Pharmacodynamic Interactions of Antibiotics Alone and in Combination

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Clinical trials show that the area under the inhibitory curve (AUIC) is predictive of antibacterial killing rates in patients with nosocomial pneumonia and is useful for predicting clinical or microbiological outcomes and making dosage adjustments with β-lactams, quinolones, aminoglycosides, and vancomycin. The AUIC values of two antibiotics are additive, and since antibiotics are often given in combination, determining the AUIC for antibiotic combinations could potentially predict the microbiological outcomes for patients given these combinations. To further address this question, mathematical modeling was used to study in vitro pharmacokinetic and pharmacodynamic interactions of the antimicrobials piperacillin and ciprofloxacin. These agents were also studied in vivo in healthy volunteers. Blood samples were obtained for analysis of serum drug concentrations, and serum inhibitory titers were determined against eight common bacterial pathogens, chosen to reflect the range of MIC values to ciprofloxacin and piperacillin. Additive AUIC relationships predictive of bacterial killing rates were typical in patients given these antibiotics in combination.

Combinations of β-lactam antibiotics with aminoglycosides have been used extensively in the treatment of serious infections. Such combinations have generally been superior to monotherapy with β-lactam agents in important subpopulations, including patients with endocarditis [1], gram-negative sepsis [2], and pseudomonas bacteremia [3]. Although not always demonstrated to be superior, combination therapy is commonly used empirically for treatment of gram-negative pneumonia and other nosocomial infections, with the additional goal of ensuring a broad spectrum of activity. Double β-lactam combinations have also been studied but are not optimal as combination treatment regimens for seriously ill patients [4]. The potential for nephrotoxicity and ototoxicity from aminoglycosides has caused some clinicians to evaluate new possibilities such as combinations of fluoroquinolones and β-lactam agents. These combinations have shown promising results in small clinical trials [5–9, 10].

One of the first goals in the development of antibiotic dosing strategies is to develop a method that can effectively describe the relationship between pharmacokinetics, pharmacodynamics, MIC, and bacterial outcomes for single antibiotic therapy. We have conducted a number of studies of patients with nosocomial pneumonia, in search of the optimum parameter for quantitation of antibiotic exposure vs. antimicrobial outcome [11–17]. The typical optimized relationship between antibiotic serum profile, as the area under the curve (AUC) and MIC, is illustrated in figure 1.

For any antibiotic given at dosing intervals of 3–4 half-lives, there is general concordance between 80% of the AUC above the MIC of the organism and an area under the inhibitory curve (AUIC) of 125. For this reason, calculations of AUC and the AUC/MIC relationships in figure 1 would correspond to an AUIC over 24 hours ($AUIC_{24}$) of 125 [15]. As the MIC rises and therefore coverage becomes <80% of AUC above MIC, the resulting AUIC values fall further and further below 125, which is a correlate of clinical and microbiological failure [14–19] and microbial resistance [20, 21].

As we developed these models, the outcome measure for correlation with the pharmacokinetic/pharmacodynamic (PK/PD) parameters was usually bacterial eradication, for several reasons. (1) Bacterial eradication is a better marker for the action of an antibiotic, since in vitro and animal model studies demonstrate more consistent concentration relationships with reductions in the infection-site colony counts than with clinical cure, survival, or success vs. failure [22, 23]. (2) Animal model studies [22, 23] clearly identify bacterial eradication or reduction in numbers in a biopsied infection site as the most useful and predictive endpoint for the relationships between concentration, MIC, and outcome. (3) Time to bacterial eradication can be approximated as a time-sensitive process, lending more powerful statistical methodology to the task of characterizing PK/PD relationships to clinical or microbiological outcomes.

