Comparison of a 5 day regimen of cefdinir with a 10 day regimen of cefprozil for treatment of acute exacerbations of chronic bronchitis

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Patients with acute exacerbations of chronic bronchitis were treated with cefdinir 300 mg bd for 5 days or cefprozil 500 mg bd for 10 days in a prospective, randomized, double-blind, multicentre study. Of the 548 patients enrolled, 281 (51\%) were evaluable. The clinical cure rates at the test-of-cure visit were 80\% (114/142) and 72\% (100/139) for the evaluable patients treated with cefdinir and cefprozil, respectively. Respiratory tract pathogens were isolated from 409 (75\%) of 548 admission sputum specimens, with the predominant pathogens being \textit{Haemophilus parainfluenzae}, \textit{Haemophilus influenzae}, \textit{Staphylococcus aureus} and \textit{Moraxella catarrhalis}. The microbiological eradication rates at the test-of-cure visit were 81\% (157 of 193 pathogens) and 84\% (166 of 198 pathogens) for the evaluable patients treated with cefdinir and cefprozil, respectively. Adverse event rates while on treatment were equivalent between the two treatment groups. The incidence of diarrhoea during therapy was higher for patients treated with cefdinir (17\%) than for patients treated with cefprozil (6\%) (\(P < 0.01\)), but most cases were mild and did not lead to discontinuation of treatment. These results indicate that a 5 day regimen of cefdinir is as effective and safe in the treatment of patients with acute exacerbations of chronic bronchitis as a 10 day regimen of cefprozil.

\textbf{Introduction}

Chronic bronchitis is an inflammatory condition of the lower respiratory tract and is characterized by cough and sputum production on most days during three consecutive months for more than two successive years.\textsuperscript{1} Contributing conditions leading to the development of the disease include a history of smoking, exposure to airborne particulate and gaseous irritants, previous episodes of respiratory tract disease, and familial and genetic factors.\textsuperscript{1,3} Acute exacerbations of chronic bronchitis (AECB) are frequently experienced by patients with chronic bronchitis and are characterized by symptoms such as increased cough and shortness of breath and increased sputum volume and purulence.\textsuperscript{6,7}

While viral infection, allergy, exposure to pollutants (including cigarette smoke) and even congestive heart failure have been implicated in the aetiology of AECB, bacterial infection also plays a significant role.\textsuperscript{7,8,9} This was well demonstrated in a study using fibre optic bronchoscopy with a protected specimen brush to sample distal secretions in patients with severe AECB, thus minimizing contamination from the oropharyngeal cavity.\textsuperscript{10} Pathogens were isolated in 50\% of patients, the predominant organisms being \textit{Haemophilus parainfluenzae}, \textit{Haemophilus influenzae}, \textit{Moraxella catarrhalis} and \textit{Streptococcus pneumoniae}.

Given the multifactorial aetiology of AECB, studies examining the role of antibiotic therapy have yielded conflicting results until recently.\textsuperscript{8} A meta-analysis done to clarify the divergent results of these studies suggested a small but statistically significant improvement in clinical outcome in patients given antibiotic therapy, particularly those with severe symptoms.\textsuperscript{11} A landmark study by Anthonisen and colleagues\textsuperscript{12} found that antibiotic-treated patients had a significantly better success rate than placebo-treated patients. Antibiotic-treated patients were also significantly less likely to have clinical deterioration after the first 72 h of treatment. Overall, the efficacy of antibiotic treatment varied with the amount of sputum produced, sputum appearance and dyspnoea seen at the
start of exacerbations. Those in whom all three cardinal symptoms were present, at the time of admittance to the study, worse than their normal condition showed the most improvement after antibiotic treatment compared with placebo controls.

Cefdinir (CI-983, FK482, Omnicef) is a semisynthetic, extended-spectrum oral cephalosporin antibiotic approved for use in patients with mild to moderate AECB, community-acquired pneumonia, acute otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis and skin and soft tissue infections. For these infections treatment is usually given for 10 days. However, according to information supplied with Omnicef packages, cefdinir is also effective as a 5 day treatment in adults and children with tonsillitis/ pharyngitis. Given issues such as patient compliance and the benefits of prompt control with short-term therapy, this study was conducted to evaluate a 5 day course of cefdinir for patients with AECB.

