Urokinase Versus VATS for Treatment of Empyema: A Randomized Multicenter Clinical Trial

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**KEY WORDS**

children, empyema, fibrinolitics, parapneumonic effusions, randomized clinical trial, urokinase, VATS, video-assisted thoracoscopic surgery

**ABBREVIATIONS**

IQR—interquartile range
UK—urokinase
VATS—video-assisted thoracoscopic surgery

Drs Marhuenda, Fuentes, and Moreno-Galdó were responsible for the study concept and design, data acquisition, data analysis and interpretation, and drafting of the manuscript; Dr Barceló was responsible for the study concept and design and acquisition of data; Drs Guillén, López, and García-Casillas were responsible for data acquisition; Drs Cano, Hernández, Pérez-Yarza, Matute, and Álvarez were responsible for and coordinated data acquisition at 1 of the 6 sites. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; they were all responsible for critical revision of the manuscript for important intellectual content; and all approved the final manuscript as submitted.

The trial was registered with the European Clinical Trials Database (2007-003416-61) before enrolling patients in this study.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-3935

doi:10.1542/peds.2013-3935

Accepted for publication Aug 5, 2014

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Empyema is the most frequent suppurrative complication of bacterial pneumonia in childhood. As a parapneumonic effusion progresses, fibrin and cellular detritus accumulate, the purulent fluid becomes sepetated, and a thick peel forms over the visceral and parietal pleura. Parapneumonic pleural effusion is thus classified into 3 stages of progression: exudative (stage 1), fibrinopurulent (stage 2), and organizational (stage 3). An estimated 0.6% to 2% of pneumonia cases in children are complicated by empyema. Since the 1990s, there has been a considerable worldwide increase in the incidence of empyema, with rates reaching 28.3% to 53% of all patients hospitalized for pneumonia. In Spain, an increase from 1.7 to 8.5 cases/100,000 children has been documented. The 2 historical pillars of treatment of empyema are antibiotics and drainage of the purulent fluid by chest tube placement. However, in advanced stages of the condition, this approach is associated with lengthy hospital stays and high failure rates. In addition to thoracotomy, less invasive treatments have been examined: fibrinolytic agents instilled into the pleural space and video-assisted thoracoscopic surgery (VATS). The aim of both these approaches is to break up the septa, extract or fluidize the fibrin and cellular detritus, and thus restore normal function of the mechanisms of pleural reabsorption, making a quick recovery possible.

Two randomized controlled pediatric clinical trials have been published comparing the effectiveness of fibrinolytic agents versus saline serum. Thomson et al found that administration of urokinase significantly reduced hospital stay and was associated with a low failure rate (7%), whereas Singh et al found no clinical benefit. In several pediatric series of empyema, VATS has been successfully used as salvage therapy or as the initial treatment, resulting in earlier and more complete resolution of empyema and shorter hospitalization than with chest tube drainage alone.

The small numbers of pediatric studies comparing VATS and fibrinolytic agents as the initial therapy for parapneumonic empyema have concluded that the 2 treatments are equivalent. One of these studies, however, was a retrospective review of a hospital experience, and the other 2 are clinical trials that included some patients with empyema without septations. In another clinical trial, which included children with empyema originating from various causes, VATS was compared with streptokinase treatment. The authors reported similar success rates with the 2 methods and some advantages with the use of VATS. To further evaluate the relative merits of these treatment modalities, the present trial was conducted to compare VATS versus urokinase instillation in a cohort of patients with septated empyema.

METHODS

The project was approved by the ethics committees of all the participating hospitals, as well as the Spanish Agency of Medicines and Medical Devices. Parental written informed consent, and consent of the children when applicable, was obtained from all participants.

Study Design and Sample Size

This study was a randomized, multicenter, open-label, parallel-group, pilot clinical trial, performed over 2 years at 6 Spanish university hospitals (Table 1). The study compared 2 treatments for parapneumonic empyema. Sample size was first calculated based on preliminary results from a previous series of patients treated by the principle investigator in Hospital Universitari Vall d’Hebron (Barcelona, Spain) between 2001 and 2005. During that period, 58 patients with complicated effusion were treated: 33 with the use of VATS and 25 by using urokinase instillation. Mean postoperative hospital stay was 12.72 ± 7.04 days in the VATS group and 14.16 ± 7.19 days in the urokinase group. These data suggested that there would be no significant differences in the duration of hospitalization between the groups. However, an equivalence test of means by using 2 one-sided tests on data from a parallel-group design to achieve 80% power at a 5% significance level, and considering equivalence limits of −1.50 and 1.50, would have had to include 378 patients in each group. We considered it unfeasible to recruit such a large number of children; hence, a pilot clinical trial without formal calculation of the sample size was conducted. Also based on our previous experience, the recruitment period was established at 2 years under the assumption that that period of time would suffice to enroll a larger number of patients than had been included in previous studies.

