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Randomized Trial Comparing Ciprofloxacin plus Netilmicin versus Piperacillin plus Netilmicin for Empiric Treatment of Fever in Neutropenic Patients

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To assess the efficacy of ciprofloxacin in neutropenic patients, we conducted a randomized prospective trial comparing the combination of ciprofloxacin and netilmicin against piperacillin plus netilmicin as an empiric treatment of fever in cancer patients with neutropenia. Of 214 evaluable episodes, 115 and 99 were randomly assigned to the ciprofloxacin and the piperacillin arms, respectively. The overall response rates were very similar (59 and 62% for the ciprofloxacin and piperacillin arms, respectively). The response for the gram-positive bacteremias was almost identical (around 40%); this low response was due in part to an outbreak of infection by a multiply resistant strain of *Staphylococcus epidermidis* (for which the ciprofloxacin MIC was ≥128 μg/ml) which occurred during the second half of the trial. Among gram-negative bacteremias, 9 of 11 infections (82%) responded to the ciprofloxacin combination compared with 3 of 7 (43%) that responded to the piperacillin combination ($P = 0.23$). The incidences of persistent, profound neutropenia were comparable in both treatments, but the susceptibility of the gram-negative organism to ciprofloxacin and netilmicin was significantly higher than was susceptibility to the other combination. Ciprofloxacin was well tolerated, and patients were able to convert from intravenous to oral therapy in 64 of 115 episodes.

Prompt initiation of broad-spectrum empiric antibiotic therapy is essential to prevent death in febrile neutropenic patients (1), and a standard combination of drugs in many centers is an aminoglycoside plus a semisynthetic penicillin with antipseudomonal activity (7, 12).

Ciprofloxacin is a new 4-quinolone antibiotic with a broad spectrum of activity, including activity against *Pseudomonas aeruginosa* (3, 13), and is available in both injectable and oral formulations. We have compared the use of ciprofloxacin in combination with netilmicin (NC) against our previous standard regimen of piperacillin plus netilmicin (NP). In particular, we were interested in observing whether the new combination was more effective in preventing death due to gram-negative septicemia and in the possibility of converting from intravenous to oral ciprofloxacin therapy.

MATERIALS AND METHODS

Eligibility criteria. The trial was conducted in a single oncology unit, the Department of Medical Oncology, Christie Hospital and Holt Radium Institute, Manchester, United Kingdom. Patients who became febrile or who had evidence of septic shock while they were neutropenic were eligible for entry into the study. Fever was indicated by two oral temperatures of 38°C or above taken 2 h apart or a single reading of 38.5°C or higher. Neutropenia was defined as an absolute neutrophil count of less than 10^9/liter. Patients with a higher neutrophil count when they became febrile but whose count was expected to fall rapidly after chemotherapy were also eligible. Within the same period of neutropenia, patients were eligible for rerandomization only if they had remained afebrile for at least 7 days after discontinuation of antimicrobial therapy. Patients who were allergic to any of the trial antibiotics or who had received any of the trial antibiotics within the preceding 72 h were not eligible. Children under 16 years old and pregnant, potentially pregnant, and lactating women were also not eligible.

Antibiotic prophylaxis. Gut decontamination was not used except for six bone marrow transplant patients in each arm of the study. These patients received oral co-trimoxazole in a dose of 80 mg of trimethoprim-400 mg of sulfamethoxazole twice daily for 5 weeks after the start of the conditioning regimen.

Trial design. (i) Prerandomization assessment, stratification, and randomization. After patients had consented to participate in the trial, a full history was taken and a clinical examination was performed. At least one set of blood cultures was taken before treatment with antibiotics. For patients with an indwelling venous catheter, samples for blood culture were drawn through the catheter and also from a peripheral vein. Additional bacterial and viral cultures were obtained from any infected sites, and blood was taken for viral serology. Chest X rays were performed as necessary.

Bacterial isolates were identified by conventional laboratory techniques, and their susceptibility to the trial antibiotics was determined by a disk diffusion method. For isolates which appeared to be moderately susceptible or resistant to ciprofloxacin, the ciprofloxacin MIC was determined by an agar dilution method. Ciprofloxacin resistance was defined as an MIC of ≥4 μg/ml.