The relationships between AUIC and bacterial eradication rate in vivo have been determined for several antibiotics. In figure 2, the relationship between the AUIC for ciprofloxacin and bacterial outcome is characterized in a plot of respiratory infection bacterial survival vs. time [19]. Typical of concentration-dependent action, there were multiple statistically significantly ($P < .001$) different AUIC breakpoints in this relation-

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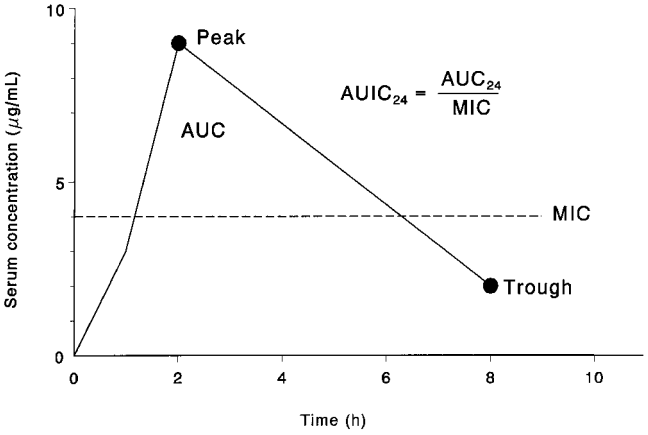

Figure 1. *Solid line,* relationship between the concentration-vs.-time curve, as area under the curve (AUC) over 24 hours (AUC_{24}), and the MIC against the organism (*dashed line*). The interaction shown is descriptive of 80% time (or AUC) above MIC or mathematically equivalent to a 24-hour area under the inhibitory curve ($AUIC_{24}$) of 125.

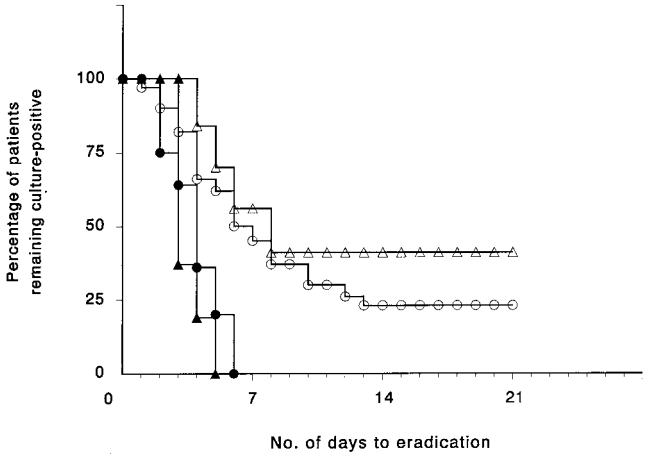

Figure 3. Relationship between ceftazidime (*triangles*) and cefmenoxime (*circles*) AUIC values and bacterial eradication rates. Shown are data for each drug at values <125 (△, ○) and >125 (▲, ●).

ship. The most important was the group with AUIC < 125, in which treatment failed for 70%. Multiple breakpoints are typical for the antibiotics with concentration-dependent killing rates, such as fluoroquinolones and aminoglycosides. Clearly, more rapid bacterial eradication can be achieved with higher AUIC values.

On the basis of these data, we have argued for an AUIC breakpoint of ⩾250 for ciprofloxacin [19]. Obviously, for relatively nontoxic drugs like the fluoroquinolones, there is an advantage to raising doses to achieve more rapid bacterial killing, especially in cases of lower respiratory tract infection, if it can be shown that care will be less expensive for patients

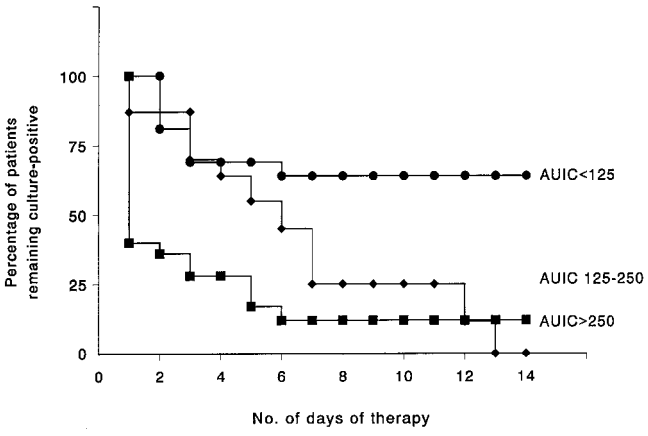

Figure 2. Relationship between the 24-hour area under the inhibitory curve ($AUIC_{24}$) for ciprofloxacin and the bacterial eradication rate for 74 patients with respiratory tract infections. Shown are three statistically different ($P < .001$) lines: AUIC < 125 (●), AUIC 125–250 (◆), and AUIC > 250 (■). (Adapted from [19].)

extubated earlier and discharged earlier from the intensive care unit [24].