<table>
<thead>
<tr>
<th>Center</th>
<th>No. of Patients Per Participating Center</th>
<th>No. of Patients Randomized to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Vall d’Hebron (Barcelona)</td>
<td>75</td>
<td>66</td>
</tr>
<tr>
<td>Hospital Doce de Octubre (Madrid)</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Hospital La Paz (Madrid)</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Hospital Gregorio Marañón (Madrid)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hospital Donostia (San Sebastián)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Hospital Central de Asturias (Oviedo)</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
<td>105</td>
</tr>
</tbody>
</table>
drainage (Table 2), and sonographic features of complicated effusion were considered candidates for enrollment. Complicated effusion was defined as hyperechoic fluid with fibrinous septa (sonographic stage 2) or hyperechoic loculations with or without thick parietal peel (sonographic stage 3).10,28

Exclusion criteria are summarized in Table 3. Diagnostic thoracentesis with no attempt at evacuating the effusion was not a reason for exclusion.

**Determinations**

All patients underwent determination of hemoglobin, white blood cell count, platelets, and C-reactive protein in blood, and white blood cell count, pH, lactate dehydrogenase, and glucose in pleural fluid. Blood and pleural fluid cultures were performed, and *Streptococcus pneumoniae* was investigated in pleural fluid by using antigen detection or polymerase chain reaction assay.

Patients were followed up for 3 months after hospital discharge, with chest radiographs at each visit. In each center, chest radiographs were assessed by a radiologist blinded to the outcome parameters. The radiographs were classified as normal, showing small changes, or showing considerable pleural thickening.

**Randomization**

Patients were randomly allocated to receive 1 of the 2 treatments. The computer-generated randomization sequence was stratified according to center and had varying block sizes to ensure balance in the number of patients per group. Once the informed consent was signed, the attending physician accessed a Web platform and obtained the treatment assigned to each new patient. Allocation was carried out at a 1:1 ratio. Treatment was not blinded.

**Treatment Protocol**

Patients were randomized to receive either VATS debridement or urokinase instillation. It was recommended that VATS be conducted by experienced surgeons or by a resident under the direct supervision of a senior surgeon. The aim of VATS was to break the fibrin septations, aspirate the purulent fluid, and abundantly irrigate the empyema cavity. After the procedure, 1 or 2 chest tubes were left in place.

In patients receiving urokinase treatment, 12F to 14F chest tubes were used, and the insertion site was previously selected by using sonography. The pleural fluid was first drained, and urokinase was then instilled into the pleural cavity through the chest tube. Ten milliliters of a 1000 IU/mL solution of urokinase in children aged <1 year and 40 mL in older children was administered every 12 hours for 3 days.14,26 After instillation, the chest tube was clamped for 4 hours. It was then unclamped and connected to a suction system at –20 cm H2O for 8 hours, until the next dose of urokinase was administered. In both treatment groups, chest tubes were removed when the drainage volume was <40 to 60 mL/24 h.

Antibiotic treatment recommendations were not included in the study protocol. It was assumed that patients would receive empiric treatment with antibiotics covering the spectrum of the most common microorganisms in our setting, with subsequent treatment adjustment based on microbiology results. After removal of the chest tube, antibiotic treatment could be administered orally, provided that the patient had been afebrile (≤37.5°C) for 24 hours. Patients could be discharged if they had been afebrile for at least 24 hours with oral treatment (suggested discharge criteria).

Persistent fever (≥38°C) for >4 days after either of the study treatments, associated with persistent purulent pleural collections on ultrasound, was considered treatment failure. In cases of failure, salvage treatment was performed, which was individually determined by the attending physician according to the needs of each patient.

**Outcome Measures**

The postoperative length of hospitalization was the primary outcome variable, defined as the number of days hospitalized, starting from the day of the intervention to discharge. The secondary outcomes were the total number of days hospitalized (including the days before initiating treatment), days the chest tube was in place, days the patient had fever after treatment, failure rate of the assigned treatment, and treatment-related complications.

