www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i8.65

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Bacterial Flora in Sputum and Antibiotic Sensitivity in Exacerbations of Bronchiectasis

Authors
Muhammed Aslam[1], Manoj D K[2], Rajani M[2], Achuthan V[2]
[1]Assistant Professor, Department of Pulmonary Medicine, DM Wayanad Institute of Medical Sciences, Kerala, India
[2]Professor, Department of Pulmonary Medicine, ACME Pariyaram, Kerala, India
Corresponding Author
Dr Muhammed Aslam
Assistant Professor, Dept. of Pulmonary Medicine, DM Wayanad Institute of Medical Sciences
Wayanad, Kerala, India
Email: *aslam646@yahoo.com*

Abstract
Background: *The present study aimed to identify Bacterial Flora in Sputum during exacerbations of Bronchiectasis and to assess the antibiotic sensitivity pattern of isolated organisms.*
Materials and Methods: *A Cross-sectional observational study was done in the Pulmonary Medicine ward of a tertiary care teaching hospital in Kerala for a period of one year. Sputum samples from 52 patients with exacerbation of bronchiectasis were subjected to bacterial culture and antibiotic sensitivity.*
Results: *This study yielded pathogenic bacterial growth in 76.9 % samples. Gram negative organisms were predominant (87.5%). Three commonest organisms identified were Pseudomonas aeruginosa in 30.8% cases, Klebsiella in 21.2% cases and Acinetobacter in 9.6 % cases. Commonest gram positive bacteria were Streptococcus Pneumoniae (60%). Modified Ziehl-Neelsen stain for acid fast bacilli was negative in all cases. Pseudomonas aeruginosa was 100% sensitive to Imipenem (p value <0.05) and ciprofloxacin (p value <0.05).Sensitivity of pseudomonas aeruginosa to Piperacillin-tazobactam was 85.7% (p value <0.05). The sensitivity to commonly used antipseudomonal cephalosporin ceftazidime was only 42.8% (p value = 0.0265).60% cases of Acinetobacter group (p value <0.05) died during the hospital stay.*
Conclusion: *The commonest organisms causing exacerbatioin of bronchiectasis in our study were gram negative organisms. The commonest isolate was Pseudomonas aeruginosa followed by Klebsiella. Initial empirical antibiotic therapy in severe bronchiectasis exacerbation canbe started with a combination of Piperacillin-tazobactam with Quinolones. Imipenem or Meropenem can be used as second line drugs.*
Keywords: *Bronchiectasis; Exacerbations ;Bacterial etiology; Antibiotic sensitivity.*

Introduction

Bronchiectasis is defined as abnormal and permanent dilatation of one or more bronchi. As a result of the associated dysfunction of mucociliary clearance, a vicious circle is established involving persistent bacterial colonization, chronic

inflammation of the bronchial mucosa, and progressive tissue destruction.[1] Bronchiectasis is associated with chronic and frequently purulent expectoration, multiple exacerbations, and progressive dyspnoea that can become disabling.[1-3]

Bronchiectasis patients suffer from recurrent acute exacerbations, many requiring hospital admission. Infective exacerbations are the main cause of morbidity in bronchiectasis and leads to utilisation of healthcare resources including hospital admissions for parenteral antibiotic therapy. An exacerbation is defined as having clinical deterioration with all of the following symptoms: increasing cough; increasing sputum volume; and worsening sputum purulence.[4]Acute infective exacerbations due to bacterial pathogens are common and is the important cause of morbidity and mortality in bronchiectasis. During the "stable" status between these exacerbations bacterial pathogens contribute to the continuation of the chronic inflammatory process and progressive lung damage. So identification and appropriate treatment of these organisms is an essential part of the management.[5]

Bronchiectasis is usually associated with increased bacterial load. Usual bacteria are Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus. Among them pseudomonas aeruginosa are a major cause of morbidity and mortality in bronchiectasis .Patients infected with pseudomonas aeruginosa have frequent acute exacerbations.[6]

In bronchiectasis, antibiotics are used during exacerbations in patients with increasing cough, increasing sputum volume and worsening sputum purulence. Assessing the response to antibiotic treatment in the management of such exacerbations is difficult. Presently, a successful result is only qualitative, relying on the patient's subjective judgment of symptom resolution. Validated, easily usable and relevant outcome measures are required.[7] The current treatment options includes the encouragement of bronchial hygiene, the reduction of bronchial inflammation, and use of directed antibiotic treatment aimed at pathogen reduction rather than eradication. These measures can enhance patient quality of life, but neither can reverse bronchial dilation nor cure the underlying pathology.