For antibiotics with concentration-independent bacterial killing rates, like the cephalosporins [12, 16, 25] and vancomycin [17], there are only two statistically significantly different AUIC breakpoints: >125 and <125 ($P < .01$). Typical data on AUIC vs. bacterial eradication times are shown in figure 3 for ceftazidime and cefmenoxime, two third-generation cephalosporins with time-dependent bacterial killing. The format is the same as in figure 2, but with the cephalosporins there is no evident improvement in the rate of bacterial killing as the AUIC becomes higher and higher above 125. Indeed, the maximum AUIC in figure 3 approached 10,000, yet there were no bacteria eradicated at 24 hours into therapy.

These results confirm that both time above MIC and the AUIC are predictive of bacteriologic outcome for these time-dependent-killing antibiotics. Both parameters are useful, because an AUIC of 125 approximates 80% of time above MIC, as well as 80% of the AUC above MIC. There is strong concordance between the two parameters whenever dosing intervals are <4 half-lives. Obviously, as intervals between doses become quite long, the concordance will disappear. Thus, it is necessary to limit dosing intervals to within 3–4 half-lives if the correlation is to be maintained.

When dosing intervals are reasonable within these guidelines (i.e., <4 half-lives of the antibiotic in question), adequate time above MIC is ensured and the AUIC is predictive of bacteriologic outcomes. In contrast, when dosing intervals vary widely, and especially when intervals are long for the relatively short-half-lifed antibiotics, then time above MIC is more often predictive of bacterial killing with β-lactams than is the AUIC. This has been a point of argument between animal models and human trials, but it is readily resolved by ''humanizing'' the

pharmacokinetic data, as has been done recently by Ebert et al. [26] and Craig and colleagues [27].

As these relationships are predictive for single agents, it seems reasonable that the clinical utility of combination antimicrobial therapy can be explored with use of the same in vitro and in vivo pharmacodynamic studies in patient trials. At a minimum, these studies must address pivotal issues such as in vivo pharmacokinetics and achievable plasma concentrations in relationship to the MIC against the organism. The differences in pharmacokinetics between humans and animals may lead to misleading conclusions in experimental therapeutic models [22, 27].

In vitro interactions are usually assessed by the checkerboard method or time-kill studies [28]. To be useful, in vitro studies must evaluate clinically relevant concentrations of both antimicrobials. Synergy determined by either the checkerboard or time-kill method has not been shown to correlate consistently with improved clinical outcome. Moreover, there is lack of concordance between these two in vitro methods [29–31], perhaps because of problems inherent in the checkerboard methods [29]. It is also likely that in vitro study design has not often been optimized to test these principles rigorously.

Serum cidal activity has also been used to assess the activity of antibiotic combinations [32, 33], thereby ensuring that clinically relevant concentrations are evaluated. Antimicrobial activity has also been assessed with use of the area under the bactericidal time curve [34]. Our laboratory has extended these methods to serum inhibitory titers and serum ultrafiltrate titers [35]. From these investigations, there is evidence that AUIC can predict microbiological and clinical cure rates [15–17].

The challenge is to use the AUIC method effectively to characterize combination therapy as well as it has done with single agents. Theoretically, AUIC values would be additive, and the effect of additivity would be characterized as bacterial killing in vivo in direct relationship to the sum of two AUIC values (in the case of two antibiotics). Obviously, any bacterial eradication that occurs more rapidly than would be predicted by the sum of the two AUIC values could meet criteria for synergy. Antibacterial killing rates that occur more slowly than predicted would potentially indicate antagonism. These additivity principles can be tested quite readily in our patients with nosocomial pneumonia.

