Drug Susceptibility pattern of Organisms Isolated During Acute Exacerbation of Chronic Obstructive Pulmonary Disease in a Tertiary Level Hospital of Nepal

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ABSTRACT

Introduction: Disease process in chronic obstructive lung disease is interrupted by acute exacerbations. Bacterial and viral infections account for majority of cases. Gram positive and Gram negative organism both are associated with exacerbations. **Methods:** Sputum samples were collected from COPD patients in acute exacerbation, on the day of emergency visit. Drug susceptibility pattern was evaluated for the study population to identify the prevalence of susceptible and resistant organisms. **Results:** Eighty-nine culture positive sputum samples were processed for drug susceptibility. Gram negative bacilli (88.76%) were isolated more than Gram positive cocci (11.24%). *Pseudomonas sp.*, *Acinetobacter sp.*, *Klebseilla sp.* and *E. coli* were the most common Gram negative bacilli. Multi-drug resistance status was identified in higher percents in *Acinetobacter sp*. (81.25%), *Pseudomonas sp*. (62.5%) and *Klebseilla* sp. (46.6%). Aminoglycosides and Quinolones showed good sensitivity to GNBs. However, Carbapenems were found to be the most effective agents against these organisms. **Conclusion:** Gram negative infection is common in COPD. Multi drug resistant pathogens are increasingly associated with acute exacerbations. Routinely used antibiotics are becoming less effective.

Keywords: chronic obstructive pulmonary disease; drug resistance; *pseudomonas aeruginosa; acinetobacter*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a chronic yet life threatening lung disease, is often interrupted by acute exacerbations (AE).[1] COPD exacerbations are mostly due to bacterial and viral infections, pollution and cold weather.[2, 3] Bacterial exacerbations account for about 40-50% of the cases.[3, 4] It is observed that there is colonization of pathogenic bacteria in lower respiratory tract which increases during acute exacerbation.[5]

The prevalent pathogens for infective exacerbations are *Pseudomonas aeruginosa*,

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Haemophilus influenzae, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*.[4,6,7] During the last two decades, prevalence of multidrug resistant (MDR) bacteria has increased in all hospitalized patients, including patients with COPD exacerbations.[8] MDR bacteria were defined as Methicillin-resistant *Staphylococcus aureus* (MRSA), Ceftazidime or Imipenem resistant *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Stenotrophomonas maltophilia*, and extended spectrum beta lactamase (ESBL) producing Gram-negative bacilli (GNB).[8,9] Most studies showed gram negative bacilli among the most frequently isolated MDR bacteria in severe COPD exacerbations. This included *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and *Stenotrophomonas maltophilia*.[8]

In this study, bacterial culture and drug susceptibility of induced sputum samples were done in severe and very severe COPD patients to identify the sensitivity pattern in infective exacerbations of COPD.

METHODS

Study population: The patients with COPD on standard optimal medical therapy were selected as the study population from Shree Birendra Hospital, Chhauni, Kathmandu. Total of 89 subjects with positive sputum culture for clinically significant bacterial pathogens were included. All the patients were admitted to the hospital due to AE. AE of COPD was defined according to the guidelines of Global Initiative for Obstructive Lung Disease (GOLD).[10] The subjects with two or more exacerbations of COPD in a year and frequent use of antibiotics were included in the study. The sputum samples were collected for the study between July 2013 and June 2014.

Sputum sample collection: Sputum samples were collected from all patients on day one of presentation before first dose of antibiotics in emergency department. All subjects rinsed mouth with sterile water which was followed by nebulisation with Salbutamol. The expectorated sputum was visually inspected for adequacy and was submitted to the microbiology lab within two hours[11].

Sample processing: Sputum samples were processed and identified according to guidelines given by American Society of Microbiology. Sensitivity was carried out by Kirby Bauer's method as per Clinical and Laboratory Standards Institute (CLSI) recommendations. Due to extensive variation in definition of MDR, this study adopted interim standards provided for acquired multi-drug resistance by European Centre for Disease Control and Prevention. Each organism was labelled MDR as per the guidelines stated in the literature[12, 13].