Data specific for bronchiectasis exacerbations (compared to role of infections in the development of bronchiectasis) are limited. No specific data is available regarding the spectrum of organism responsible for infective exacerbations of bronchiectasis in Kerala especially in Malabar area. The main objective of this study is to determine the range and sensitivity of bacterial pathogens that are isolated from the sputum of patients admitted with infective exacerbations of bronchiectasis.

Identifying the causative organisms and the antimicrobial sensitivity pattern will help in making a treatment protocol for the effective management of infective exacerbations of bronchiectasis.

Materials and Methods

This hospital Based Cross-sectional Observational Study was conducted on patients getting admitted in respiratory medicine wards of a tertiary care teaching hospital in Kerala with exacerbation of bronchiectasis for a period of one year .Patients who received antibiotic therapy in the immediate past , those with other active lung diseases and age less than 18 years were excluded from the study. Fifty two patients were selected according to inclusion and exclusion criteria. Informed consent of patients was taken. Those patients were evaluated starting from history according to pre written questionnaire. General examination and systemic examination were done. Routine investigations and other relevant investigation were done. Early morning sputum samples were collected in a sterile container and sent to microbiology department for Gram staining, Culture and sensitivity and AFB staining. X-ray chest, ECG and finger pulse oximetry was done. Patients were started on empirical antibiotic

therapy after sputum collection and antibiotics were changed after sputum culture and sensitivity report. Patients prognosis were noted based on changes in ; frequency of cough, sputum volume; sputum purulence , finger pulse oximetry value ,systemic inflammatory markers like white cell count(WCC), erythrocyte sedimentation rate (ESR).

Statistical analysis

The data were entered into the Microsoft Office Excel and analysis was done using Statistical Package for Social Sciences (SPSS) version 17. To find out statistical significance of observations made, Fisher's exact test and Chi-square test were done. A P-value of <0.05 was taken as statistically significant.

Results

The age group of the patient in the study ranged from 38 to 81 years. Out of 52 patients, the most common age group was 50 to 59 years (34.6%). The Mean age of the study population was 58.44. In this study 28(54%) were males and 24(46%) were females. 27 (51.9%) patients were smokers and 25 (48.1%) were non-smokers. All the patients had increased cough, increased sputum volume and worsened sputum purulence. 88.5% had breathlessness.76.9% had fever .23.1% had hemoptysis.

Sputum culture and sensitivity yielded pathogenic bacterial growth in 76.9 % of study sample and in 23.1% normal pharyngeal flora yielded. Among the pathogenic organisms isolated gram positive were 12.5% (n=5) gram negative organisms were 87.5% (n=35) (Figure 1). Among the total organisms isolated 30.8% were Pseudomonas aeruginosa (Table 1)

Table 1: Distribution of bacterial flora

Causative Organisms	Frequency	Percentage
Pseudomonas aeruginosa	16	30.8
Klebsiella	11	21.2
Acinetobacter	5	9.6
E.coli	2	3.8
Streptococcus Pneumoniae	3	5.8
Moraxella Catarrhalis	1	1.9
Staphylococcus aureus	2	3.8
Normal pharyngeal flora	12	23.1

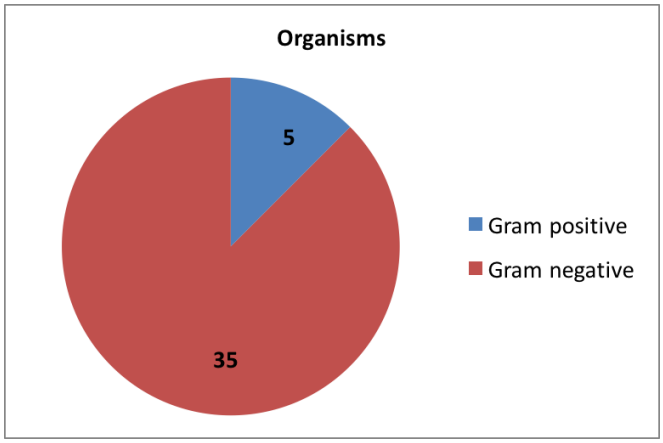

Figure 1: Gram positivity profile

Among the 35 gram negative organisms cultured 45.7% were Pseudomonasaeruginosa and 31.4% were Klebsiella (Figure 2)