After initial assessment, patients were classified into two groups on the basis of their underlying malignancy: stratum A comprised patients with leukemia and any patient undergoing a bone marrow transplant, and stratum B consisted of patients with lymphomas and solid tumors. Within each

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stratum, patients were randomized to receive either NC or NP therapy according to the following schedules. (i) Netilmicin at 7 mg/kg per day was given as an intravenous bolus every 8 h. Netilmicin levels in serum were determined within 48 h after commencement of treatment and then twice weekly for the duration of aminoglycoside therapy. Dosages and frequency were adjusted to produce a 1-h peak level of between 8 and 12 μg/ml and a trough level between 2 and 3 μg/ml. (ii) Ciprofloxacin was initially given intravenously to all assigned patients as a 200-mg infusion over 30 min every 12 h. After at least 3 days of intravenous therapy, patients who had responded and who were able to receive oral therapy were switched over to ciprofloxacin tablets at a dose of 750 mg every 12 h. A specific timing in relation to meals was not required. If the patient weighed less than 45 kg or had a creatinine clearance of less than 20 ml/min, the dose of ciprofloxacin was halved. (iii) Piperacillin was given as a 4-g infusion over 30 min every 6 h.

Randomization was made from sealed envelopes provided by the Statistics Department of the Christie Hospital. Standard methods were used, and treatment was not blinded. Antibiotics were administered within 1 or 2 h of randomization.

(ii) Follow-up studies. After entry into the study, patients had their temperatures taken every 4 h and were evaluated daily. Routine cultures of the throat (including viral cultures) and urine were performed weekly. For patients whose infection had not improved or who remained febrile, blood cultures were performed frequently, usually daily. Additional cultures were taken from infected sites. Chest X rays were taken of patients with clinical evidence of a chest infection; they were taken weekly for patients whose fever persisted while they remained neutropenic. Special procedures (e.g., bronchoscopy and lavage or open-lung biopsy) were performed on an individual basis. Complete blood counts were performed daily, biochemistry profiles were performed twice weekly, and coagulation profiles were performed once weekly.

(iii) Modification of initial treatment. Once a treatment was assigned, the patient was continued on that treatment unless it was considered necessary to modify the therapy. Modified therapy was defined as the use of any other antibiotic (except oral vancomycin) or any intravenous antifungal or antiviral agent, whether in addition to or as a substitute for any of the assigned trial antibiotics.

Therapy was modified primarily on a clinical basis, i.e., the persistence or worsening of the fever or infection. The type of modification was based on clinical assessment and guided, when relevant, by the results of cultures. One or more antibiotics were added or substituted if there was evidence of bacterial infection not responding to the assigned regimen (e.g., vancomycin was used for *Staphylococcus epidermidis* infections). An intravenous antifungal agent was added either empirically on the basis of persistent pyrexia despite adequate antibiotic therapy or if there was clinical or microbiological evidence of invasive fungal disease. During prolonged neutropenia, further modifications of therapy were made as necessary.

(iv) Duration of therapy and of observation period. Therapy, whether modified or not, was continued at least until recovery of the neutrophil count to 0.5×10^9/liter, together with resolution of fever and infection. An exception to the guideline of neutrophil recovery was permitted as follows. For patients with *S. epidermidis* bacteremia, minor infections, or possible infection, who had been afebrile for at least 5 days with clinical improvement, therapy could, at the discretion of the investigator, be discontinued before neutrophil recovery. This occurred in a small minority of episodes. Patients were observed until death or until resolution of the infection with neutrophil recovery, when they could be discharged.

(v) Study size. In an earlier analysis of 344 episodes of neutropenic fever treated with NP, the response rate was 65% (data on file). Assuming a difference of 20% to be clinically important, we wished to have a 90% chance of detecting this difference at a significance level of 5%. When using a two-sided test, the numbers required were 97 per arm, and we intended to recruit 100 evaluable episodes per arm.