Volunteer Model

In order to evaluate these relationships in advance of studies of patients, we have developed a pharmacodynamic model to evaluate antimicrobial interactions in healthy volunteers given single and combination antimicrobials. This method allows assessment of combination antimicrobial activity and interactions from clinically relevant concentrations. This study utilized serial serum ultrafiltrate inhibitory titers along with pharmacodynamic modeling to address the interaction between ciprofloxacin and piperacillin. The study [36] utilized a crossover design and included 12 healthy subjects (6 males and 6 females). The subjects received each of the following treatments iv at weekly intervals: 4.0 g of piperacillin over 30 minutes, 400 mg of ciprofloxacin over 1 hour, and 400 mg of ciprofloxacin over 1 hour plus 4.0 g of piperacillin over 30 minutes. Serum drug concentrations for ciprofloxacin and piperacillin were determined by means of high-pressure liquid chromatography methods that were developed and validated at this laboratory.

Table 1. MIC and calculated $AUIC_{24}$ values for ciprofloxacin, piperacillin, and the combination of these agents.

	MIC (μg/mL)		$AUIC_{24}$		
Organism (strain)	Cip	Pip	Cip	Pip	Cip + Pip
Enterobacter cloacae (1)	0.25	48	140	28	168
E. cloacae (2)	0.03	3	1,166	452	1,618
Klebsiella pneumoniae (1)	0.06	48	583	28	611
K. pneumoniae (2)	0.05	24	700	56	756
Pseudomonas aeruginosa (1)	0.5	6	70	226	296
P. aeruginosa (A)	0.25	12	140	113	253
Staphylococcus aureus (1)	0.25	48	140	28	168
S. aureus (A)	0.5	0.5	70	2,710	2,780

NOTE. $AUIC_{24}$ = area under the inhibitory curve over 24 hours; Cip = ciprofloxacin; Pip = pipercillin.

There were eight test organisms, including two strains each of *Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae,* and *Enterobacter cloacae.* Serum ultrafiltrate inhibitory testing was performed as described by Leggett et al. [37]. The individual pharmacokinetic parameters for each drug were estimated with use of ADAPT II (Biomedical Simulations Resource, Los Angeles) and the MAP Bayesian algorithm. Model discrimination was accomplished with use of Akaike's information criterion [38]. Statistical comparisons were made with the Systat software package (Systat, Evanston, IL).

The MIC and $AUIC_{24}$ values calculated for each organism are shown in table 1. These values are derived from the pharmacokinetic parameters in table 2 [36]. A good mix of organisms was chosen for this study, in that some of the bacteria were more susceptible to ciprofloxacin or piperacillin, some were susceptible to both approximately equally, and some were relatively unsusceptible to both, clearly justifying combination therapy. *Pseudomonas* typically is the latter: against this organism, MIC values of both antibiotics are on the high end (table 1).

In theory, a measured serum inhibitory titer can be predicted from the drug concentration as the $AUIC_{24}$ and the bacterial MIC. Figure 4 shows the relationship between measured inverse serum ultrafiltrate inhibitory titers and the predicted serum inhibitory titer. The calculation of predicted serum activity was adjusted 16% for protein binding of ciprofloxacin and piperacillin [39, 40]. This figure demonstrates concordance between the measured and predicted serum activity.

Table 2. Pharmacokinetic parameters for ciprofloxacin and piperacillin.

Parameter	Ciprofloxacin	Piperacillin
Dose (24 h)	1,200 mg	16,000 mg
V_c (L)	52.2	11.4
$V_{peripheral}$ (L)	88.9	0.99
V_{ss} (L)	141.2	11.4
CL_D	48.1	0.68
CL_{total}	34.0	11.8
AUC_{24} ([mg·h]/L)	35	1,355

NOTE. AUC_{24} = area under the curve over 24 hours; CL_D = distributional clearance; CL_{total} = total clearance; V_c = volume of control compartment; $V_{peripheral}$ = apparent volume of the peripheral compartment; V_{ss} = apparent volume of distribution of steady state.

The pharmacokinetic characteristics of piperacillin and ciprofloxacin provided in table 2 were similar to values in previously published data [40, 41]; however, concomitant administration of piperacillin caused a statistically significant reduction in the clearance and steady state volume of distribution of ciprofloxacin [36]. A similar interaction has been reported with the combination of ciprofloxacin and azlocillin [42, 43]. As β-lactams and quinolones are both secreted in the proximal tubule, the mechanism is probably a competition for active transport. The predominance of the effect on ciprofloxacin is probably a consequence of the higher molar concentration of piperacillin present in the proximal renal tubule.