Statistical analysis: Statistical analysis was done with IBM SPSS version 20. All the categorical data were expressed in percentage and absolute numbers. The continuous numerical data were expressed as mean ± Standard deviation. The statistical significance was set at $p<0.05$ with 95% confidence. The statistical evaluation for categorical variables were done using chi square test.

RESULTS

The eighty nine positive sputum cultures were included in the study. Isolated bacterial pathogens were tested for relevant antibiotics as per recommendations for their drug

Table 1: The organisms isolated in the bacterial cultures of expectorated sputum samples. Total samples: 89.

Organisms	Number(n)	Percent
Gram Negative	**79**	**88.76%**
Pseudomonas aeruginosa	26	29.22
Acinetobacter sp.	18	20.22
Klebsiella Sp.	18	20.22
Klebsiella pneumonia	15	-
Klebsiella oxytoca	3	-
Escherichia coli	11	12.36
Citrobacterfreundii	4	4.49
Moraxella catarrhalis	2	2.25
Gram Positive	**10**	**11.24%**
Streptococcus sp.	6	6.75
Staphylococcus	4	4.49
MRSA	3	-
MSSA	1	-

sensitivity. The isolated pathogens in sputum cultures are enlisted in table no. 1.

Sensitivity and Resistance of Organisms

Pseudomonas aeruginosa: was the most commonly isolated organism in our study. Among the penicillin group of antibiotics all growths of Pseudomonas sp. were found resistant to Amoxicillin (4 out of 4) and Co-amoxyclav (9 out of 9). Eighteen out of 21 (85.71 % of 21) isolated Pseudomonas sp. were sensitive to PTZ. Only 3 out of 21 (14.28 % of 21) were found to resistant to PTZ. Among the quinolones 83.33 % (20 of 24) isolates were sensitive and 16.66 % (4 of 24) were resistant to Ciprofloxacin whereas 71.42 % (5 of 7) isolates were sensitive and 28.57 % (2 of 7) were resistant to Ofloxacin. All growths tested with Co-trimoxazole were resistant to it (4 of 4). Twelve growths tested for Chloramphenicol sensitivity showed sensitive strains in seven (58.3 %, 7 of 12) and resistant strains in five (41.67 %, 5 of 12). Among the aminoglycosides Amikacin was sensitive in 91.30% (21 of 23) isolates and resistant in two isolates (8.69 %, 2 of 23) whereas Gentamycin was sensitive in 84.21% (16 of 19) isolates and resistant in 15.78 % (3 of 19). Tobramycin was tested in twoisolates and both were sensitive. Doxycycline sensitivity was tested in 22 culture isolates where 40.90 % (9 of 22) were sensitive and 59.09 % (13 of 22) were resistant. Cephalexin resistance was shown by all tested isolates (2 of 2), Ceftriaxone resistance was shown by 66.66 % isolates (4 of 6) and sensitivity by 33.33 % (2 of 6), Cefotaxime resistance was shown by 83.33 % isolates (5 of 6) and sensitivity by 16.67 % (1 of 6). All 24 culture growths showing pseudomonas were tested for Ceftazidime sensitivity. 69.23% (18 of 26) were sensitive and 30.70 % (8 of 26) were resistant. All samples tested for Cefixime sensitivity were found resistant (2 of 2). Cefepime sensitivity was shown by 57.89 % isolates (11 of 19) and resistance by 42.11 % (8 of 19). All isolates tested for Imipenem sensitivity were found sensitive (9 of 9) whereas 88.89% were sensitive to Meropenem (8 of 9) and 11.11 % (1 of 9) were resistant. All isolates tested for Carbenicillin (6 of 6), Colistin (9 of 9) and Polymyxin B (7 of 7) were found sensitive to respective drugs. Pseudomonas sp. showing resistance to two or more drugs of different mechanism of actions (MDR) were 62.5 % (15 of 24).