Diagnostic criteria and classification of infection status. On the basis of assessment at randomization, the febrile episode was defined as follows. (i) Microbiologically documented infection occurred when definite clinical features of infection were found and identification (from cultures, histology, serology, etc.) of the etiological agent, subdivided as bacteremic (pathogen isolated in blood) and nonbacteremic (pathogen isolated from another site), was made. (ii) Clinically documented infection occurred when definite clinical features of an infected site were present but microbiological proof was lacking either for the blood or for the infected site (e.g., pneumonias with mixed floras and no predominating organism). (iii) Possible infection occurred when equivocal features of infection and negative microbiological data were found but the clinical course was compatible with the presence of infection. (iv) Doubtful infection occurred when, in retrospect, infection was probably not present and the fever may have been due to blood products, drugs, or cancer.

Bacteremia was indicated when one or more blood culture bottles were positive for any organism, except that at least two positive cultures were necessary for *S. epidermidis* bacteremias. Septic shock was defined by conventional criteria. Pneumonia was diagnosed when there were clinical or radiological features of pulmonary consolidation not obviously attributable to a noninfectious cause, with or without microbiological documentation.

Evaluation of response to empiric treatment. Response was evaluated as follows. (i) Resolution occurred when, on trial antibiotics alone, there was a lasting return of temperature, signs, and symptoms to normal or to the preinfectious state. (ii) Improvement with relapse occurred when, on trial antibiotics alone, at least 3 days without fever and clinical improvement had been initially achieved, followed by a relapse, which required modification of therapy. (iii) Failure occurred when the treatment was unable to achieve a response as defined above. (iv) Not evaluable indicated that the presence of infection was doubtful; that there was documented fungal or viral infection; or that the trial antibiotic therapy was prematurely terminated because of toxicity, a noninfective death, or protocol violation.

Patients whose infection resolved or improved with relapse, according to the first two categories defined above, were considered to have responded to the trial antibiotics.

The assessment was made 72 to 96 h after antibiotic therapy was begun, and it was therefore an evaluation of true empiric therapy. Patients were considered afebrile if the maximum daily temperature did not exceed 37.5°C (higher temperatures clearly related to blood products or to drugs were excluded). The afebrile state was accepted as indicating a response only in conjunction with clinical improvement in well-being and in features related to any infected site.

Radiological and other parameters may have lagged behind clinical ones.

Later infection. Infections that developed during prolonged periods of neutropenia were documented.

Evaluation of deaths. The cause of death was defined as follows. (i) Death from proven infection occurred when clinical deterioration from infection, together with definite microbiological identification of a pathogen or pathogens, was the main cause or an important cause of death. Noninfective features, such as unresponsive or progressive malignancy, organ failure, or hemorrhage, may have been additional factors contributing to death. (ii) Death from probable or possible infection was defined as described above, except that a definite microbial pathogen could not be identified. The definition of this category was meant to be broad ranging and included both well-defined features such as pneumonia and less-well-defined features such as persistent fever and general ill health at the time of death in patients in whom an infective process could not reasonably be excluded. (iii) Noninfective death could clearly be attributed to noninfective factors.

When infection was the cause, the time to death was defined as follows. For death from the initial infection, death was clearly related to the presenting infection state and occurred within the first 7 days. For death from later infection, death was due to infection separate from and unrelated to the presenting infection and occurred 7 days or more after randomization.

Evaluation of toxicity. Nephrotoxicity was defined as an increase of at least 0.04 μmol/liter from the base-line serum creatinine level. Patients who presented with septic shock or who received cyclosporin A were excluded. Audiometry was not routinely performed, but patients who developed hearing loss, tinnitus, or vestibular dysfunction unrelated to other causes were considered to show clinical ototoxicity. Potential toxicities of ciprofloxacin were sought on the basis of known toxicities of nalidixic acid and quinolones (10) and reports available on ciprofloxacin itself (6, 9; P. Schact, G. Arcieri, J. Branolte, H. Bruck, V. Chysky, R. Hullman, C. Konopka, C. Papachriston, A. Westwood, and H. Wenta, Proc. 14th Int. Congr. Chemother., abstr. no. WS-6-12, 1985). Development of rashes was also recorded.

RESULTS

Characteristics of the trial population. Between May 1986 and July 1987, 265 episodes of fever in neutropenic cancer patients were entered into the trial. Fifty-one episodes were not evaluable for the following reasons: protocol violation (17 episodes), neutrophil count $>10^9$ (8 episodes), insufficient fever (8 episodes), penicillin allergy or toxicity (7 episodes), fungal infection (5 episodes), viral infection (3 episodes), early death from noninfectious causes (2 episodes), and fever from lymphoma (1 episode). There was no difference in the distributions of these reasons between the two treatment arms, except for penicillin allergy or toxicity. This nonevaluable group did not contain a significantly higher number of bacteremias or deaths compared with the remaining 214 evaluable episodes, which occurred in 111 patients.