The MICs for monotherapy with ciprofloxacin and piperacillin showed ciprofloxacin to be more potent than piperacillin. Consistent with lower MIC values, ciprofloxacin showed greatest activity against *Klebsiella* and *Enterobacter* and lesser activity against *Pseudomonas* and *Staphylococcus* organisms. Piperacillin showed greatest activity against *Pseudomonas* and *Klebsiella* organisms and least activity against *Enterobacter.* The pharmacodynamic interaction was additive for the combination of piperacillin and ciprofloxacin [36].

Discussion

Clinical and microbiological outcomes after therapy with single agents are becoming considerably more predictable now that studies are emerging that correlate microbial, clinical, or microbiological outcomes with PK/PD parameters like the time above MIC, peak-to-MIC ratio, and AUIC. However, the same level of predictability is definitely not afforded by antimicrobial combination regimens, even though the use of single-agent regimens is uncommon for seriously ill patients in critical care units.

Anxiety with regard to the PK/PD of combination regimens is lessened if (1) one assumes additivity occurs in most cases of antibiotic interaction (which is likely to be true, given the outcome of the majority of in vitro studies) and (2) one agrees that the AUIC is the only additive parameter of the available choices. Although many combination regimens could be chosen to illustrate the impact of combination regimens on bacteriologic, clinical, or microbiological outcomes, there are actually few useful clinical PK/PD-vs.-outcome data on any combination except ciprofloxacin plus piperacillin.

In order for a study to provide data useful for a clinical PK/PD discussion, it should note all of the following for each patient: results of daily infection site cultures, to estimate rate of bacterial eradication; serial measurements or estimates of serum concentration for AUC; and an accurate measurement of the MIC against the infecting pathogen, for use in calculation of the AUIC. Not only is at least one of these elements missing from virtually all clinical trials, but even animal models may miss one or more of the elements necessary for full model development. Accordingly, our choice of ciprofloxacin and piperacillin tapped the most extensive combination data available, even if here, too, the data are rather sparse.

Several in vitro studies have been performed to evaluate quinolone/β-lactam combinations. Among 220 clinical isolates of Enterobacteriaceae and *P. aeruginosa,* checkerboard studies of ciprofloxacin plus piperacillin revealed an additive interaction for >99% of the isolates [43]. Among 108 clinical isolates of *P. aeruginosa,* synergy was demonstrated by the checkerboard method for ≥50% of isolates that were resistant to ciprofloxacin (MIC, >2 μg/mL) but susceptible to a β-lactam. However, among quinolone-susceptible, β-lactam-resistant organisms, synergy was demonstrated in ≤10%. Among organisms that were susceptible to both drugs, synergy occurred at a rate of ≤20% [44]. No antagonism was seen. Ciprofloxacin-resistant isolates (MIC_{90}, 4 μg/mL) showed synergy between ciprofloxacin and piperacillin at a rate of 21%; however, the MIC_{90} of piperacillin was not stated [45]. In another study (piperacillin MIC_{90}, 256 μg/mL; ciprofloxacin MIC_{90}, 1 μg/mL), synergy occurred at a rate of 12.5%, and no antagonism was noted [46].

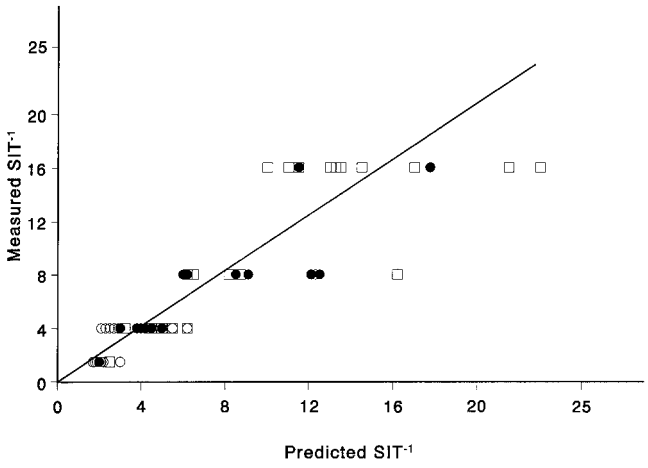

Figure 4. Measured vs. predicted inverse serum inhibitory titers ($SITs^{-1}$). Data are shown for ciprofloxacin (○), piperacillin (●), and ciprofloxacin plus piperacillin (□).