Table 2: Gram Negative Bacilli isolated from the COPD subjects during study period are listed along the columns. The rows enumerate the antibiotics tested for individual organisms. The highlighted cells show number of samples in denominators. S = Sensitive and R = Resistant.

	Gram Negative Bacilli						
Antibiotics	**Pseudomonas**	**Klebsiella pneumoniae**	**Klebsiella oxytoca**	**E coli**	**Acinetobacter Sp**	**Citrobacter Sp**	**Moraxella Cattarhalis**
Ampicillin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Amoxycillin	R-4/4	S 1/4 R 3/4	R 1/1	S 1/4 R 3/4	R 9/9	S 1/4 R 3/4	Not tested
Amoxyclav	R-9/9	S 1/10 R 9/10	R 1/1	R 8/8	R12/12	S 1/4 R 3/4	Not tested
cloxacillin	S-2/2	Not Tested	Not tested	R 1/1	R 1/1	Not tested	Not tested
PTZ	S-18/21 R-3/21	S 4/10 R 6/10	S 1/1	S 3/7 R 4/7	S 3/15 R 12/15	S 1/1	Not tested
Nalidixic acid	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Norfloxacin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Ciprofloxacin	S-20/24 R 4/24	S 7/13 R 6/13	S 2/2	S 4/9 R 5/9	S 2/14 R 12/14	S 1/4 R 3/4	S 2/2
Ofloxacin	S 5/7 R 2/7	S 3/9 R 6/9	S 1/1	S 3/7 R 4/7	S 2/10 R 8/10	R 1/1	S 2/2
Nitrofurantoin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Cotrimoxazole	R 4/4	S 4/8 R 4/8	S 1/1	S 4/6 R 2/6	S 1/6 R 5/6	S 3/4 R 1/4	R 2/2
Chloramphenicol	S 7/12 R 5/12	S 7/10 R 3/10	S 2/2	S 7/8 R 1/8	S 4/9 R 5/9	S 3/4 R 1/4	S 2/2
Erythromycin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	S 2/2
Azithromycin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	S 2/2
Amikacin	S 21/23 R 2/23	S 8/13 R 5/13	S 1/1	S 7/8 R 1/8	S 3/15 R 12/15	S 3/4 R 1/4	Not tested
Gentamicin	S 16/19 R 3/19	S 6/11 R 5/11	S 1/1	S 5/8 R 3/8	S 4/11 R 7/11	S 4/4	Not tested
Tobramycin	S 2/2	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Tetracycline	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Doxycycline	S 9/22 R 13/22	S 9/12 R 3/12	S 2/2	S 4/8 R 4/8	S 4/13 R 9/13	S 4/5 R 1/5	Not tested
Cefalaxin	R 2/2	S 2/7 R 5/7	Not tested	S 2/4 R 2/4	R 3/3	Not tested	Not tested
Ceftriaxone	S 2/6 R 4/6	S 6/11 R 5/11	S 1/1	S 4/7 R 3/7	S 2/9 R 7/9	S 3/4 R 1/4	S 2/2
Cefotaxim	S 1/6 R 5/6	S 5/12 R 7/12	S 2/2	S 4/4 R 4/4	S 1/10 R 9/10	S 3/4 R 1/4	R 2/2
Cefepime	S 11/19 R 8/19	S 6/12 R 6/12	S 1/1	S 2/8 R 6/8	S 1/11 R 10/11	S 5/5	Not tested
Ceftazidime	S 18/26 R 8/26	S 4/10 R 6/10	S 1/1	S 4/4 R 4/4	R 11/11	S 4/4	Not tested
Cefixime	R 2/2	R 1/1	Not tested	Not tested	Not tested	Not tested	Not tested
Vancomycin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Imipenem	S 9/9	S 1/1	Not tested	S 2/2	S 5/5	Not tested	Not tested
Meropenam	S 8/9 R 1/9	S 2/3 R 1/3	Not tested	S 3/4 R 1/4	S 3/7 R 4/7	S 3/3	S 2/2
Polymyxin B	S 7/7	Not Tested	Not tested	Not tested	S 1/1	Not tested	Not tested
Colistin	S 9/9	Not Tested	Not tested	Not tested	S 1/1	Not tested	Not tested
Clindamycin	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Carbeniclin	S 6/6	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested
Levoflox	Not Tested	Not Tested	Not tested	Not tested	Not tested	Not tested	Not tested

