

## Influence of Thoracentesis and Pleural Biopsy on Biochemical Parameters and Cytology of Pleural Fluid

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**OBJECTIVE:** To assess the influence of thoracentesis and pleural biopsy on biochemical parameters and cytology of pleural fluid from patients with lymphocytic exudate.

**PATIENTS AND METHODS:** A prospective, descriptive study was performed in 72 patients with pleural effusion who had lymphocytic exudate and in whom biopsy was indicated. Biochemical variables and cytology of pleural fluid were analyzed at baseline, 48 hours later (immediately prior to biopsy), and 48 hours after biopsy.

**RESULTS:** The patients had a mean (SD) age of 63 (17) years, 57% were smokers, and 61% were men. Effusion was right-sided in 36% of patients, unilateral in 80%, and massive in 21%. The etiology was benign in 43 cases and neoplastic in 29 (40%). Pleural lactate dehydrogenase (LDH) was found to be increased following biopsy. This effect was significant in the overall population of 72 patients (649 [481] U/L just prior to biopsy and 736 [536] U/L 48 hours after biopsy; mean increase, 86 U/L; 95% confidence interval, 45-128 U/L;  $P < .001$ ), in patients with pleural tumors (799 [529] U/L prior to biopsy and 957 [571] U/L 48 hours later,  $P < .001$ ), and in those with LDH concentration greater than 266 U/L.

**CONCLUSIONS:** The results of our study show that a single thoracentesis procedure does not alter biochemical parameters or pleural cytology after 48 hours in lymphocytic exudates. Pleural needle biopsy leads to a significant increase in the concentration of LDH in patients with pleural tumors or higher baseline concentrations of LDH. Thoracentesis, pleural biopsy, or a combination of the two do not lead to significant changes in the number of eosinophils in pleural fluid.

**Key words:** Pleural fluid. Thoracentesis. Pleural biopsy. Eosinophilia.

Influencia de la toracocentesis y la biopsia pleural en la bioquímica y la citología del líquido pleural

**OBJETIVO:** Valorar la influencia de la toracocentesis y la biopsia pleural en la bioquímica y la citología del líquido en los pacientes con un exudado linfocitario.

**PACIENTES Y MÉTODOS:** Se ha realizado un estudio prospectivo y descriptivo de 72 pacientes con derrame pleural que tenían un exudado linfocitario e indicación de biopsia. Se analizaron y compararon la bioquímica y citología del líquido pleural al inicio, a las 48 h de la punción (antes de la biopsia) y a las 48 h de la biopsia pleural.

**RESULTADOS:** Los pacientes tenían una edad media  $\pm$  desviación estándar de 63  $\pm$  17 años, el 57% eran fumadores y el 61%, varones. El derrame era derecho en un 36%, unilateral en un 80% y masivo en el 21%. La etiología era benigna en 43 casos y neoplásica en 29 (40%). La lactatodeshidrogenasa (LDH) pleural aumentó después de la biopsia en el análisis de todos los pacientes (649  $\pm$  481 U/l antes de ésta y 736  $\pm$  536 U/l a las 48 h; aumentó en promedio 86 U/l; intervalo de confianza del 95%, 45-128 U/l;  $p < 0,001$ ), en los pacientes con neoplasia pleural (799  $\pm$  529 U/l de LDH antes de la biopsia y 957  $\pm$  571 U/l a las 48 h;  $p < 0,001$ ) o valores de LDH superiores a 266 U/l.

**CONCLUSIONES:** Nuestro estudio demuestra que una única toracocentesis no modifica los valores de la bioquímica o la citología pleural a las 48 h en los exudados linfocitarios. La biopsia pleural transparietal aumenta de forma significativa los valores de la LDH en los pacientes con neoplasia pleural o valores iniciales de LDH más elevados. La realización de la toracocentesis, la biopsia pleural o ambas técnicas no modifica de forma significativa el número de eosinófilos del líquido pleural.