The patient episodes randomly assigned to their respective treatment arms were comparable in age, sex, underlying malignancy, median initial neutrophil count, and median duration of neutropenia and infection status (Table 1).

Response by infection status. The overall responses for all episodes were very similar, at 59% for NC and 62% for NP (Table 2). Clinical and possible infections also responded in a comparable fashion. Within the small nonbacteremic group, more patients responded to NC, but the difference was not statistically significant ($P = 0.17$). The response in patients with bacteremia is discussed in further detail below.

TABLE 1. Patient characteristics at randomization

Characteristic	Data for patients on:	
	NC	NP
No. of evaluable episodes	115	99
Mean age (yr) (range)		
Overall	46 (16–73)	44 (16–66)
Stratum A	42	38
Stratum B	50	51
Sex (male/female)	72/43	59/41
Underlying malignancy		
Stratum A: leukemia or bone marrow transplant	65 (57%)	48 (48%)
Stratum B: lymphoma	16 (14%)	13 (13%)
Other malignancies	34 (30%)	38 (38%)
Median initial neutrophil count (10^9/liter)	0.0	0.0
Median duration of neutropenia, $<0.5 \times 10^9$/liter, in days (range)		
Overall	8	7
Stratum A	16 (1–63)	13 (1–47)
Stratum B	4 (1–14)	4 (1–15)
Infection status		
Bacteremia	41 (36%)	35 (35%)
Other bacterial	6 (5%)	7 (7%)
Clinical	29 (25%)	29 (29%)
Possible	39 (34%)	28 (28%)

Gram-positive bacteremias. Gram-positive organisms caused the majority of all bacteremias: 29 of 41 (71%) in patients on NC and 22 of 35 (63%) in patients on NP (Table 3). The responses of this group were very similar, at 41 and 40%, respectively. More than half the infections were due to *S. epidermidis*, and the responses of this infection were comparable in both arms of the trial.

Mixed gram-positive and gram-negative bacteremias. Mixed gram-positive and gram-negative organisms were isolated in the blood of one patient receiving NC and from six patients receiving NP (Table 3). Five patients presented with septic shock, and only two of the seven patients responded to the empiric therapy. Those failing to respond all died.

Gram-negative bacteremias. Of 11 patients with gram-negative bacteremias, 9 (82%) responded to NC, compared with 3 of 7 patients on NP (43%) ($P = 0.23$). All organisms in the NC arm were susceptible to both antibiotics. Three of the *Escherichia coli* strains and the one *Klebsiella aerogenes* strain causing bacteremias in the NP arm were resistant to piperacillin, although all were susceptible to netilmicin. The

TABLE 2. Response by infection status

Infection	No. of responses/no. in group (%) on:	
	NC	NP
Bacteremia	21/41 (51)	14/35 (40), NS[a]
Other bacterial	2/6 (33)	6/7 (86), NS
Clinical	18/29 (62)	17/29 (59), NS
Possible	27/39 (69)	24/28 (86), NS
All episodes	68/115 (59)	61/99 (62)

[a] NS, Not statistically significant.

TABLE 3. Response of bacteremias by organism isolated

Bacteremia	No. of responses/no. in group on[a]:	
	NC	NP
Gram-positive		
S. epidermidis	7/16	8/16
S. aureus	2/4	0/3
Streptococci	3/5	1/2
Other	0/4	0/1
Mixed[b]	0/1	2/6
Gram-negative (single)		
E. coli	2/2	1/4 RRR[c]
P. aeruginosa	2/3	0/1
K. aerogenes	1/1	1/1 R
Proteus mirabilis	1/2	
Other	3/3	1/1

[a] The total numbers for gram-positive bacteremias were 12 of 29 (41%) and 9 of 22 (40%) for patients on NC and NP, respectively, and the total numbers for single gram-negative bacteremias were 9 of 11 (82%) and 3 of 7 (43%) (P = 0.23) for patients on NC and NP, respectively.

