

# The impact of early cystic fibrosis diagnosis on pulmonary function in children

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**Objective:** To investigate the impact of early diagnosis on pulmonary function in a large cohort of children with cystic fibrosis (CF).

**Study design:** CF cases identified from the CF Foundation National Patient Registry and diagnosed between 1982 and 1990 were categorized as: early asymptomatic diagnosis (EAD; n = 157), early symptomatic diagnosis (ESD; n = 227), later asymptomatic diagnosis (LAD; n = 161), and later symptomatic diagnosis (LSD; n = 3080). Early CF diagnosis was diagnosis before 6 weeks of age; later diagnosis was diagnosis at 6 weeks to 36 months of age, inclusive. Asymptomatic diagnosis included diagnosis by either family history, genotype, prenatally, or neonatally. Pulmonary function was measured as percentage of predicted forced expiratory volume in one second (FEV<sub>1</sub>).

**Results:** There were no overall differences in pulmonary function among the 4 diagnostic groups. However, EAD cases born more recently (1987 or later) had a higher mean FEV<sub>1</sub> throughout the study, compared with the remaining diagnostic groups. For this later birth cohort, Cox regression analysis for those diagnosed later and/or symptomatically, demonstrated a 2-fold increase in risk (P = .06) for having moderate-to-severe pulmonary function (FEV<sub>1</sub> <70%) at ages 6 to 10 years, compared with EAD cases.

**Conclusions:** Children diagnosed with CF early, asymptotically and more recently may have better pulmonary function throughout early childhood, probably as a result of improved CF treatments in recent years. (J Pediatr 2002;141:804-10)

During the past two decades there has been much debate regarding whether early diagnosis of cystic fibrosis (CF) by newborn screening is beneficial in reducing long-term morbidity. Although most CF cases in the United

States are diagnosed by three years of age,<sup>1</sup> many subjects are already malnourished and have lung disease at diagnosis.<sup>2,3</sup> By implementing newborn screening (NBS) for CF, infants can be identified before the onset of the signs

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and symptoms of CF and nutritional supplementation can be initiated.

Pulmonary obstruction and infection, which lead to a decline in lung function, are the primary causes of morbidity and mortality among persons with CF. Sev-

## See related article, p 758.

eral observational studies have suggested that early diagnosis of CF may result in better long-term pulmonary function compared with CF cases diagnosed traditionally after the onset of signs and symptoms.<sup>4,5</sup> Although clinical trial data have not yet confirmed these findings, extensive data from a Wisconsin clinical trial demonstrated nutritional benefits in CF cases who were diagnosed by NBS compared with those diagnosed based on signs and symptoms

CDC	Centers for Disease Control and Prevention
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
EAD	Early asymptomatic diagnosis
ESD	Early symptomatic diagnosis
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
LAD	Later asymptomatic diagnosis
LSD	Later symptomatic diagnosis
NBS	Newborn screening

of the disorder, based on 13 years of follow-up (1985-1994).<sup>6,7</sup>

Using data from the Cystic Fibrosis Foundation (CFF) National Patient Registry, we investigate the impact of early diagnosis on pulmonary function in children 6 to 10 years of age. Asymptomatic CF cases diagnosed at <6 weeks of age were used as proxies for NBS, because one of the purposes of NBS is

to identify cases before the onset of symptoms. Pulmonary function of these CF cases was compared with the pulmonary function of subjects who were diagnosed between 6 weeks and 36 weeks of age.

## METHODS

### *Study Population*

The current study population included 3625 children with CF, diagnosed between 1982 and 1990 and followed to 1996, as reported to the CFF National Patient Registry; data collection methods were previously described.<sup>1,8</sup> Approximately 14,000 CF patients were enrolled in the patient registry in 1982, which grew to approximately 17,800 patients by 1990, reflecting ~75% CF patients in the United States.<sup>9</sup> During this time, the median survival age of CF patients increased from 21 years to 28 years.<sup>9</sup>

Our current analysis included children diagnosed with CF by 36 months of age. Children who had meconium ileus were excluded from the analysis. Furthermore, whereas as many as 17 years of follow-up were available, we limited analysis to 6- to 10-year-old children because of small numbers in the upper age groups.<sup>10</sup>