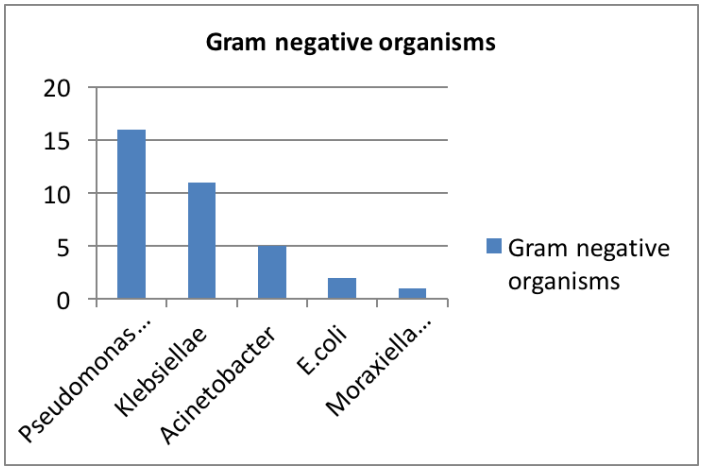

Figure 2: Gram negative organism distribution

Out of 5 gram positive bacteria 3 (60%) were Streptococcus Pneumoniae and 2 (40%) were Staphylococcus aureus

In our study modified Ziehl-Neelsen stain for acid fast bacilli was negative in all cases.In patients with Diabetes Mellitus commonest organism cultured was Pseudomonas aeruginosa (40.9%) followed by Klebsiella (27.3%).In non diabetic patients commonest isolate was normal pharyngeal flora (36.7%) followed by Pseudomonas aeruginosa (23.3%).In patients using immunosuppressive drugs like systemic steroids commonest isolated organism were Pseudomonas aeruginosa (58.8 %) followed by Klebsiella (29.4 %)

Pseudomonas was isolated in 16 subjects. The sensitivity to imipenem was 100% (p value 0.0198) (Table 2).. Sensitivity to ciprofloxacin

among 14 subjects was 100% (p value<0.001). The sensitivity to commonly used antipseudomonal cephalosporin ceftazidime was only 42.8% (p value = 0.0265).

Table 2: Antibiotic sensitivity pattern of pseudomonas

Antibiotics	Sensitivity	Resistance	Total
Cefotaxime	6(42.8%)	8(57.2%)	14
Cefoxitin	2(100%)	0	2
Ceftriaxone	6(42.8%)	8(57.2%)	14
Ceftazidime	6(42.8%)	8(57.2%)	14
Cefepime	2(100%)	0	2
Ofloxacin	0	2(100%)	2
Ciprofloxacin	14(100%)	0	14
Ampicillin+sulbactam	4(28.6%)	10(71.4%)	14
Imipenem	16(100%)	0	16
Meropenem	12(85.72%)	2(14.28%)	14
Piperacillin	10(71.4%)	4(28.6%)	14
Piperacillin+tazobactam	12(85.72%)	2(14.28%)	14
Cotrimoxazole	8(80%)	2(20%)	10
Aztreonam	0	2(100%)	2
Cefoperazone+sulbactam	2(100%)	0	2
Tobramycin	10(71.4%)	4(28.6%)	14
Netilmicin	12(75%)	4(25%)	16
Amikacin	8(50%	8(50%)	16
Tigecycline	8(80%)	2(20%)	10

Klebsiella was highly sensitivity for Imipenem (72.7%) with a p value >0.05 (Table 3). There was 100% resistant for ceftriaxone (p value = 0.0060), cefotaxime, ceftazidime, ofloxacin, ciprofloxacin, ampicillin-sulbactam, cotrimoxazole and aztreonam.