**Statistical Analysis**

Due to the multicenter nature of the study, demographic characteristics of the children in the 2 treatment groups were compared by using the Wilcoxon rank-sum stratified test (van Elteren test) for quantitative variables and the Cochran-Mantel-Haenszel test for categorical
variables. Differences between median results with their confidence intervals were calculated by using the Hodges-Lehmann method, adjusting for center clustering. Statistical significance was set at a P value of <.05. Data were analyzed by using SAS version 9.2 (SAS Institute, Inc, Cary, NC) and Stata version 13.1 (StataCorp, College Station, TX). An intention-to-treat analysis was applied, including all randomized patients who received the assigned treatment.

RESULTS
Over the study period (July 1, 2008–June 30, 2010), 149 patients were assessed as candidates for the trial. Forty-four patients were excluded before randomization for the following reasons: declined to participate (n = 20), did not meet selection criteria (n = 12), and other reasons (n = 12). Thus, 105 patients were randomized to treatment: 53 in the VATS group and 52 in the urokinase group. All patients in the VATS group received the allocated treatment. Another patient was erroneously randomized twice and received the first treatment assigned (VATS). Thus, 53 patients in the VATS group and 50 patients in the urokinase group were analyzed. The 2 populations were comparable in terms of baseline characteristics (Table 4).

Primary End Point
The median length of postintervention hospitalization was 10 days in patients undergoing VATS (interquartile range [IQR]: 7–13) and 9 days in those undergoing urokinase instillation (IQR: 8–12). There were no significant differences between groups (Table 5).

Secondary End Points
No significant differences were found for total hospital stay, with a median of 14 days (IQR: 10–18) in the VATS group and 13 days (IQR: 10–18) in the urokinase group (P = .60), or duration of fever after treatment (4 days [IQR: 2–7] with VATS versus 6 days [IQR: 3–7] with urokinase; P = .62) (Table 5). The chest tube was retained longer in patients receiving urokinase (5 days) than in those undergoing VATS (4 days) (P < .001). Eight (15.1%) patients treated with VATS and 5 (10%) treated with urokinase required another procedure to resolve empyema and were considered treatment failures; these differences were not significant. Analysis of potential factors predisposing to failure (gender, age, duration of symptoms, and days of antibiotic treatment before the procedure) yielded no predisposing factors in either group. Reinterventions are shown in Table 6.

Microbiology Findings
In 40 (75%) patients from the VATS group and 34 (68%) from the urokinase group, S pneumoniae was identified as the cause of pneumonia (P = .51).

Adverse Events
Forty-three (81.1%) patients in the VATS group and 41 (82%) in the urokinase

<table>
<thead>
<tr>
<th>TABLE 4 Baseline Characteristics of the Participants</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>-----------------------</td>
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<tr>
<td>Male gender, n (%)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
</tr>
<tr>
<td>Symptoms before diagnosis, median (IQR), d</td>
</tr>
<tr>
<td>Symptoms before intervention, median (IQR), d</td>
</tr>
<tr>
<td>Oxygen requirement, n (%)</td>
</tr>
<tr>
<td>Blood parameters</td>
</tr>
<tr>
<td>Hemoglobin, median (IQR), g/dL</td>
</tr>
<tr>
<td>LDH, median (IQR), IU/L</td>
</tr>
<tr>
<td>pH, median (IQR)</td>
</tr>
<tr>
<td>Glucose, median (IQR), mg/dL</td>
</tr>
<tr>
<td>CRP, median (IQR), mg/dL</td>
</tr>
<tr>
<td>Pleural fluid characteristics</td>
</tr>
<tr>
<td>VD, median (IQR), IU/L</td>
</tr>
<tr>
<td>Leukocyte count, median (IQR), ×10^9/L</td>
</tr>
<tr>
<td>Platelets, median (IQR), ×10^9/L</td>
</tr>
<tr>
<td>CRP, median (IQR), mg/dL</td>
</tr>
<tr>
<td>CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell count.</td>
</tr>
</tbody>
</table>

| TABLE 5 Results for the Primary and Secondary Study Outcomes |
|-----------------|-----------------|-----------------|
| Outcome         | VATS (n = 53)   | Urokinase (n = 50) |
| Primary outcome |                 |                  |
| PO hospital stay, median (IQR), d | 10 (7–13) | 9 (8–12) | 0 (–1 to 1) | .45 |
| Secondary outcomes |               |                  |
| Total hospital stay, median (IQR), d | 14 (10–16) | 13 (10–18) | 0 (–2 to 2) | .60 |
| Chest tube in place, median (IQR), d | 4 (3–5) | 5 (4–6) | –1 (–2 to –1) | <.001 |
| PO fever, median (IQR), d | 4 (2–7) | 6 (3–7) | –1 (–2 to –1) | .62 |
| Failure rate, n (%) | 8 (15.1) | 5 (10) |                  |