### *CF Diagnosis*

The diagnosis of CF was confirmed by sweat test or by DNA analysis. CF cases were grouped into 4 categories: early asymptomatic diagnosis (EAD,  $n = 157$ ), early symptomatic diagnosis (ESD,  $n = 227$ ), later asymptomatic diagnosis (LAD,  $n = 161$ ), and later symptomatic diagnosis (LSD,  $n = 3080$ ). Early diagnosis was defined as diagnosis before 6 weeks of age; later diagnosis was defined as diagnosis between 6 weeks and 36 months of age inclusive. Asymptomatic diagnosis was defined as diagnosis by family history, genotype, prenatal diagnosis (chorionic villus sampling [CVS] or amniocentesis), or neonatal screening. Symptomatic diagnosis was defined as

diagnosis due to clinical presentation with acute or persistent respiratory symptoms, failure to thrive or malnutrition, steatorrhea, abnormal stools, malabsorption, electrolyte imbalance, nasal polyps, sinus disease, rectal prolapse, or liver disease. The individual diagnoses were not mutually exclusive and more than one diagnoses may have been indicated per person; therefore, any diagnosis that included clinical presentation superceded any concurrent asymptomatic diagnosis recorded in the patient registry.

### *Pulmonary Function*

Pulmonary function was measured by forced expiratory volume in one second ( $FEV_1$ ) and forced vital capacity (FVC); as part of their accreditation by the CF Foundation, CF care centers are requested to perform spirometry in accordance with American Thoracic Society standards.<sup>11</sup> In the registry database, a single measure for lung function is recorded at the annual visit; whereas three expiratory maneuvers are conducted at each visit, only the best maximal effort is recorded as FVC and  $FEV_1$ .<sup>12</sup>  $FEV_1$  percent predicted measurements were calculated by using a modification of the Knudson equation.<sup>10</sup> We present data on  $FEV_1$  in the current manuscript because  $FEV_1$  is the best clinical predictor of CF mortality and prognosis<sup>13-16</sup>; results for FVC were similar to  $FEV_1$  results (eg, consistent risk estimates, statistical significance), and the  $FEV_1$ /FVC ratio was not informative for the outcomes of interest (eg, time to pulmonary impairment). Consistent with previous studies,<sup>10</sup> severe pulmonary function was defined as  $FEV_1 < 40\%$ , moderate pulmonary function was defined as  $FEV_1 < 70\%$ . Because of small numbers, we combined the groups with moderate and severe pulmonary function. We assessed impaired pulmonary function as  $FEV_1 < 90\%$  to increase sensitivity when delineating between impaired and moderate/severe pulmonary function abnormalities, and with the understanding

that some children with adequate pulmonary function might be misclassified as "impaired" under this definition. Because children  $< 6$  years of age are generally not able to perform pulmonary function tests reliably, pulmonary function by diagnostic category (EAD, ESD, LAD, and LSD) was analyzed beginning at 6 years of age.

### *Statistical Methods*

All analyses were performed using SAS, versions 6.12 and 8.2 for Windows (SAS Institute, Cary, NC). Statistical significance was set at  $P < .05$ , 2-sided. Mean  $FEV_1$  and percentages of children with moderate-to-severe pulmonary function and impaired pulmonary function were calculated by age for each diagnostic category. Univariate analysis was conducted to assess the association between early diagnosis and pulmonary function; all variables were analyzed as continuous outcomes before categorization as dichotomous outcomes. Stratification by gender and birth year was conducted; although gender did not modify the effect of early diagnosis on pulmonary function, birth year did appear to modify the effect on risk estimates of early diagnosis for pulmonary function. We illustrate the birth cohort effect by presenting stratification by the median year of birth for this cohort, 1987; we also use this cut-off because the data suggested a natural dichotomization at this point. For the birth cohort born after 1987, we limit data presented to 6 to 9 years of age because of the limited numbers with available pulmonary measurements at 10 years of age. Demographic and other relevant variables were compared across the 4 diagnostic groups to identify potential confounders, and subsequently explored in stratified analyses and/or included in the final regression model.