Our in vitro experiments used more rigorous methods [29] than employed by the checkerboard model and demonstrated additivity between ciprofloxacin and piperacillin for the eight organisms tested. For some of the organisms, there were a few isolated cases in the ''possible synergy'' and ''possible antagonism'' range. In subsequent studies, this variability has been reduced by more intensive prior characterization of the MICs. In the current study, none of the test organisms exhibited resistance to ciprofloxacin. Thus, it is unknown whether synergy would be shown in the circumstance of quinolone resistance and β-lactam susceptibility, as was shown in the in vitro study mentioned previously [44].

A few clinical trials involving febrile neutropenic patients have been conducted to evaluate the combination of a quinolone and a β-lactam agent [5–9]. Four randomized trials compared ciprofloxacin/azlocillin to a β-lactam/aminoglycoside combination [5–7, 9]. These small trials showed similar response rates between the two treatment groups and suggested that a quinolone/β-lactam combination was as efficacious as a β-lactam/aminoglycoside regimen.

In a noncomparative trial of ciprofloxacin/piperacillin used in 47 episodes of febrile neutropenia (41 patients), an overall success rate of 61% was noted [8]. This study and another, larger trial [47] employed a low dose of ciprofloxacin (200 mg twice daily), which has been shown to be suboptimal as monotherapy [19, 47]. Area under the inhibitory-activity-vs.-time curve (AUC/MIC) has been shown to correlate with clinical and microbiological outcome and with time to bacterial eradication for ciprofloxacin and cefmenoxime [16, 19].

There are many situations in which AUC/MIC cannot be optimized with monotherapy because dose limits would be exceeded. In these situations, combination therapy is warranted. This concept was employed in a clinical study [10] in which ciprofloxacin was compared with ceftazidime. When the AUIC (AUC/MIC) of either monotherapy was suboptimal ($<$target AUIC of 250), a second drug was added. Piperacillin was added to ciprofloxacin and tobramycin was added to ceftazidime. In calculation of the target, AUIC was assumed to be additive for the two drugs. However, the outcome parameter would show faster-than-predicted response if synergy were present, and the predicted time of eradication would be earlier than actually observed if there was antagonism.

In vitro studies and serum ultrafiltrate models can be used to define the type of interaction present and to evaluate activity of antibiotic combinations against a panel of representative pathogens. This information can be helpful in designing more effective combination regimens to treat infections when a single agent is not adequate.

In conclusion, our studies provide strong evidence that the combination of ciprofloxacin and piperacillin is additive. When the fractional maximal effect method is used to describe the interaction [29], there are more cases of additive interaction than synergy. In patient trials, AUIC values are additive, lending support to this mode of describing the action of antibiotics in combination.

The combination of ciprofloxacin and piperacillin has the greatest potential for measurable benefit when the AUIC provided by ciprofloxacin alone is inadequate. This occurred with the *P. aeruginosa* strain 1 and *S. aureus* strain A listed in table 1. Organisms such as *Serratia marcescens* and *P. aeruginosa* for which the MICs of ciprofloxacin are >0.5 μg/mL are often included in this category. The combination of ciprofloxacin and piperacillin, although additive, would boost the total AUIC to values above 125, which are associated with better outcome.

An interesting situation is evolving with *P. aeruginosa* and piperacillin/tazobactam. It appears that a small proportion of *P. aeruginosa* strains are more susceptible to piperacillin/tazobactam than to piperacillin alone [48]. Our work [49] confirms that this in vitro advantage can translate into substantial increases in AUIC for ciprofloxacin in combination with piperacillin/tazobactam, compared with AUICs for ciprofloxacin combined with piperacillin alone [36, 49]. This situation is yet another example of how AUIC values, determined from the calculated or measured AUC and the MIC, can aid evaluations of combination therapy regimens, bridging the gap between studies in vitro, in animal models, and in the patient care setting.

Empirical therapy does not always require multiple combinations of the most expensive broad-spectrum agents in our armamentarium. The methods described here can help to make the distinction. When combinations are required, the AUIC values can promote selection of the best combination and calculation of the optimal dose. In this manner, the AUIC is a strong adjunct to the desired positive clinical outcome.

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