Acinetobacter sp.: was predominantly resistant to pencillins: Amoxycillin 100 % (9 of 9), Amoxyclav 100 % (12 of 12), PTZ 80 % (12 of 15). Quinolones also had low sensitivity: Ciprofloxacin was resistant in 85.71 % (12 of 14) and sensitive in 14.29 % (2 of 14). Ofloxacin was resistant in 80 % (8 of 10) and sensitive in 20 % (2 of 10). Co-trimoxazole was resistant in 83.33 % (5 of 6) and sensitive in 16.67 % (1 of 6) whereas Chloramphenicol was sensitive in 44.44 % (4 of 9) and resistant in 55.55 % (5 of 9). Amikacin sensitivity was 20 % (3 of 15) and resistance 80 % (12 of 15) whereas Gentamycin sensitivity was 36.36 % (4 of 11) and resistance was 63.64 % (7 of 11). Doxycycline sensitivity was 30.77 % (4 of 13) and resistance was 69.23 % (9 of 13). Cephalexin was resistant in all tested isolates (3 of 3).

Ceftriaxone resistance was 77.78 % (7 of 9) and sensitivity was 22.22 % (2 of 9). Ninety percent (9 of 10) isolates showed resistance to Cefotaxime and sensitivity was 10 %. Cefepime resistance was 90.9% (10 of 11) with sensitivity of 9.1 % (1 of 11). All isolates tested for Ceftazidime sensitivity showed resistance (100%, 11 of 11). On the contrary, all isolates tested for Imipenem sensitivity showed sensitive results (100 %, 5 of 5) whereas 42.85% (3 of 7) showed sensitivity to Meropenem and 57.15 % (4 of 7) showed resistance. Colistin and Polymyxin B were tested in one culture growth each showing sensitivity. Thirteen out of 16 Acinetobacter isolates (81.25 %) showed resistance to two or

more drugs of different mechanism of action (MDR).

Klebsiella: was isolated in total 15 samples. 13 samples were Klebsiella pneumoniae and 2 samples were Klebsiella oxytoca. The isolated species of Klebsiella were drug sensitive Non-MDR pathogens in eight samples. Whereas MDR pathogens were detected in seven instance. Among the B-lactam group of antibiotics, organisms were found resistant to amoxicillin in 4 out of 5 samples (80 %), to Co-amoxyclav in 10 out of 11 samples (90.9 %) and to PTZ in 6 out of 11 samples (54.54 %). When Cephalosporins were evaluated Cephalexin was resistant in 5 out of 7 samples (71.42 %), Ceftriaxone was resistant in 5 out of 12 samples (41.67 %), Cefotaxime was resistant in 7 out of 14 samples (50 %), Cefepime was resistant in 6 out of 13 samples (46.15 %) and Ceftazidime was resistant to 6 out of 11 samples (54.54 %). Among the Quinolones Klebsiella was found sensitive to Ciprofloxacin in 9 out of 15 samples (60 %) and to Ofloxacin in 4 out 10samples (40 %).When aminoglycosides were evaluated Amikacin was found sensitive in 9 out of 14 samples (64.28 %) and Gentamicin was found sensitive in 7 out of 12 samples (58.33 %). Among tetracyclines only Doxycycline was evaluated which showed sensitive results in 11 out of 14 samples (78.57 %). Chloramphenicol was found sensitive in 9 out of 12 samples (75 %) whereas Co-trimoxazole was found sensitive in 5 out of 9 samples (55.56 %). Carbapenem was tested in only three suptum samples. Meropenem was sensitive in 2 out of 3 samples (66.66 %) whereas Imipenem was sensitive in all three samples (100 %).