CI, confidence interval; PO, postoperative.
changes in 66.7% (24 of 36) of VATS-treated patients and 59.5% (25 of 42) of those receiving urokinase ($P = .40$).

**DISCUSSION**

The present study is the third randomized clinical trial in children that compared VATS and fibrinolytic agents as alternative treatments for parapneumonic empyema. In addition, it is the first multicenter study and the first to exclusively include patients with septated empyema.

The results show that urokinase instillation is as effective as VATS as the initial therapy for treating septated pleural empyema. There were no significant differences between the 2 groups in the length of postoperative hospitalization (ie, the main outcome measure). Furthermore, the only difference found among all the variables studied was the fact that the chest tube was in place longer in the urokinase group. The study design, which required urokinase instillation through the tube for 3 days, may have resulted in bias regarding this variable. Nonetheless, this required use did not lead to lengthier postoperative hospitalization in the urokinase group.

Our results support the notion that initial treatment of purulent pleural effusion in children with VATS or urokinase instillation speeds pus drainage and recovery and, therefore, shortens hospital stay and duration of chest tube placement. In a meta-analysis by Avansino et al.,$^{29}$ the mean hospital stay of 3418 patients was 18 days in our series, but we believe the main reason is possible differences in pediatric population.

Two previous randomized clinical trials involving fibrinolytic agents and VATS have been conducted in children. The first of these, reported by Sonnappa et al. in 2006, included 60 patients and compared VATS with urokinase instillation,$^{26}$ whereas the second, reported by St Peter in 2009 and including 36 patients,$^{27}$ compared VATS with instillation of alteplase. Both studies were performed in a single center and had similar designs.

Follow-up

Clinical and radiologic follow-up for 3 months after hospital discharge was possible in 36 (67.9%) patients in the VATS group and 42 (84%) in the urokinase group ($P = .28$). At the 3-month visit, radiologists considered chest radiographs normal or showing only small group had no treatment- or pneumonia-related complications.

The treatment-related complications encountered were minor, except for a severe bronchospasm requiring tracheal intubation and mechanical ventilation in 1 urokinase-treated patient and a bronchopleural fistula in 1 patient who underwent VATS. There were no bleeding complications in the urokinase group. Complications considered to be related to the patients' pneumonia included 2 bronchopleural fistulas in the VATS group and 1 bronchopleural fistula in the urokinase group, all occurring in patients who had necrotizing pneumonia or a pulmonary abscess (Table 7). There were no deaths.

**TABLE 6** Reinterventions According to Treatment Group

<table>
<thead>
<tr>
<th>Reintervention</th>
<th>VATS Group</th>
<th>Urokinase Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VATS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Chest drain</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

**TABLE 7** Treatment and Pneumonia-Related Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>VATS (n = 53)</th>
<th>UK (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Extravasation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea and pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung abscess</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal insufficiency/nephritic syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Although the design of the present study is very similar to the study of Sonnappa et al.,$^{26}$ there are 2 main differences. First, our study included patients with parapneumonic pleural effusion in sonographic stages 2 and 3 but not those with anechoic, nonseptated effusion (stage 1), who accounted for 16 patients in the study of Sonnappa et al. The second difference was that our trial was a multicenter study. As noted by Sonnappa et al., the results of multicenter studies can be more reliably extrapolated to the general population.

The duration of postoperative hospital stay was longer in both our patient groups than in the earlier studies: 10 days for VATS and 9 days for urokinase versus 6 and 6 days in the study by Sonnappa et al.$^{26}$ and 6.9 and 6.8 days in the study by St Peter et al.$^{27}$ respectively. These differences are not attributable to a delay in transferring our patients for treatment, as the interval was similar to that reported in the study by Sonnappa et al. The lengthier hospitalization in our study may be due, in part, to the fact that children with anechoic, nonseptated effusions were not included in our series, but we believe the main reason is possible differences in pediatric
management between countries. In our hospitals, the drain was not withdrawn until drainage volume was minimal (<40–60 mL/24 h), and patients were not discharged until they had been afebrile for 24 hours. This practice may have differed in the previous studies reporting a shorter hospital stay.