**Palabras clave:** Líquido pleural. Toracocentesis. Biopsia pleural. Eosinofilia.

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### Introduction

The characteristics and composition of pleural fluid are very useful for the diagnosis, prognostic assessment, and treatment of pleural effusion.<sup>1,2</sup> All of the guidelines on the management of patients with pleural effusion recommend systematic analysis of the cytology and

biochemistry of pleural fluid and indicate that biochemical parameters are essential for differentiation between a pleural exudate and a transudate.<sup>1,3,4</sup> Analysis of pleural fluid is diagnostic in up to 25% of cases but is only of use as a guide in most situations.<sup>5,6</sup> Predominance of neutrophils is indicative of an acute process, eosinophilia is often attributable to the presence of air or blood in the pleural fluid, and an increased percentage of lymphocytes is attributable to longer lasting diseases such as cancer or tuberculosis.<sup>1,2,4,6</sup>

Thoracentesis and pleural needle biopsy are 2 of the most widely used techniques for the study of pleural effusion of unknown etiology.<sup>7,8</sup> In patients with suspected tuberculosis or cancer, it is advisable to repeat the study when a definitive diagnosis is not obtained initially so that more invasive techniques can be avoided.<sup>1,4,9</sup> Pneumothorax, bleeding, pain, or vagal response are the most frequent complications.<sup>4,10</sup> Nevertheless, except for the possible appearance of pleural eosinophilia following thoracentesis, no accurate data are available in the literature on the influence of thoracentesis and pleural needle biopsy on the cytology and biochemistry of pleural fluid in patients who have not received any form of prior treatment.<sup>11,12</sup>

The aim of this study was to assess changes in the cytology and biochemistry of pleural fluid following thoracentesis and pleural needle biopsy in a group of patients with lymphocytic exudate of varying etiology and to assess the importance or clinical significance of those changes. Particular attention was paid to the concentrations of inflammatory markers such as lactate dehydrogenase (LDH) and the presence of eosinophils in the fluid, along with the etiology of pleural effusion.

## Patients and Methods

We undertook a prospective, descriptive study between June 2001 and December 2004 in a group of 72 consecutive patients who were admitted to a tertiary level hospital with pleural effusion and were selected based on a series of inclusion and exclusion criteria. Patients were included in the study if thoracentesis and pleural needle biopsy were indicated and no examinations or procedures had been performed in the previous 30 days. The following exclusion criteria were applied: failure to provide signed informed consent, pleural fluid inconsistent with lymphocytic exudate, contraindications for thoracentesis or pleural needle biopsy,<sup>13</sup> need to initiate any form of intervention for the purpose of treating the pleural effusion or that could affect its characteristics prior to completion of the study, suspicion of trauma during thoracentesis, and insufficient fluid obtained for all analyses. Trauma during thoracentesis was diagnosed by extraction of blood in nonsanguineous fluids, presence of blood clots in the extracted fluid, or intermittent aspiration of serosanguineous fluid. The same biochemical analyses were performed in samples of circulating blood within 24 hours of obtaining all pleural fluid samples.

### Techniques and Parameters Analyzed

Thoracentesis was performed with patients in a sitting position and local anesthetic was administered with a 10-mL syringe (2% mepivacaine chlorohydrate without vasoconstrictor, Scandibsa, Inbsa SA, Barcelona, Spain). Three different 20-mL syringes were used to obtain a 60-mL sample for biochemistry (proteins, glucose, LDH, cholesterol, triglycerides, amylase, and adenosine

deaminase), microbiological analysis (smear test and culture), and cytology. Local anesthesia was performed with 3 to 4 mL of local anesthetic injected into the skin and intercostal space up to the level of the parietal pleura, without crossing the pleura or injecting anesthetic into the pleural cavity at any point during the procedure. The syringe containing the anesthetic was then discarded to prevent interferences.<sup>14,15</sup> Samples of 2 to 3 mL of pleural fluid were immediately transferred to heparinized syringes (3 mL syringe for arterial blood samples containing 200 units of heparin and a 22-gauge needle; Quick ABG, ref 4022, Marquest Medical Products, Englewood, Colorado, USA) for analysis of pH. The presence of residual air bubbles was avoided by removing a portion of the transferred liquid prior to sealing the syringe and only opening it once at the time of analysis. Pleural needle biopsy was also performed with the patient in a seated position using an Abrams needle and the same local anesthesia as for thoracentesis. In all cases, between 5 and 6 biopsies were obtained that were processed for microbiological and histologic analysis.<sup>16</sup>

Thoracentesis was performed on 3 occasions in all patients to analyze biochemical and cytologic parameters of pleural fluid: at baseline, at the beginning of the study; at 48 hours, coinciding with pleural needle biopsy; and 48 hours after pleural needle biopsy. The second thoracentesis was performed prior to needle biopsy using the same procedure as in the other thoracenteses. A chest radiograph was obtained in all patients 6 hours after pleural needle biopsy to rule out possible complications that would interfere with the final measurement.