Patients and methods

Patient selection

This was a double-blind, prospective, randomized, study conducted at 32 sites in the USA between January 1996 and July 1997. Patients all had chronic bronchitis, defined as cough and sputum production for at least three consecutive months in at least two years. Inclusion criteria included: AECB (confirmed by the presence of increased cough/ sputum production in the absence of an infiltrate on a chest X-ray) and age ≥13 years. Women of child-bearing potential were required to have a negative urine pregnancy test. Patients were excluded from the study if they were pregnant or lactating, had concomitant diseases which may have precluded proper assessment of the disease under study, had hepatic disease or obstruction of the biliary tract, had a baseline serum creatinine level more than twice the upper limit of normal or a known creatinine clearance of <30 mL/min, were allergic to β-lactam antibiotics, had concomitant infections requiring systemic antibacterial therapy, received any other investigational compound within 4 weeks before entering this study, participated in any other cefdinir study, were receiving probenecid or iron-containing supplements, or had taken an antibiotic within 7 days before anticipated study admission. All investigators received Institutional Review Board approval for the protocol before beginning the study and all patients (or their guardians) provided written informed consent before study entry. The study was conducted according to the Declaration of Helsinki.

Microbiological investigations

All patients produced a sputum specimen at study entry. Those specimens that contained ≥25 neutrophils and ≤10 epithelial cells per low-power (100×) microscopical field were submitted for culture. A central laboratory (Mayo Medical Laboratories, Rochester, MN, USA) performed cultures and susceptibility testing according to NCCLS criteria. Cefdinir was tested by disc diffusion (with a 5 µg disc) and microdilution (with Sensititre plates). Cefprozil was tested by disc diffusion only. For cefdinir testing by disc diffusion, susceptibility was defined as a zone diameter of ≥20 mm, intermediate susceptibility as a zone diameter of 17–19 mm, and resistance as a zone diameter of <16 mm. For cefdinir testing by microdilution, susceptibility was defined as an MIC of ≤1 mg/L, intermediate susceptibility as an MIC of 2 mg/L, and resistance as an MIC of ≥4 mg/L. Published standards were used for the cefprozil susceptibility breakpoints. Penicillin susceptibility results were used to define susceptibility of Streptococcus pneumoniae to cefdinir and cefprozil. Appropriate strains (Haemophilus spp. and M. catarrhalis) were also tested for β-lactamase production with nitrocefin discs.

Antimicrobial therapy

Patients were randomized (1:1) to either cefdinir 300 mg bd or cefprozil 500 mg bd. Cefprozil was chosen as the comparator agent because it is approved for the treatment of patients with AECB and for more severe lower respiratory infections such as pneumonia. Medication was supplied as capsules in a double-blind, double-dummy fashion. Patients were asked not to take antacids for 2 h before and after study medication dosing. Medication was taken without regard to meals. The investigator, the patient and the sponsor were blinded to the treatment regimen until all patients had completed the study and all assessments had been performed.

Clinical, microbiological and safety assessments

Each patient was assessed at admission (study entry) and on study days 12–16, 17–21 and 28–42. The test-of-cure (TOC) visit for each regimen was conducted 7–11 days after patients had stopped taking study medication. A constant time interval between completion of study medication and assessment would allow equal intervals for suppressed clinical symptoms and cultures to reappear in the two groups. Thus the TOC for those patients randomized to cefdinir was on study days 12–16 and that for patients randomized to cefprozil was on study days 17–21. The long-term follow-up visit (LTFU), conducted to examine long-term clinical and microbiological outcomes, was not considered as crucial as the TOC and, hence, was conducted on study days 28–42 for both regimens.

Clinical signs and symptoms of cough, sputum production and dyspnoea were graded at each study visit as absent, mild, moderate or severe. Sputum was graded as absent, mucoid, mucopurulent/blood-streaked or purulent. Rales, rhonchi, wheezing and pleural rub were graded as...
Patients were deemed clinically evaluable if they had clinical evidence of AECB without radiographic evidence of pneumonia, had no resistant organisms at baseline, took study drug as prescribed, did not take non-study systemic antibacterial therapy for concurrent infections and were clinically assessed on the days specified in the protocol. Therapy duration and prior antibacterial rules described above for evaluable patients also applied for clinically evaluable patients. Patients were not excluded from this data set as a result of inadequate microbiological data (i.e. no baseline pathogen, missing microbiological data at baseline or follow-up, or microbiological data collected on days other than those specified in the protocol).

Patients in the intent-to-treat population were all those randomized to treatment.

**Statistical analyses**

The study was designed with a sample size of 190 evaluable patients per treatment group. Assuming a clinical response rate of 90%, this sample size would provide at ≥80% power to assess the equivalence of the cefdinir and cefprozil treatment groups.