E. coli: Total 11 sputum cultures showed E.coli. Among these 6 isolates were MDR pathogens (54.54 %) and five isolates were sensitive organisms (45.45 %). Among Penicillin groups: Amoxicillin was resistant in 3 out 4 samples (75 %), Co-amoxyclav was resistant in 8 out of 8 samples (100 %) and PTZ was resistant in 4 out of 7 samples (57.14 %). When Cephalosporins were evaluated Cephalexin was resistant in 2 out of 4 samples (50 %), Ceftriaxone was resistant in 3 out of 7 samples (42.85 %), Cefotaxime was resistant in 4 out of 8 samples (50 %), Cefepime was resistant in 6 out of 8 samples (75 %) and Ceftazidime was resistant in 4 out of 8 samples (50 %). Among the Quinolones E.coli was found sensitive to Ciprofloxacin in 4 out of 9 samples (44.44 %) and to Ofloxacin in 3 out 7 samples (42.85 %).When aminoglycosides were evaluated Amikacin was found sensitive in 7 out of 8 samples (87.5 %) and Gentamicin was found sensitive in 5 out of 8 samples (62.50 %). Among tetracyclines only Doxycycline was evaluated which showed sensitive results in 4 out of 8 samples (50 %). Chloramphenicol was found sensitive in 7 out of 8 samples (87.5 %) whereas Co-trimoxazole was found sensitive in 4 out of 6 samples (66.67 %). Carbapenem was tested in only four sputum samples. Meropenem was sensitive in 3 out of 4 samples (75 %) whereas Imipenem was sensitive in all two samples (100 %).

Citrobacter sp.: There were four isolates of Citrobacter freundii. Two of these were MDR pathogens (50 %). Amoxicillin was resistant in 75 % samples (3 out of 4), Co-amoxyclav in 75 % samples (3 out of 4) and PTZ in 100 % (1 out of 1). Cephalosporins were evaluated showing both Ceftriaxone and Cefotaxime resistance in 1 out of 4 samples (25 %). Cefepime and Ceftazidime were sensitive in all four samples (100 %).Among the Quinolones,

Citrobacter was found sensitive to Ciprofloxacin in 3 out of 4 samples (75 %) and resistant to Ofloxacin in 1 out 1 sample (100 %).When aminoglycosides were evaluated Amikacin was found sensitive in 3 out of 4 samples (75 %) and Gentamicin was found sensitive in all 4 (100 %).Among tetracycline only Doxycycline was evaluated which showed sensitive results in 3 out of 4 samples (75 %). Chloramphenicol and Co-trimoxazole were found sensitive in 3 out of 4 samples (75 %). Among Carbapenem only Meropenem was tested which was sensitive in all 3 samples (100 %).

Moraxella catarrahalis: Two isolates of Moraxella catarrahalis were both sensitive to Ciprofloxacin, Ofloxacin, Chloramphenicol, Azithromycin, Ceftriaxone and Meropenem. But these isolates were resistant to Co-trimoxazole and Cefotaxim.

Gram Positive Organisms: Six isolates of Streptococcus were resistant to Amoxicillin, Co-amoxyclav, Erythromycin and Gentamicin but were sensitive to Chloramphenicol and Vancomycin. Among the four isolates of Staphylococcus three were MRSA and one MSSA. MRSA was resistant to Ampicillin, Amoxicillin, Co-amoxyclav, Ofloxacin, Doxycycline and Ceftriaxone. The overall susceptibility pattern of individual antibiotics is given in figure no. 6.