### Statistical Analysis

A descriptive analysis of the main characteristics of the patients and the pleural effusion was performed along with independent analyses of each of the 3 measurement groups (percentages and means [SD]): initial or baseline (Group 1), at 48 hours along with pleural needle biopsy (Group 2), and final measurement (Group 3). The means of the values obtained for biochemical and cytologic variables in pleural fluid were compared after determining whether the data was normally distributed. Data that followed a normal distribution were compared with the Student-Fisher *t* test for repeated means (*t* test for paired data) and in data that was not normally distributed comparisons were made using the Wilcoxon nonparametric test. The mean differences between the parameters analyzed in the different measurements were calculated along with their confidence intervals (CI). The presence of a linear trend or association was calculated by multiple comparisons when the variances were homogeneous. Later, the same comparative analysis was performed considering the etiology and pleural LDH concentration. The cut points analyzed to group the patients according to LDH concentration were the 25th, 50th, and 75th percentiles (interquartile range). All statistical calculations were carried out using SPSS, version 11.0. Statistical significance was established at  $P \leq .05$ .

## Results

Table 1 shows the main characteristics of the patients and pleural effusions studied. The pleural tumors included 3 malignant mesotheliomas and 26 metastases (16 from the lung, 4 from the breast, 2 from the stomach, 1 from the ovary, 1 from the pancreas, 1 from a lymphoma, and 1 of unknown origin). The etiology of the nonneoplastic effusions included 27 nonspecific effusions, 10 cases of tuberculosis, and 3 cases of effusion following cardiac surgery; the remainder were individual cases of amyloidosis, hypothyroidism, and yellow nail syndrome.

TABLE 1  
Main Characteristics of the Patients and Pleural Effusions\*

	Total	Neoplastic	Nonneoplastic
Patients	72	29 (40%)	43 (60%)
Mean age, y	63 (17)	64 (12)	62 (19)
Men	44 (61%)	12 (41%)	32 (74%)†
Karnofsky score	76 (13)	68 (14)	81 (10)†
Smokers	41 (57%)	15 (52%)	26 (61%)
Right-sided effusion	26 (36%)	14 (48%)	12 (28%)
Unilateral effusion	57 (79.2%)	24 (83%)	32 (74%)
Massive effusion	15 (21%)	12 (41%)	10 (23%)†
Effusion 1/3 of hemithorax	22 (31%)	3 (10%)	19 (42%)†
pH	7.33 (0.1)	7.31 (0.1)	7.36 (0.1)
Glucose, mg/dL	94 (36)	81 (35)	102 (34)†
Proteins, mg/dL	4.5 (0.9)	4.5 (0.6)	4.4 (1.0)
Lactate dehydrogenase, U/L	607 (422)	719 (457)	531 (384)†
Cholesterol, mg/dL	86 (23)	86 (14)	86 (28)
Amylase, U/L	133 (86)	242 (487)	60 (36)†
Triglycerides, mg/dL	36 (21)	38 (21)	35 (22)
Adenosine deaminase, U/L	23 (18)	19 (11)	26 (22)
Platelets per $\mu$ L	71 287 (76 695)	74 819 (107 246)	68 904 (212 360)
Leukocytes per $\mu$ L	2031 (1953)	1437 (1151)	2432 (2271)†

\*Data are shown as number of patients (%) or means (SD).

† $P < .05$  between neoplastic and nonneoplastic etiology.