Table 3: Antibiotic sensitivity pattern of klebsiella

Antibiotics	Sensitivity	Resistance	Total
Cefotaxime	0	9(100%)	9
Cefoxitin	2(100%)	0	2
Ceftriaxone	0	11(100%)	11
Ceftazidime	0	9(100%)	9
Levofloxacin	2(66.67%)	1(33.33%)	3
Ofloxacin	0	5(100%)	5
Ciprofloxacin	0	6(100%)	6
Ampicillin+sulbactam	0	7(100%)	7
Imipenem	8(72.7%)	3(27.3%)	11
Meropenem	3(27.3%)	8(72.7%)	11
Piperacillin	4(36.4%)	7(63.6%	11
Piperacillin+tazobactam	4(57.1%)	3(42.9%)	7
Cotrimoxazole	0	9(100%)	9
Aztreonam	0	2(100%)	2
Tobramycin	5(55.6%)	4(44.4%)	9
Gentamicin	0	2(100%)	2
Netilmicin	5(55.6%)	4(44.4%)	92
Amikacin	4(36.4%)	7(63.6%	11
Colistin	2(100%)	0	2
Polymixin	2(100%)	0	2
Tigecycline	2(40%)	3(60%)	5

All the 5 Acinetobacter were resistant to Cefoxitin, ceftazidime, ofloxacin, ciprofloxacin (p value = 0.0081), piperacillin (p value = 0.0411) .Sensitivity to colistin, polymixin, tigecycline was 100%. Resistance to ampicillin-sulbactam, piperacillin-tazobactam, aztreonam, amikacin was 100%.

Mean hospital stay duration for the total study population was 8.06 days, with a Std. Deviation of 2.191. Among the patients with pathological

bacteria isolated maximum hospital stay was for Acinetobacter (9.60 days). Minimum duration was for Streptococcus Pneumoniae (5.67days).

All the patients with Pseudomonas, E coli, streptococcus pneumonia, moraxella, staphylococcus aureus on sputum culture got relieved with treatment.60% cases of Acinetobacter group and 9.09% cases of klebsiella group died during the hospital stay. When we compared both these organism groups with normal pharyngeal flora group using Fisher's exact test, the association was statistically significant for Acinetobacter group (p value=0.015) and not significant for klebsiella group (p value>0.05).

Out of 22 Bronchiectasis patients with Diabetes 3 (13.64%) died. Whereas out of 30 Bronchiectasis patients without Diabetes only 1 (3.33%) died.The increase in mortality among diabetic patients was not statistically significant (Fisher's exact test p value >0.05)

Out of 17 Bronchiectasis patients who are using immunosuppressive drugs 16(94.1%) got relieved and 1(5.9%) died. Whereas out of 35 Bronchiectasis patients who are not using immunosuppressive drugs 32 (91.4%) got relieved and 1 3 (8.6%) died.But these relations between mortality and use of immunosuppressive drugs were not statistically significant (Fisher's exact test p value >0.05).In the total study sample 48 (92.3%) patients improved with appropriate antibiotic treatment and 4 (7.7%) patients died.

Discussion

In this study the most common age group was 50 to 59 years (34.6%). The mean age of cases in the current study was 58.44.This was comparable with another study, conducted by Abdullah Al-Mobeireek et al with a mean age of 60.[10] In another study by Onen ZP et al the mean age was 61.[11] Out of fifty two (52) patients 28(54%) were males and 24(46%) were females which shows not much gender difference in bronchiectasis exacerbation. Most of the males were in older age group (70 to 79 years) compared to females (50 to 59 years).In a study by Finklea JD et al 30.2% were males and 69.2% were females.[12]In another study by MP Murray et al 31.3% were males and 68.7% females.[4]

In the study population 27 patients (51.9%) were smokers and 25 patients (48.1%) were non-smokers. This shows that in our study there is no difference in occurrence of bronchiectasis between smokers and nonsmokers. In the study by Finklea JD et al 33.3% were smokers and 66.7% were non smokers.[12] In a study by MP Murray et al 71.9% were non smokers and 28.1% were smokers.[4]