The treatment failure rates were similar in the 2 groups (15% for VATS and 10% for urokinase) and were comparable to the values reported by the studies of Sonnappa et al and St Peter et al (16.6% for fibrinolysis).26,27 Among the 13 patients in whom the initial treatment failed, only 5 subsequently underwent surgery; the remaining 8 patients were treated by drain placement or urokinase instillation.

Of note, only 1 patient of the 103 subjects analyzed in our study needed a thoracotomy, as compared with 4 of 30 in the VATS group and an unspecified number in the urokinase group in the trial by Sonnappa et al.26 All 4 patients in that study were converted to thoracotomy during the initial VATS procedure, based on the surgeon’s perception that the pleural peel would impede proper expansion of the lung. Because the radiologic and functional course of our previously treated patients had demonstrated that residual pleural thickening resolves spontaneously over follow-up,25 our surgical protocol in the present study did not include debridement of pleural peel on the lung. Debridement is not performed in patients undergoing fibrinolytic treatment, and the risk of parenchymal injury is higher when attempts are made to remove the fibrin layer. In our series, findings on radiographic follow-up at 3 months after hospital discharge were considered normal in 66.7% of patients in the VATS group and 59.5% of those receiving urokinase. There were no later hospital referrals for “trapped lung.” Therefore, we believe that the surgeon’s subjective perception of lung distensibility during the acute phase of empyema should not guide the surgery performed.

Our study has some limitations that should be mentioned. First, it was conducted without previous calculation of the sample size because of the unfeasibly large number of patients who would be needed to perform an equivalence study. Nonetheless, the number of patients ultimately randomized for this trial is the largest among the existing prospective studies having the same objective. Second, the diagnostic sonographic images did not undergo centralized review, and there is a possibility of variability between the readers in the different centers.

The present study has some practical implications. Many second-level pediatric hospitals have the capability to perform ultrasound diagnosis of severe empyema and image-guided chest tube placement, enabling treatment with fibrinolytic drugs. Surgical treatment would not be possible in these centers; children requiring surgery must be transferred to third-level hospitals with surgeons trained to treat them. Second, VATS is a procedure lasting ~1 hour that requires general anesthesia and involves considerable aggressiveness in a severely ill patient, as was noted in the recent review by Islam et al.22 Urokinase instillation is much less invasive. Lastly, although we did not perform a comparative cost study between the 2 treatments, previous trials have shown that the surgical option is more costly than fibrinolytic therapy.26,27

**CONCLUSIONS**

Initial treatment of septated parapneumonic empyema with fibrinolytic agents is as effective as VATS in children. This multicenter study adds strength to current recommendations23,24 to use chemical debridement as first-line therapy in these patients.

**ACKNOWLEDGMENTS**

The authors are grateful to the members of the Departments of Pediatric Surgery, Pediatrics, and Radiology of the participating hospitals, whose invaluable help contributed to make this study possible. We thank Xavier Vidal (Department of Clinical Pharmacology, Hospital Vall d’Hebron, Barcelona) for his help with the statistical analysis and Celine Cavallo for English language support.

**REFERENCES**


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PEDIATRICS (ISSN Numbers: Print, 0031-4005, Online, 1098-4275).
Copyright © 2014 by the American Academy of Pediatrics
FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.
FUNDING: This clinical trial was funded by a Health Research Fund Grant (EC07/80385) from the Institute of Health Carlos III, under the Spanish Ministry of Science and Innovation. The funding within the program of support for research unrelated to commercial interests was essential for completion of this study.
POtENTIAL CONFLICT OF INTEREST: Dr Moreno-Galindo has been an advisory board member of and has received institutional research funding from AbbVie Inc; has received funding for travel to conferences by Actelion, Novartis, Gilead, Bayer Pharma AG, and Ferrer Laboratories; and received a fee for speaking from Merck Sharp & Dohme. Dr Pérez-Yarza is an advisory board member of AbbVie Inc; has received institutional research funding from AbbVie Inc, and has received fees for speaking from Merck Sharp & Dohme. The other authors have indicated they have no potential conflicts of interest to disclose.
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Pediatrics 2014;134;e1301
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