TABLE 2  
Biochemical and Cytologic Analysis in Pleural Fluid From the 3 Thoracenteses Performed in the 72 Patients Included in the Study\*

	Group		
	1	2	3
pH	7.33 (0.1)	7.33 (0.1)	7.34 (0.1)
Glucose, mg/dL	94 (36)	90 (36)	90 (34)
Proteins, mg/dL	4.5 (0.9)	4.5 (0.8)	4.4 (0.9)
Proteins, PBR	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
LDH, U/L	607 (422)	649 (481)	736 (536)†
Median	521.5	521.5	537
LDH, PBR	1.9 (1.4)	2 (1.6)	2.3 (1.8)†
Cholesterol, mg/dL	86 (23)	86 (23)	87 (24)
Amylase, U/L	133 (86)	130 (100)	127 (113)
Triglycerides, mg/dL	36 (21)	36 (21)	39 (26)
Adenosine deaminase, U/L	23 (18) 2	4 (19)	24 (23)
Platelets per $\mu$ L	71 287 (76 695)	76 539 (74 477)	79 500 (76 258)
Leukocytes per $\mu$ L	2031 (1953)	1785 (1948)	1772 (1805)
Lymphocytes per $\mu$ L	1546 (1559)	1363 (1521)	1460 (1561)
Eosinophils per $\mu$ L	120 (212)	110 (287)	102 (216)
Eosinophils, %	2.7 (13)	2.1 (10)	2.3 (10)
No. of cases with eosinophils >10%	4	3	5
Absence of eosinophils, %	92	90	90

\*Data are expressed as mean (SD) unless otherwise indicated. Group 1, initial measurements. Group 2, measurements at 48 hours, immediately prior to biopsy. Group 3, measurements 48 hours after biopsy. PBR indicates pleural to blood ratio; LDH, lactate dehydrogenase.

† $P < .05$  compared with the previous group.

Table 2 shows the values obtained and the comparative analysis of the biochemical and cytologic data from the 3 thoracenteses. Pleural LDH concentration was the only variable for which significant increases were observed following pleural biopsy. LDH concentration in Group 3 increased by 86 U/L compared with Group 2 (95% CI, 45-128;  $P < .001$ ) and by 130 U/L compared with Group 1 (95% CI, 66-192;  $P < .001$ ). LDH concentration in Group 2 increased by a mean of 43 U/L compared with Group 1 (95% CI, 1.2-87;  $P = .06$ ). The mean ratio of pleural fluid to peripheral blood concentrations of

LDH in Group 3 was 0.24 higher than in Group 2 (95% CI, 0.08-0.4;  $P = .003$ ) and 0.37 higher than in Group 1 (95% CI, 0.14-0.59;  $P = .001$ ). The ratio in Group 2 increased by a mean of 0.13 compared with Group 1 (95% CI, 0.01-0.3;  $P = .8$ ). A positive linear relationship was observed between pleural LDH concentration and thoracentesis ( $F = 4.5$ ,  $P = .035$ ). Pleural needle biopsy maintained this linear tendency and introduced an exponential component seen in the greater increase ( $F = 6.4$ ,  $P = .04$ ). The other parameters analyzed, including the percentage or number of eosinophils, did not show

TABLE 3  
Lactate Dehydrogenase Concentration and Eosinophils in Pleural Fluid From Patients With or Without Pleural Tumors\*

Etiology	Group		
	1	2	3
Neoplastic			
LDH, U/L	719 (457)	799 (529)	957 (571)†,‡
Median	591	594	879
LDH, PBR	2.1 (1.3)	2.4 (1.6)	2.8 (1.7)†,‡
Eosinophils per $\mu$ L	0	0	25 (10)
Eosinophils, %	0	0	1.3 (2)
No. of cases with eosinophils >10%			
> 10%	0	0	2
Absence of eosinophils	100%	100%	93%
Nonneoplastic			
LDH, U/L	531 (384)	549 (423)	587 (459)†
Median	418	411	428
LDH, PBR	1.7 (1.4)	1.8 (1.6)	1.8 (1.7)
Eosinophils per $\mu$ L	171 (293)	202 (159)	175 (169)
Eosinophils, %	4.5 (17)	3.5 (14)	3.3 (12)
No. of cases with eosinophils >10%			
>10%	4	3	3
Absence of eosinophils	86%	84%	88%

\*Data are expressed as mean (SD) unless otherwise indicated. Group 1, initial measurements. Group 2, measurements at 48 hours, immediately prior to biopsy. Group 3, measurements 48 hours after biopsy. LDH indicates lactate dehydrogenase; PBR, plasma to blood ratio. † $P \leq .05$  between groups 1 and 2; ‡ $P \leq .05$  between groups 2 and 3.

a significant linear or exponential relationship following either technique.

