or chamber). The most common investigations that were recommended and considered for the diagnosis and management of AECB patients were X-ray Chest, Complete Blood Count (CBC), Culture and Sensitivity, and Spirometry. Almost all the physicians reported that they were regularly following GOLD recommendation (Global Initiative for Chronic Obstructive Lung Diseases) in diagnosis and management of AECB[2]. They had also suggested that those patients should be vaccinated for Pneumonia and Influenza. All the 525 patients were prescribed antibiotics either any single one or in combination with another one. 172 (32.76%) of the patients were visited their physicians within 3-7 days of visit 1 as an optional follow up visit mainly due to either no change or worsening of their condition. During this visit an evaluation on clinical outcome was done by the physician and categorized as cured, improved, failure/no change and relapse. Out of 172 only two patients found cured, 145 improved, 24 no changed/failure, and one patient had relapsed. Modification of antibiotics either changes of their dosage was required for 90 patients. 13 patients were advised to be hospitalized during this intermediate visit for better management of their acute condition. At the final visit 508 (96.8%) of the patients had completed prescribed course of antibiotics and 17 (3.2%) were not able to complete it. Of them two patients were lost to follow up (LTFU), and four patients had died during the study. Five patients discontinued antibiotics due to economic reason and another four patients didn't want to continue it without explaining any reason. One patient discontinued due to worsening of his condition and another one had to take anti TB treatment. An evaluation on clinical outcome was done on the final visit by the physician and categorized as cured, improved, failure/no change and relapse. Out of 519 (4 deaths and 2 LTFU were excluded) evaluated patients 32.4% (170) found cured, 62.7% (329) improved, 2% (11) no changed/failure, and 1.7% (9) had relapsed. 10 patients were advised to be hospitalized.

In this study (AECB) the most common factors that the physicians considered to prescribe empirical antibiotics were cardinal symptoms of the patients followed by guidelines/recommendations, local sensitivity/resistant patterns and cost of antibiotic treatment which were reflected in the responses of the Physician's questionnaire. All most all the physicians participated in this study reported that they were regularly following GOLD recommendation[2] (Global Initiative for Chronic Obstructive Lung Diseases) in diagnosis and management of AECB. Although many of these patient related factors and the causative organism related factors were considered during taking decision on the selection of antibiotic regimen by the physician in outdoor setting in Bangladesh but it could not be confirmed if the participating physicians systematically categorize the patient based on their historical information, lung function and shifting of associated organisms in the decision making.

This study has been conducted in 20 different centers from the two districts towns which do not represent entire population especially patient from the rural part of Bangladesh. A longer follow-up could evaluate the effect of antibiotic therapy in reducing the subsequent exacerbation in patient with chronic bronchitis.

Conclusion:

Patients with chronic bronchitis frequently develop AECB, a devastating illness if not appropriately managed. Not all patients with AECB need antibiotic therapy, but this intervention is valuable. It could be mentioned that in the AECB study while patients were treated at outdoor setting the physicians advised almost three fourth of the patients the chest x ray and more than 9 patients out of 10 were prescribed Co-amoxiclav, cefuroxime, cefixime, ceftriaxone, levofloxacin or azithromycin.

Acknowledgement:

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