In present study all the patients had increased cough, increased sputum volume and worsened sputum purulence.88.5% patients had breathlessness.76.9% had fever 23.1% had hemoptysis. In the study by Abdullah Al-Mobeireek, et al all the patients had Increase in sputum quantity and Change in sputum color . Dyspnoea, fever, haemoptysis was present in 70%, 65% and 30% respectively.[10] In a study by Finklea JD et althe most common symptoms associated with exacerbation were change in the characteristics of sputum (88%), increase cough (84%), and increase dyspnea (72%).[12]

In the present study sputum culture showed significant bacterial growth in 76.9% of cases. These results were comparable with previous studies by Kecelj P et al[13], Abdullah Al-Mobeireek et al[10], and K.W.T. Tsang et al[15].

In our study out of 40 pathological bacteria, gram negative (87.5%) were more than gram positive (12.5%). Among the gram negative organisms most common was Pseudomonas aeruginosa (45.7%), and the most common gram positive bacteria was Streptococcus Pneumoniae (60%). Three commonest organisms identified in our study were Pseudomonas aeruginosa in 30.8% cases, Klebsiella in 21.2% cases and Acinetobacter in 9.6 % cases.

In a study by M.P. Murray et al, in 32 exacerbations of Bronchiectasis sputum bacteriology showed P. aeruginosa in 19 Patients (59.3%). In another study by Kecelj P et al, in 33 patients with exacerbation of bronchiectasis,

normal flora in sputum was found in 24% of patients. Most frequent isolates were: P. aeruginosain 30%, H. influenzae in 6%, Streptococcus spp. in 3%, MSSA in 15%, MRSA in 6% of patients. In an another study K.W.T. Tsang et al found out that P. aeruginosa(29.4%) and H. influenza(11.8%) were the commonest pathogens isolated in sputum in exacerbation of bronchiectasis.[15]

In another study conducted prospectively at King Khalid University Hospital (KKUH) and Sahary Chest Hospital in Riyadh by Abdullah Al-Mobeireek et al. Pseudomonas aeruginosa (PA) was the most common organism (43%) isolated followed by Hemophilus influenzae (10%) and Klebsiella spp.[10] In a study by Chan TH et al commonest organism isolated from sputum was Pseudomonas aeruginosa (34%) followed by other Pseudomonas species and Haemophilus influenzae 19%, respectively.[16] In the study by Finklea JD et al commonest organisms were Pseudomonas. Aeruginosa.[12]

Commonest organisms in our study were Pseudomonas aeruginosa which is consistent with previous studies done by M PMurray et al[4], Kecelj P et al[13], K.W.T. Tsang et al[15] and Abdullah Al-Mobeireek et al (Table 4). Our study showed increased growth of Klebsiella and Acinetobacter when compared with previous studies. Growth percentage of gram positive organisms was consistent with previous studies. In our study there was no growth of Haemophilus influenzae, which was conflicting with other previous studies. This may be due to the fastidious nature of Haemophilus influenza which requires supplemented media to isolate. Also Haemophilus influenza may be overgrown by other bacteria.

Table 4: Isolated organism in different studies

Organism	Our Sudy	M P Murray et al[7]	Kecelj P et al[43]	K.W.T. Tsang et al[45]	Abdullah Al-Mobeireek et al[46]
Pseudomonas aeruginosa	30.8%	59.3%	30%	29.4%	43%
Klebsiella	21.2%	0%	3%	0%	5%
Acinetobacter	9.6%	0%	0%	2.9%	1%
Streptococcus Pneumoniae	5.8%	9.4%	3%	2.9%	2%
Staphylococcus aureus	3.8%	6.3%	21%	2.9%	0%
Haemophilusinfluenzae	0%	12.5%	6%	11.8%	10%

In our study modified Ziehl-Neelsen stain for acid fast bacilli was done in all cases and was negative in all cases. In a study by Chan CH et al In 91 patients with bronchiectasis seen over 6 years, a positive mycobacterial culture was obtained in 12 cases (13%).[17] The organisms isolated were Mycobacterium tuberculosis in nine cases, Mycobacterium avium in two cases and Mycobacterium tuberculosis and chelonei were obtained on separate occasions in one case. Whereas M Wickremasinghe et al reported NTM in 2% of their prospective study of 100 patients.[18]

Commonest organism cultured in diabetic patients and those who are using immunosuppressive drugs were Pseudomonas aeruginosa(40.9% and 58.8% respectively) followed by Klebsiella (27.3% and 29.4% respectively).