Two-tailed 95% confidence intervals (CI) were calculated around the difference between microbiological eradication and clinical response rates (e.g. cefdinir minus cefprozil) and compared with a set of fixed criteria. For the treatments to be equivalent, each 95% CI had to contain 0 and fall within specific boundaries (if the estimated response rate was ≥90%, the 95% CI for the difference had to be ±10%; if the estimated response rate was 80–89%, the 95% CI had to be ±15%; and if the estimated response rate was 70–79%, the 95% CI had to be ±20%).

Cochran–Mantel–Haenszel tests using a 5% level of significance, stratified by study centre, were performed to detect treatment differences with respect to the incidence of adverse events, associated adverses and diarrhoea, and to discontinuation of study medication owing to adverse events, as well as differences in baseline susceptibility to study drugs. All statistical tests were performed with SAS software.

**Results**

Of the 548 patients enrolled, 278 were randomized to the cefdinir group and 270 to the cefprozil group. Patients were evenly distributed by gender, race and age across both treatment groups. About one-third of the patients in each treatment group were aged ≥65 years (Table I).

The median time for which patients took study medication was 5 days for cefdinir and 10 days for cefprozil.

The presence and severity of clinical signs and symptoms at study admission were similar for patients in the two treatment groups (data not shown). Most of the patients in both treatment arms were current or former smokers.
Evaluable patients were classified according to sputum production, sputum purulence and dyspnoea at admission using the criteria proposed by Anthonisen et al.\textsuperscript{12} Table II shows that the majority of the evaluable patients were of type 1 or type 2.

**Antimicrobial susceptibility**

Of the 548 patients enrolled, 409 (75%) had at least one respiratory tract pathogen isolated from the admission sputum specimen. For the most prevalent of these isolates, their susceptibilities to the study drugs are shown in Table III. At admission, 6% \((37/598)\) of the pathogens were resistant to cefdinir and 10% \((61/594)\) to cefprozil. (These rates include \textit{S. pneumoniae} strains intermediately susceptible to penicillin.) This difference in resistance rates was statistically significant \((P < 0.01)\). Twenty-five per cent of the \textit{H. influenzae}, 7\% of the \textit{H. parainfluenzae} and 87\% of the \textit{M. catarrhalis} obtained at admission were \textit{\beta}-lactamase producers.

**Efficacy**

Of the 548 randomized patients, 281 (51\%) were fully evaluable, 142 in the cefdinir arm and 139 in the cefprozil arm. Table IV presents the microbiological and clinical efficacy outcomes at TOC for these patients. The observed clinical cure rate among cefdinir-treated patients of 80\% was not equivalent to that for cefprozil-treated patients (72\%), since the 95\% CI around the difference in clinical cure rates \((-1.6\%, 18.3\%)\) exceeded the predefined criterion of \(\pm 15\%\).

The overall rates of microbiological eradication of pathogens were 81\% for cefdinir-treated patients and 84\%
Cefdinir vs cefprozil for treating AECB

Table III. Susceptibilities of the most prevalent admission pathogens to cefdinir and cefprozil

<table>
<thead>
<tr>
<th>Pathogen and characteristic</th>
<th>Number of isolates</th>
<th>Antimicrobial agent</th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>U</th>
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<tbody>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
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<tr>
<td>β-lactamase-negative</td>
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<td></td>
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<td>cefprozil</td>
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<td></td>
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<td>cefprozil</td>
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<td></td>
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<td></td>
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<td>1</td>
<td>1</td>
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<tr>
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<td>cefprozil</td>
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<td></td>
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<td>cefprozil</td>
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<td>19</td>
<td>10</td>
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<td>0</td>
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<tr>
<td></td>
<td></td>
<td>cefprozil</td>
<td>19</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*S, susceptible; I, intermediate; R, resistant; U, unknown.

*bRefers to penicillin susceptibility

for cefprozil-treated patients (95% CI: –10.0%, 5%), demonstrating equivalence. Table IV also presents microbiological eradication data at TOC for the most prevalent pathogens.

Patients were most frequently excluded from the evaluable subset because no respiratory tract pathogen was isolated from the admission sputum specimen (83 cefdinir-treated patients, 56 cefprozil-treated patients). Other common reasons for exclusion included clinical and microbiological assessments having been done at different times from those specified in the protocol, both occurring slightly more frequently in the cefprozil treatment group. Patients could have been excluded for more than one reason.

Among qualified patients who had all admission pathogens eradicated at the TOC visit, the rates of microbiological eradication by pathogen at the LTFU visit were 94% (135/143) in the cefdinir group and 89% (127/142) in the cefprozil group. Among qualified patients who were classified as cures at the TOC visit, the continued cure rates at the LTFU visit were 84% (84/100) in the cefdinir group and 87% (82/94) in the cefprozil group.