Risk estimates were generated with Cox proportional hazards regression models, with age (in years) as the time scale and time to moderate/severe pulmonary function or impaired pul-

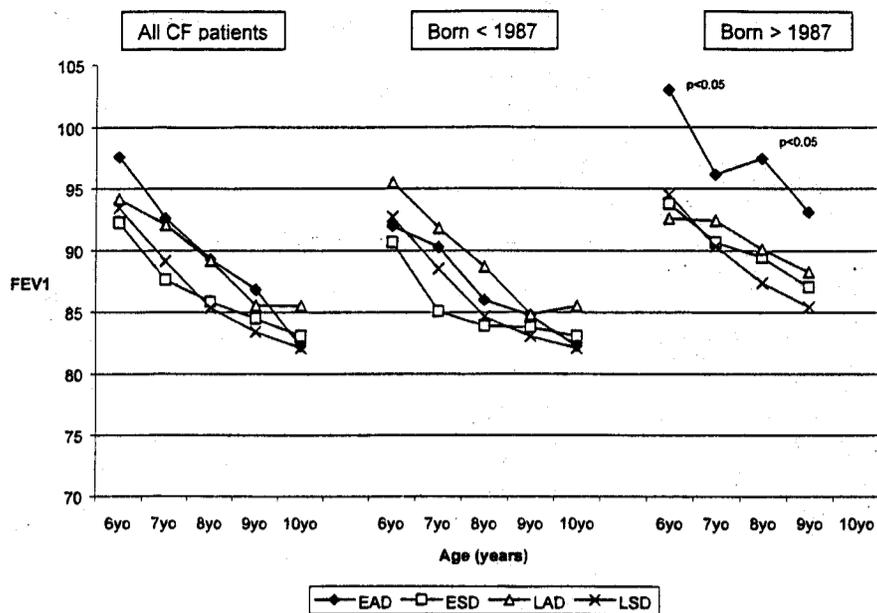


Fig 1. Mean FEV<sub>1</sub> values for patients with CF.

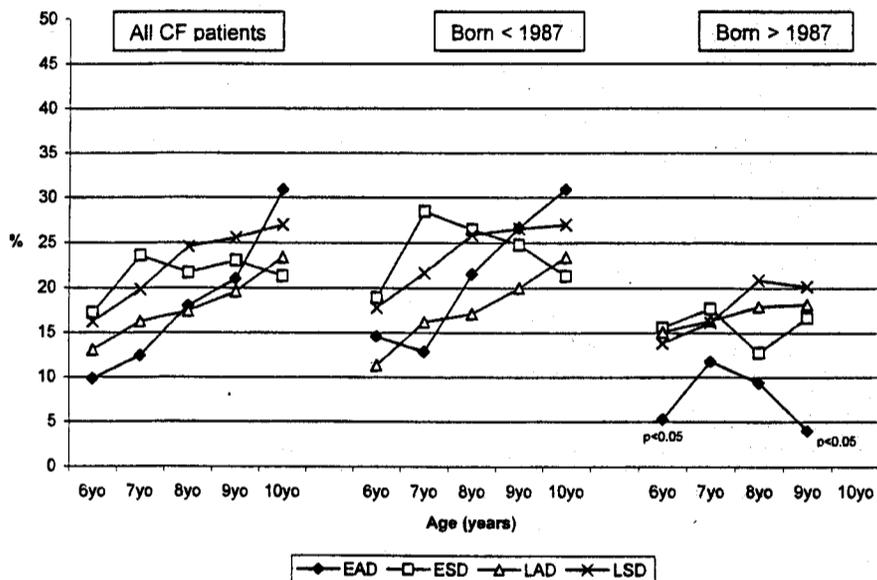


Fig 2. Cases with moderate-to-severe pulmonary function.

monary function developing as the outcome. Moderate-to-severe pulmonary function for each CF patient was defined as the first documented FEV<sub>1</sub> measurement <70%. Impaired pulmonary function was defined as the year of the first FEV<sub>1</sub> measurement <90%. Relative hazards analyses were adjusted for race, gender, pancreatic status, and place of birth; we report adjusted relative hazards with 95% confi-

dence intervals for moderate/severe pulmonary function.

## RESULTS

Table I displays demographic and clinical characteristics of all children included in the study at their baseline visit. The median ages of diagnoses were 3.6 weeks for EAD, 4.2 weeks for

ESD, 11.4 weeks for LAD, and 25 weeks for LSD. There were no significant differences among the 4 diagnostic groups in gender, ethnicity, or DF508 mutation status; however, there were statistically significant differences among the groups for race, year of birth, geography, pancreatic status, weight percentile, and height percentile (Table I). Race, geography, and pancreatic status were included in the final regression model; we present results stratified by year of birth to examine potential cohort effect.

To identify potential biases regarding the EAD group, we examined this group in relation to states with NBS programs (WI, CO, WY). Although persons in the EAD group did include those from states with NBS programs, the absolute number of persons categorized as EAD from these states was small; in fact more children from states with NBS programs contributed to groups other than EAD (Table I). The majority of those in the EAD and LAD group consisted of those diagnosed with CF via family history.