Stratification of the patients according to the presence or absence of neoplastic etiology did not reveal statistically significant differences in cytologic or biochemical parameters of pleural fluid, with the exception of LDH (Table 3).

Pleural LDH concentration showed a significant increase following pleural needle biopsy in patients with cancer. In patients with or without tumors, LDH concentration increased following both thoracentesis and biopsy (comparing Groups 1 and 3). Analysis of patients with effusion of nonspecific etiology or caused by tuberculosis showed values and changes similar to other patients without pleural tumors.

Changes in biochemical and cytologic variables were analyzed after grouping effusions according to initial concentration of LDH. The following were chosen as cut points: LDH concentration of 266 U/L (25th percentile), 521 U/L (50th percentile), and 759 U/L (75th percentile). No significant changes were observed in cytologic or biochemical parameters following thoracentesis and/or pleural needle biopsy, with the exception of LDH concentration (Table 4). In all subsets of patients, the LDH concentration increased following both procedures. LDH concentration was significantly higher following pleural needle biopsy in all cases except those in whom the initial concentration of LDH was less than 266 U/L. Analysis of the medians confirmed that the increase in LDH

TABLE 4  
Pleural Lactate Dehydrogenase Concentrations According to Initial Concentration\*

	Group		
	1	2	3
<i>LDH &lt; 266 U/L</i> (n=18)			
LDH, U/L	210 (50)	225 (46)	287 (167)†
Median	223.5	224.5	260.5
LDH, PBR	0.7 (0.3)	0.8 (0.3)	0.9 (0.5)†
<i>LDH <math>\geq</math> 266 U/L</i> (n=54)			
LDH, U/L	739 (409)	794 (473)	886 (534)†,‡
Median	596	623	798
LDH, PBR	2.3 (1.4)	2.5 (1.6)	2.7 (1.8)†,‡
<i>LDH &lt; 521 U/L</i> (n=36)			
LDH, U/L	289 (101)	330 (250)	398 (291)†,‡
Median	268	275	348
LDH, PBR	0.9 (0.4)	1.1 (0.9)	1.3 (1)†,‡
<i>LDH <math>\geq</math> 521 U/L</i> (n=36)			
LDH, U/L	924 (380)	969 (444)	1074 (512)†,‡
Median	752	799	984
LDH, PBR	2.8 (1.4)	2.9 (1.6)	3.2 (1.8)†,‡
<i>LDH &lt; 759 U/L</i> (n=54)			
LDH, U/L	398.4 (179)	432 (160)	517 (331)†,‡
Median	367	384	419
LDH, PBR	1.3 (0.7)	1.4 (1)	1.7 (1.2)†,‡
<i>LDH <math>\geq</math> 759 U/L</i> (n=18)			
LDH, U/L	1233 (304)	1302 (394)	1391 (501)†,‡
Median	1236	1275	1299
LDH, PBR	3.7 (1.3)	3.9 (1.6)	4.1 (2)

\*Data are expressed as means (SD) and medians. Group 1, initial measurements; Group 2, measurements at 48 hours, immediately prior to biopsy; Group 3, measurements 48 hours after biopsy. LDH indicates lactate dehydrogenase; PBR, plasma to blood ratio. † $P \leq .05$  between Groups 1 and 2. ‡ $P \leq .05$  between groups 2 and 3.

concentration in the final measurement was greater with increasing initial LDH concentrations until values above 759 U/L were achieved, after which point the increase was more moderate.

## Discussion

In our study, LDH concentration was the only variable that displayed a significant increase at 48 hours after pleural needle biopsy in a group of patients with lymphocytic exudate of differing etiology. Serial measurement of the influence of thoracentesis and pleural needle biopsy showed that there are no significant changes in the cytology or biochemistry of pleural fluid from thoracentesis and that LDH concentration increases following biopsy in patients with pleural tumors or initial concentrations of LDH greater than 266 U/L.