In the clinically evaluable population at the TOC visit, the overall clinical cure rates were 82% (180/220) in the cefdinir group and 74% (142/192) in the cefprozil group (95% CI: –17.2%, 15.90%).

In the intent-to-treat population, the clinical cure rate in cefdinir-treated patients (78%, 217/278) was equivalent to that of cefprozil-treated patients (74%, 200/270) (95% CI: –3.2%, 11.1%). The overall rate of microbiological eradication of admission pathogens in cefdinir-treated patients (79%, 225/286) was equivalent to that in cefprozil-treated patients (81%, 255/316) (95% CI: –8.5%, 4.4%).

No admission strains of *H. influenzae* resistant or intermediate to cefdinir were isolated from cefdinir-treated patients. Three admission strains of *H. influenzae* resistant to cefprozil were isolated from three cefprozil-treated patients. All three of these patients were classified as cures at the TOC visit; two of the three strains were eradicated at the TOC visit. Six admission strains of *H. influenzae* intermediate to cefprozil were isolated from six cefprozil-treated patients. Four of these six patients were classified as cures at TOC; all but one strain was eradicated at TOC.

Four admission isolates of *S. aureus* were methicillin resistant (MRSA). One of these strains was isolated from a patient randomized to cefdinir. This patient was lost to follow up. Three of the admission MRSA were isolated from patients randomized to cefprozil. Two of these three patients were classified as a cure at TOC and one was a failure. All three strains were eradicated at TOC.

One admission isolate of *S. pneumoniae* was resistant to penicillin. This strain was isolated from a cefprozil-treated
patient and was susceptible to cefprozil. The patient was classified as a failure at TOC and the strain persisted at TOC. Ten admission isolates of *S. pneumoniae* were initially susceptible to penicillin. Four of these isolates were from four patients randomized to cefdinir. Three of these four strains were susceptible to cefdinir; one was intermediately susceptible to cefdinir. All four patients were cures at TOC and all four strains were eradicated at TOC. Six admission isolates of *S. pneumoniae* intermediately susceptible to penicillin were from six patients randomized to cefprozil. All of these isolates were susceptible to cefprozil. Four of these six patients were classified as failures at TOC, one was a cure and one was unknown. Five of the six strains persisted at TOC; the status of the sixth strain was unknown.

Nineteen (7%) cefdinir patients and 21 (8%) cefprozil patients experienced superinfections. The most prevalent superinfecting pathogen was *H. parainfluenzae* (in seven patients in the cefdinir group and six in the cefprozil group). None of these superinfecting *H. parainfluenzae* were resistant to cefdinir, but two of six were resistant to cefprozil. Reinfections were seen in eight patients in the cefdinir arm and five patients in the cefprozil arm.

Ten cefdinir-treated patients satisfied all evaluability criteria except that they had at least one admission pathogen that was susceptible to cefdinir and resistant to cefprozil. Cefdinir eradicated 75% (nine of 12) of admission pathogens from these patients at the TOC visit. Six of the 10 patients were assessed as clinical cures at the TOC visit.

### Safety

Safety of the drugs was analysed for all patients who received study medication. Of these patients, 95 (34%) patients receiving cefdinir and 89 (33%) patients receiving cefprozil experienced at least one adverse event during treatment (*P* = 0.90). Sixty-two (22%) of the patients treated with cefdinir and 51 (19%) of patients treated with cefprozil experienced at least one adverse event during the treatment phase which the investigator considered to be drug-related (possibly, probably or definitely caused by the study drug) (*P* = 0.39).

The most frequent adverse events on therapy for both cefdinir- and cefprozil-treated patients were diarrhea and headache. Seventeen percent of cefdinir-treated patients and 6% of cefprozil-treated patients experienced diarrhea during treatment (*P* < 0.01).

Eleven (4%) patients treated with cefdinir and seven (3%) treated with cefprozil stopped treatment as a result of an adverse event (*P* = 0.44). The most common adverse events given as reasons for discontinuing cefdinir were diarrhea and abdominal pain.

Two patients died during the study, one in the cefdinir arm and one in the cefprozil arm. Neither death was related to study medication.