Fig 1 shows mean FEV<sub>1</sub> values for all CF patients 6 to 10 years old, those born before 1987, and those born on or after 1987. With increasing age, an increasing amount of pulmonary data were available, including 73% with pulmonary measurements at age 6 years, 86% at age 7 years, 92% at age 8 years, 95% at age 9 years, and 97% at age 10 years; these percentages did not significantly differ by diagnostic group. Although no significant differences are observed overall in CF patients, when stratified by birth year, those diagnosed early and asymptotically (EAD) and born on or after 1987 appear to possess higher mean FEV<sub>1</sub> values from ages 6 to 9 years (statistical significance at ages 6 and 8 years by *t* test), compared with those in other diagnostic groups.

Fig 2 shows the proportion of cases with moderate-to-severe pulmonary function, defined as FEV<sub>1</sub> <70%, among the 4 diagnostic groups. Overall, there was no significant difference in

**Table 1.** Characteristics of patients identified from the CFF National Patient Registry at time of diagnosis (1982-1990), excluding patients diagnosed at >3 years of age or with meconium ileus

Characteristic	EAD (n = 157) n (%)	ESD (n = 227) n (%)	LAD (n = 161) n (%)	LSD (n = 3080) n (%)	P value
Age at diagnosis (wk)					
Median	3.6	4.2	11.4	25	
Sex					
Male	78 (50)	130 (57)	80 (50)	1639 (53)	.379
Female	79 (50)	97 (43)	81 (50)	1441 (47)	
Race					
White	156 (99)	223 (98)	160 (99)	2931 (95)	.012
Black	1 (1)	4 (2)	1 (1)	128 (4)	
Other				20 (1)	
Ethnicity					
Non-Hispanic	147 (95)	213 (97)	152 (96)	2860 (95)	.591
Hispanic	8 (5)	6 (3)	6 (4)	136 (5)	
Birth year					
1979-1986	89 (57)	127 (56)	94 (58)	1999 (65)	.004
1987-1990	68 (43)	100 (44)	67 (42)	1081 (35)	
Geography*					
WI, CO, WY	55 (35)	10 (4)	35 (22)	91 (3)	.001
All other states	101 (65)	217 (96)	125 (78)	2975 (97)	
Pancreatic status					
Insufficient	118 (95)	171 (98)	101 (91)	1965 (96)	.022
Sufficient	6 (5)	3 (2)	10 (9)	81 (4)	
$\Delta$ F508 status					
$\Delta$ F508/ $\Delta$ F508	56 (58)	55 (50)	49 (54)	751 (54)	.562
$\Delta$ F508/other	12 (13)	23 (21)	16 (18)	216 (16)	
$\Delta$ F508/unknown	21 (22)	17 (16)	19 (21)	264 (19)	
Other	7 (7)	14 (13)	6 (7)	153 (11)	
NCHS weight percentile					
$\leq$ 5th percentile	27 (18)	59 (27)	32 (21)	1421 (48)	.001
>5th percentile	120 (82)	160 (73)	123 (79)	1543 (52)	
NCHS height percentile					
$\leq$ 5th percentile	14 (10)	49 (24)	25 (17)	1208 (42)	.001
>5th percentile	126 (90)	157 (76)	120 (83)	1642 (58)	

\*Indicates states with universal NBS programs for CF (Wisconsin, Colorado, Wyoming) versus states without universal NBS programs for CF.

the proportions of cases with moderate-to-severe pulmonary function. When stratified by birth year, however, the proportion of CF cases with moderate-to-severe pulmonary function was lower in the EAD group compared with the other groups among CF cases born during 1987 or later. Differences between mean FEV<sub>1</sub> levels were also more pronounced in the later birth cohort, reaching statistical significance at

6 and 9 years old, by  $\chi^2$  analysis. There was no significant difference for impaired pulmonary function overall or stratified by birth cohort (data not shown).