In the diagnosis of pleural effusion of unknown cause it is recommended that 3 serial cytologic analyses be performed as well as a pleural needle biopsy, as was the case in our study.<sup>1,17-19</sup> Thoracentesis and pleural needle

biopsy lead to a limited number of complications associated with the technique or the cause of the effusion.<sup>10,20</sup> In addition, it is unclear whether these techniques can alter the biochemistry and/or cytology of the pleural fluid.<sup>1,2,12</sup> According to available data, most authors have confined analysis to pleural eosinophilia and only 2 studies have considered the influence of thoracentesis on the biochemistry of the pleural fluid (PubMed search, 1966-2006).<sup>21-24</sup> Paya et al,<sup>23</sup> who performed a prospective study in a small group of patients with pleural transudate due to heart failure prior to initiation of treatment, ruled out the presence of significant changes in the biochemistry of the pleural fluid after 3 thoracenteses performed at intervals of 2 hours. Chung et al<sup>24</sup> analyzed a group of 26 patients with symptomatic pleural tumors in whom 3 thoracenteses were performed with collection of up to 500 mL of fluid for relief of dyspnea, with an interval of 24 hours between procedures and without use of pleural needle biopsy. That group only observed an increase in the concentration of cytokines, in fibrinolytic activity, and in neutrophil count, and confirmed the possibility of an inflammatory effect due to repetition of thoracentesis with aspiration of pleural fluid. Our study is the only one in the literature to date to have assessed changes in the biochemistry of pleural fluid following diagnostic thoracentesis and pleural needle biopsy in untreated patients with lymphocytic exudate of differing etiology. The results show that only pleural needle biopsy leads to an increase in LDH concentration.

Pleural LDH is one of the main indicators of the degree of inflammation and is very useful for differentiating between pleural exudate and transudate.<sup>2,4</sup> Increased LDH concentration during serial measurements is an indicator of progression or worsening of the condition, and it obliges the use of more invasive diagnostic procedures and initiation of treatment.<sup>4,25</sup> However, the results of our study demonstrate that an increase in pleural LDH concentration or the ratio of pleural fluid to circulating blood concentrations can also occur when measured 48 hours after pleural needle biopsy in some patients in whom rapid progression of the disease is unexpected. LDH concentration would increase following pleural needle biopsy in patients with pleural tumors, initial concentrations of LDH above 266 U/L, and following both procedures irrespective of the etiology or initial concentration of LDH. It is likely that, unlike in transudates, fluid with a higher LDH concentration is associated with greater pleural inflammation and sensitivity to manipulation.<sup>7,8,23,24</sup> Thoracentesis or needle biopsy performed in pleura with a higher degree of inflammation would generate a more pronounced increase in the final LDH concentration, although our results also indicate that in the most inflamed pleura (LDH>759 U/L) these variations would not be so marked. The possibility that temporal changes in the pleural effusion itself influence the cytology and biochemistry cannot be definitively ruled out. However, we believe that this is highly unlikely given the absence of other procedures, the short time interval employed, the selection of the etiology of the effusions, and the absence of treatment during the study period.

Cytology performed in all of the samples revealed no significant changes in the number of platelets, total leukocytes, lymphocytes, neutrophils, or eosinophils. Pleural eosinophilia or the presence of a percentage of eosinophils of at least 10% in the pleural fluid is rare and, in most cases, secondary to the presence of blood or air in the pleura of patients with pneumothorax and 1 or more thoracenteses or pleural procedures.<sup>4,11,26,27</sup> Its true cause is unknown but is commonly attributed to contact of the pleura with unusual or external elements that act as nonspecific irritants.<sup>21,28</sup> However, an updated literature review did not reveal conclusive data on the presence of eosinophilia following these procedures, as shown in our study and in contrast to the situation that occurs with pneumothorax.<sup>29</sup> Aside from its etiology or the initial concentrations of pleural LDH, these results even reflect a general trend towards a reduction in the number of eosinophils and rule out the possibility that thoracentesis and pleural needle biopsy, separately or together, should be considered an important risk factor for pleural eosinophilia. Our findings with a limited number of procedures are consistent with those of other recent or older case series in which a larger number of thoracenteses or pleural needle biopsies were analyzed retrospectively.<sup>11,30</sup> These types of procedure, which are more or less invasive for the pleura, and the possibility of air or traces of blood entering the samples would not explain the systematic presence of eosinophilia or the benign nature of its presence, and would oblige further analysis to rule out other possible causes that are usually considered less frequent.<sup>22</sup>

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