[b] Mixed bacteremias included those with gram-positive and gram-negative organisms.

[c] Each R represents one organism resistant to piperacillin.

number of organisms susceptible to both trial antibiotics was therefore significantly higher in the NC arm than in the NP arm (11 of 11 versus 3 of 7; P = 0.025). The frequencies of persistent profound neutropenia (neutrophil count less than 0.1×10^9/liter for at least the first 5 days of therapy) were comparable on both arms (6 of 11 patients on NC and 3 of 7 patients on NP). Two patients on the NP arm died from resistant *E. coli* bacteremias, and one patient on the NC arm died from a *P. aeruginosa* strain that was susceptible in vitro to both antibiotics. These three patients who died from the presenting infection included two patients with septic shock.

Outbreak of *S. epidermidis* infection. During the second half of the trial, there was an outbreak of infection by a multiply resistant strain of *S. epidermidis* (Table 4). Although there was only a slight increase (from 14 to 18) in the total number of *S. epidermidis* bacteremias, those that were ciprofloxacin resistant had risen from 1 of 14 to 10 of 18, of which 6 were due to the outbreak strain. The outbreak strain was detected on one ward and was isolated from numerous surveillance cultures. The strain was characterized by the ciprofloxacin MIC, which was ≥128 μg/ml.

Later infections. In a small minority of patients who had stopped receiving therapy while still neutropenic, two patients on the NC arm developed streptococcal bacteremia, one with *Streptococcus (Enterococcus) faecalis* and one with *Streptococcus pneumoniae*. Two patients on the NP arm developed *K. aerogenes* bacteremia. In the majority of patients who continued therapy while still neutropenic, five breakthrough bacteremias occurred on the NC arm, one with *Streptococcus faecalis* and four with *S. epidermidis*. On the NP arm, there was one breakthrough bacteremia with *Acinetobacter calcoaceticus* and one with *S. epidermidis*. A small number of minor bacterial infections were detected later on both arms. All these infections were successfully treated, either by restarting the same assigned antibiotic therapy or by appropriate modification, and none caused any deaths.

TABLE 4. *S. epidermidis* bacteremias during the first and second halves of the trial

S. epidermidis bacteremia	No. of bacteremias in patients on:			
	NC		NP	
	1st half	2nd half	1st half	2nd half
Total	7	9	7	9
Ciprofloxacin resistant	1	6	0	4
Outbreak strain	0	4	0	2
Piperacillin resistant	6	7	6	8

Three patients developed invasive fungal disease. One patient on the NC arm died of disseminated infection with *Aspergillus fumigatus*. On the NP arm, there was one death from *Candida albicans* fungemia and one patient was successfully treated for an *A. fumigatus* sinus infection.

Deaths. A total of 24 deaths (11.2%) (11 on NC, 13 on NP) occurred during the trial; 10 (4.7%) were due to microbiologically proven infection, 8 (3.7%) were from probable or possible infection, and 6 (3 on NC, 3 on NP) were noninfective.

Ten patients (three on NC, seven on NP) died from their presenting infection. Of these, eight deaths were from proven pathogens that caused the three gram-negative bacteremias and the five mixed bacteremias mentioned above. Two other patients, from whom pathogens could not be isolated, died from severe pneumonia. All of these 10 deaths occurred in stratum B patients (patients with lymphoma or solid tumors).

Eight patients (five on NC, three on NP) died of a later, separate infection. Only two infections were microbiologically proven, and they were both fungal as described above. The remaining six patients who died from probable or possible infection included five patients with pneumonia.

Toxicity. Nephrotoxicity occurred in 6.5% of episodes in patients on NC and in 9.8% on NP ($P > 0.5$) when trial antibiotics alone were given. The incidences were higher and were comparable in both arms when therapy was modified. Ototoxicity occurred in one patient, who developed moderate deafness due to elevated vancomycin levels in serum; this patient had received long-term netilmicin treatment during his 63 days of neutropenia. Rashes occurred in 18 episodes (11 on NP and 7 on NC). However, the distribution of the rashes by malignancy group (17 in stratum A and 1 in stratum B) was highly significant (P = 0.0006). This difference was still present within each treatment arm. There were three side effects directly attributable to ciprofloxacin. One patient had aggravation of a rash of unknown cause, one developed dyspepsia with the oral formulation, and transient myalgia was observed with the first intravenous dose in one patient.