In our study we found that pseudomonas aeruginosasa was 100% sensitive to Imipenem (p value <0.05) and 87.5% sensitive to meropenem. Among quinolones pseudomonas as 100% sensitive to ciprofloxacin (p value <0.05). Sensitivity of pseudomonas aeruginosasa to Piperacillin-tazobactam was 85.7%.Highest resistance of pseudomonas observed was to Ampicillin sulbactam combination. Susceptibility to Aminoglycosides ranged from 50% (amikacin) to 75% (netilmicin).The sensitivity to commonly used antipseudomonal cephalosporin ceftazidime was only 42.8%(p value = 0.0265).

In our study 72.7% of Klebsiella showed sensitivity to Imipenem. Klebsiella was 100% resistant for 3rd generation cephalosporins (p value <0.05), ofloxacin, ciprofloxacin, ampicillin-sulbactam, cotrimoxazole and aztreonam. When

studied in Two patients Klebsiella showed 100 % Susceptibility to Cefoxitin, Polymixin and colistin .Susceptibility of Klebsiella to piperacillin tazobactam combination was 57.1%.In our study Sensitivity of Klebsiella to aminoglycosides varied from 36.4%(amikacin) to 55.6% (tobramycin).

In present study all the cases of Acinetobacter were resistant to cephalosporins, quinolones and piperacillin (p value <0.05). Sensitivity of Acinetobacter to colistin, polymixin, tigecycline was 100%. Acinetobacter also showed 100 % resistance to ampicillin-sulbactam, piperacillin-tazobactam and aztreonam .Among aminoglycosides sensitivity to tobramycin and netilmicin was 60%, but 100% resistance to amikacin.

In our study mean hospital stay duration was 8.06 days with a maximum of 9.6 days for Acinetobacter and a minimum of 5.67 days for Streptococcus Pneumoniae. Present study showed that mean hospital stay was more in Gram negative group than Gram positive group. In a study by Säynäjäkangas O et al in Finland the average length of stay for bronchiectasis-associated hospitalizations was 7 days.[19]

When comparing association between organism cultured and final outcome it was found that 60% cases of Acinetobacter group (p value <0.05) and 9.09% cases of klebsiella group died during the hospital stay. This showing high mortality rate when infected with Acinetobacter .All the patients with Pseudomonas, Ecoli, streptococcus pneumonia, moraxella, staphylococcus aureus on sputum culture got relieved with treatment.

When we compared final outcome with diabetic status and history of use of immunosuppressant drugs like steroids following facts observed. Among Bronchiectasis patients with Diabetes 13.64% died. Among Bronchiectasis patients without Diabetes only 3.33% died. This shows a high mortality in Bronchiectasis patients with diabetes. Our study showed lower mortality rate (5.9%) in patients with a past history of using immunosuppressant drugs than not using these drugs (8.6%). But both these observations were statistically not significant.

There are some clinical implications from this study. First, antibiotics are still considered a mainstay in the management of infective exacerbations of bronchiectasis. In patients hospitalized with severe infection, Pseudomonas aeruginosa should be considered as a possible pathogen, and antibiotics coverage should, at least initially, include Pseudomonas until information on culture and sensitivity is available. Strains of Psudomonas in this study were sensitive to Piperacillin-tazobactam, Ciprofloxacin and Imipenem.

Conclusion

The commonest organisms causing exacerbatioin of bronchiectasis in our study were gram negative organisms and most common organism isolated was Pseudomonas aeruginosa. Pseudonionas aeruginosa was sensitive to Piperacillin-tazobactam, Ciprofloxacin and Imipenem. So initial empirical antibiotic therapy in severe bronchiectasis can be started with a combination of Piperacillin-tazobactam with Quinolones. Imipenem or Meropenem can be used as second line drugs. Most commonly isolated gram positive organism was Streptococcus pneumonia which was sensitive to both Cefotaxime/Ceftriaxone and Ampicillin/Amoxicillin.The study also shows high mortality rate in patients infected with Acinetobacter.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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