The clinical laboratory changes from admission to the first visit after therapy showed no clinically significant changes except for a trend toward lower leucocyte and polymorphonuclear leucocyte counts, as well as lower urine leucocyte counts and urine ketone concentrations, for both treatment groups. Cefprozil patients also tended to have lower urine protein, urine blood and urine bilirubin con-

### Table IV. Efficacy rates in evaluable patients at the TOC visit

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>Value for group</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>cefdinir</td>
<td>n/N%</td>
<td>cefprozil</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>114/142</td>
<td>80.3</td>
<td>100/139</td>
</tr>
<tr>
<td>Microbiological eradication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>32/43</td>
<td>74.4</td>
<td>26/33</td>
</tr>
<tr>
<td><em>H. parainfluenzae</em></td>
<td>48/57</td>
<td>84.2</td>
<td>49/58</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>16/19</td>
<td>84.2</td>
<td>15/18</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>29/30</td>
<td>96.7</td>
<td>24/26</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>3/4</td>
<td>75.0</td>
<td>9/11</td>
</tr>
<tr>
<td>other</td>
<td>29/40</td>
<td>72.5</td>
<td>43/52</td>
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<tr>
<td>total</td>
<td>157/193</td>
<td>81.3</td>
<td>166/198</td>
</tr>
</tbody>
</table>

*“n/N (clinical)” is the number of clinical cures divided by the number of patients; “n/N (microbiological)” is the number of pathogens eradicated divided by the number of pathogens isolated.*

b*All were susceptible to penicillin.*
centrations at the first visit after therapy compared with admission values.

Discussion

This study demonstrated that a 5 day course of cefdinir was associated with improved clinical outcome and equivalent microbiological outcome, compared with a conventional 10 day course of cefprozil. These results confirm those of several other studies which have shown that AECB can be treated successfully with short-course therapy. In one study, a favourable clinical response (cure or improvement) was seen in 89.5% of dirithromycin-treated patients (5 days of therapy) and 94.8% of patients treated with the comparative agent, clarithromycin (7 days of therapy), at the first visit after therapy. At the same visit, a favourable bacteriological response was seen in 68.8% of dirithromycin-treated patients and 71.9% of clarithromycin-treated patients.

A study involving AECB patients treated with cefixime for 5 or 10 days demonstrated clinical efficacy (cure or improvement) in 91% of patients who received cefixime for 5 days and in 89% of those patients who received cefixime for 10 days. Successful bacteriological efficacy was achieved in 71% of patients in the 5 day group and 82% of those in the 10 day group. Langan and colleagues treated AECB patients with cefuroxime axetil for 5 days. In this study, clinical success (cure or improvement) in the intention-to-treat population was achieved in 82% of patients who received cefuroxime axetil for 5 days and 82% in patients who received clarithromycin for 7 days. Post-treatment bacteriological response in those patients who had a pre-treatment pathogen was 73% for cefuroxime axetil and 82% for clarithromycin. Guest & Langan found clinical success (cure or improvement) at the end of therapy was 92% for patients who received cefituben for 5 days and 93% for those who received amoxycillin–clavulanate for 10 days.

Staphylococcus aureus was one of the most common isolates from patients in this study. Traditionally, this organism has not been considered a common respiratory tract pathogen in patients with AECB. However, there are now many reports in the literature suggesting that the organism is isolated regularly from patients with AECB. The presence of purulent or mucopurulent sputum in all admission sputum specimens, and the presence of Gram-positive cocci in the majority of sputum specimens in evaluable patients whose admission cultures yielded S. aureus (data not shown), also support the pathogenic role of this organism. Anthonisen and colleagues have proposed a grading scale for chronic bronchitis exacerbations: type 1 exacerbations are those in which increased dyspnoea, sputum volume and sputum purulence all occur; type 2 exacerbations are those where two of the three above symptoms are present; type 3 exacerbations are those in which only one of the three above symptoms is present with at least one of several additional respiratory tract findings. In a placebo-controlled trial of patients with AECB, Anthonisen’s group found c. 40% of the exacerbations were classified as type 1 and 40% as type 2. Similar findings were observed in our evaluable patient population: 87.3% of cefdinir-treated patients and 91.4% of cefprozil-treated patients were of type 1 or 2 (Table II).

The incidence of adverse events or drug-associated adverse events experienced by patients while on treatment, and the incidence of treatment discontinuations owing to adverse events, did not differ between the two treatment groups. Significantly more patients in the cefdinir group experienced diarrhoea during study therapy than in the cefprozil group, but most cases were mild and did not lead to discontinuation of treatment.

In this study, clinical outcomes were better in cefdinir-treated patients than in cefprozil-treated patients. Cefdinir and cefprozil were microbiologically equivalent in the eradication of admission pathogens. The advantage of less drug exposure (leading to a decreased risk of selecting resistant organisms), the convenience of 5 day dosing and the greater in vitro antimicrobial activity of cefdinir compared with cefprozil, make cefdinir an attractive agent for the treatment of AECB.

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