Conversion to oral therapy with ciprofloxacin. In stratum A, in 43 of 65 episodes patients were able to change from intravenous to oral ciprofloxacin for a median duration of 8 days. In stratum B, conversion to oral ciprofloxacin occurred in 21 of 50 episodes for a median duration of 3.5 days.

DISCUSSION

Neutropenic fever represents a dangerous clinical condition, during which the patient remains vulnerable to death not only from infection but also from progression of underlying malignancy, organ failure, and hemorrhage. There is, as yet, no consensus on how best to give a comprehensive assessment and presentation of results of studies with empiric antibiotic treatment. The reporting of response rates alone is inadequate; if the main aim is to reduce mortality,

evaluation of the deaths is at least as important. A further difficulty is that even the criteria for response have not been standardized. Our criteria follow closely those of the European Organisation for the Research and Treatment of Cancer (EORTC) (4, 5).

The overall response rates were very similar for both treatment arms (averaging 60%) compared with the corresponding figures of 78, 81, and 65% for the first three EORTC trials (4, 5, 8). This relatively lower figure was due in part to the decrease in response in the second half of the trial associated with the outbreak of ciprofloxacin-resistant *S. epidermidis* infection. This led to a tendency for the early addition of intravenous vancomycin, which was defined as clinical failure. Reflecting the lack of antistaphylococcal cover, the response within the gram-positive bacteremias was low at 40%; however, as a group, they behaved as relatively low-grade infections, and with the appropriate modification of therapy, all patients were successfully treated.

The main aim of this trial concerned the prevention of death from gram-negative bacteremias. The performance of these bacteremias must be discussed in relation to three factors: the recovery of neutropenia, antibiotic susceptibility, and synergy. De Jongh et al. have shown that the first of these is the most important (2). Patients whose neutrophil count rose tended to do well, irrespective of the other two factors. However, with persistent neutropenia, response was higher when the organism was susceptible to two antibiotics as opposed to one and again when synergy was present. Applying these considerations to our analysis, the comparable incidences of persistent profound neutropenia in both treatment arms meant that this factor operated neutrally. Susceptibility to both trial antibiotics was significantly higher during NC treatment. Although there was no statistically significant difference either in response to gram-negative bacteremias or in the three related deaths, the numbers were small, and there did appear to be a trend in favor of NC, a result which would be consistent with the in vitro susceptibility data.

The other seven deaths from presenting infection (five mixed bacteremias and two culture-negative pneumonias) occurred in a group with a high proportion of patients presenting with septic shock. Although six of the deaths occurred in patients treated with NP, this group contained patients with many poor prognostic factors.

All 10 deaths from presenting infection occurred in patients with solid tumors and lymphomas (stratum B), which may reflect the more intensive monitoring of leukemic patients following chemotherapy. The majority of patients with solid tumors or lymphomas were treated as outpatients, and there was inevitably a delay in starting their antibiotic therapy. In comparison with other studies, our death rate of 16.7% (3 of 18) from single gram-negative bacteremia is almost identical to the 16.9% (14 of 83) from the third EORTC trial (8). Our death rate of 8.4% from both proven and probable or possible infection is higher than the 4% (22 of 550) from a recent study conducted at the National Cancer Institute (11), but the mean age in that study was lower (28 years), as was the overall rate of bacteremia (81 of 550 [14.7%]).

Ciprofloxacin was very well tolerated, with only three minor side effects attributed to it. The switch to oral therapy was certainly feasible. Oral administration was more convenient for both patients and nursing staff and also reduced the cost of therapy. The high oral dose of ciprofloxacin was chosen because of lack of information concerning its absorption in neutropenic patients. Subsequently, Smith et al. have shown mean peak concentrations of 3.6 ± 2.2 μg/ml following oral doses of 750 mg twice daily in such patients (14).

In summary, the new combination of ciprofloxacin and netilmicin is as effective as piperacillin and netilmicin for the empiric treatment of fever in neutropenic patients. Ciprofloxacin was well tolerated, and the conversion to its oral formulation is both feasible and advantageous.

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