DISCUSSION

The most commonly isolated community acquired organisms in AE COPD are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* on lower respiratory tract samples.[14] Our study showed very few isolates of community acquired pathogens in COPDs. On the contrary, *Pseudomonas sp*., *Klebsiella sp*., *Acinetobacter sp.* and *Enterobacter sp*. were commonly isolated from AE COPD patients requiring intensive care and mechanical ventilations in an article published from Thailand in 2012.[15] In accordance to this our study also isolated GNBs as the most common organisms in COPD subjects during AE. Our study isolated significantly larger number of GNBs as compared to GPCs, which is in accord to other South East Asian Studies.[16, 17]

Though viruses are the most common pathogens for AE of COPD[17], due to the lack of virology facility in our institute we were not able to conduct virological isolations. Hence our study prospectively limited the protocol to bacterial cultures. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumonia* and *E. coli* (in descending order) were the most common GNBs isolated in severe and very severe COPD patients in our study. Similar sequence of pathogens were identified by a study conducted by Dai M.Y. et al on AE of COPD in People's Republic of China.[17]

Incidence of MDR pathogens occurring in COPD patients is also well documented. Frequent exacerbations and frequent visits to hospital for treatment with repeated use of antibiotics tend to play significant role in involvement of MDR GNBs in AE of COPD. In severe COPD *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* are often MDR.[18] Resistance to two or more class of drugs was observed in all these organisms in high percentage in our study. This probably represented the hospital acquired pathogens with repeated visits and frequent use of antibiotics in this study population.

Pseudomonas sp. was completely resistant to Amoxicillin, Co-amoxiclav, Cotrimoxazole, Cephalexin and Cefixime. Good sensitivity was identified for PTZ, Quinolones and aminoglycosides. Carbapenems, Polymyxin B and Colistin were the most effective antibiotics. Similar resistance pattern was also observed in a large multicentre Chinese study[19] where Amoxicillin, Co-amoxiclav and Cotrimoxazole were the most ineffective drugs against *Pseudomonas sp.* In their study Amikacin and Cefoperazone faired best but in our study Amikacin and Carbapenems were the best agents. Imipenem resistance for *Pseudomonas* was very high in the Chinese study. On the contrary, Imipenem was the most effective drug in our study population for all the GNBs.

Most of the other GNB in our study showed similar sensitivity pattern with Penicillin groups being the most ineffective and Carbapenems being the most effective drugs. However Aminoglycosides and Quinolones had good sensitivity for GNBs as the first line agents.

On the contrary, *Acinetobacter sp.* showed worst resistance pattern, with penicillins, PTZ, Quinolones, Co-trimoxazole, Aminoglycosides and Cephalosporins being largely ineffective. High occurrence of MDR Acinetobacter (81.25 %) might represent circulation from a common hospital source. In a retrospective study on occurrence of *Acinetobacter sp.*, 79.5 % initial isolates were MDR pathogens in a single health institute, which was similar to our study[20]. Afore mentioned study also highlighted COPD as the risk factor for mortality with *Acinetobacter* infection. Carbapenem resistance among MDR Acinetobacter circulating in institutes have been well documented.[20] However Imipenem was the most effective antibiotic in our study. Colistin and polymyxin B were tested on limited MDR samples and were also found sensitive.

Very few GPCs were isolated in our study. Considering the study population with chronic airway disease with repeated hospital visits and repeated use of antibiotics, predominant growth of GNBs are explainable.[16-19] Laboratory limitations on the growth of GPCs, if at all they exist, are unexplainable. And the transportation time and processing time has been strictly followed during the study period.

During the study period a very good sensitivity to Carbapenems were observed particularly Imipenem. Such relative sparing of a group of antibiotics could be attributed to limited use of the agent under proper authorization during the study period in the institute. However, sensitivity has gradually declined to Carbapenems with their relative ease of availability after this study period. Colistin and Polymyxin B still have good sensitivity with its less frequent availability in the institute.

CONCLUSION: Gram negative bacteria are more commonly isolated in AE of COPD as compared to Gram positives. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumonia* and *E. Coli* are the most common Gram negatives isolated. The multi drug resistant gram negatives are common in COPDs with frequent exacerbations, antibiotic use and hospital visits. Aminoglycosides and Quinolones have good sensitivity to GNBs. However, Carbapenems were found to be the most effective agents against these organisms.

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