To assess whether early diagnosis was associated with the incidence of moderate-to-severe pulmonary function, we calculated a Cox proportional hazard model adjusting for race, gender, pancreatic status, and place of birth. This

model yielded no differences in risk for moderate-to-severe pulmonary function for the overall cohort or for the cohort of CF cases born before 1987. However, for children 6 to 10 years old, among CF cases born in 1987 or later, increases in risk for moderate-to-severe pulmonary function in ESD (OR = 2.17; 95% CI = 0.91, 5.21), LAD (OR = 2.18; 95% CI = 0.88, 5.35), and LSD (OR = 2.12; 95% CI = 0.97, 4.64) groups com-

**Table II.** Results from Cox proportional hazards model for moderate-to-severe pulmonary function, defined as <70% predicted for FEV<sub>1</sub>, in patients\* with CF, for all CF patients, those born before 1987, and those born in 1987 and after

Variable	Relative hazards (95% CI)		
	All CF patients	Born before 1987	Born 1987 and after
ESD	1.21 (0.78, 1.86)	1.00 (0.60, 1.66)	2.17 (0.91, 5.21)
LAD	1.23 (0.78, 1.96)	1.02 (0.58, 1.77)	2.18 (0.88, 5.35)
LSD	1.20 (0.84, 1.72)	0.99 (0.67, 1.48)	2.12 (0.97, 4.64)
Race (referent: white)	1.42 (1.05, 1.90)	0.97 (0.62, 1.51)	2.22 (1.49, 3.31)
Pancreatic status	1.74 (1.06, 2.86)	1.81 (0.99, 3.30)	1.66 (0.68, 4.03)
Gender (referent: male)	1.11 (0.97, 1.27)	1.10 (0.93, 1.29)	1.10 (0.87, 1.40)
Geography	1.22 (0.86, 1.73)	1.25 (0.78, 1.98)	1.01 (0.59, 1.75)

\*Excludes patients diagnosed at >3 years of age or with meconium ileus.

pared with the EAD group were observed (Table II). Although the risk estimates suggest a 2-fold increase in risk for moderate-to-severe pulmonary function, they were not statistically significant (eg, all confidence intervals included the null [1.0]). Nevertheless, the data do appear to suggest that those diagnosed later and/or symptomatically were roughly twice as likely to reach moderate-to-severe pulmonary status within 6 to 10 years of age, compared with those diagnosed early and asymptotically. This is consistent with Fig 1 of mean FEV<sub>1</sub> values where EAD children start off with higher mean FEV<sub>1</sub> values (in the latter birth cohort) and remain so for the duration of the study period. For impaired pulmonary function, no increases in risk were observed for the ESD, LAD, or LSD groups compared with the EAD group in either the cohort born before 1987 or the cohort born in 1987 or later (data not shown).

Lastly, growth parameters including weight and height percentiles dichotomized into ≤5th percentile or >5th percentile, were assessed at baseline, age 6 years and age 10 years. Height and weight measurements were analyzed in part to assure the validity of our current study by demonstrating its consistency with the findings from the Wisconsin clinical trial. Both height and weight were significantly different among the 4 groups at the time of diagnosis/enroll-

ment into the patient registry (Table I), with the EAD group having a smaller proportion of cases with height percentiles ≤5th and weight percentiles ≤5th. Differences in height percentile remained statistically significant at age 6 years and age 10 years; these results did not differ by birth cohort.

## DISCUSSION

Although the benefits and risks of neonatal screening for CF have been assessed in numerous studies,<sup>4-7,17,18</sup> few studies have reported direct effects of neonatal screening for CF on pulmonary function.<sup>4,5</sup> Two smaller observational studies have reported on the effect of CF neonatal screening on pulmonary function.<sup>4,5</sup> These studies reported mean FEV<sub>1</sub> and FVC levels significantly higher in children identified by NBS for CF, compared with children diagnosed with CF through other methods,<sup>5</sup> and demonstrated a greater decline in FEV<sub>1</sub> for CF patients not diagnosed through NBS.<sup>4</sup> Confirmation of these results from a population with a larger sample size and from a clinical trial-based design are therefore important.

Using data on all available CF cases from the CFF National Patient Registry, no statistically significant differences in pulmonary function were found among the 4 diagnostic groups from 6 to 10

years of age. However, when stratified by birth year, EAD cases born in 1987 or later had a higher mean FEV<sub>1</sub> compared with the other groups. This is further supported by results from our Cox proportional hazards model that indicate a 2-fold increase in risk (albeit not statistically significant) for developing moderate-to-severe pulmonary function within 10 years of age for those diagnosed later and/or symptomatically, compared with those diagnosed early and asymptotically. These results suggest that children diagnosed early and asymptotically possess better pulmonary function at 6 years old and likely remain so through 10 years of age. It is important to note that although mean FEV<sub>1</sub> values are higher for this group, an approximation of decline in FEV<sub>1</sub>, based on the slope of the line, appear consistent with that of the other diagnostic groups. The increases in risk for moderate or severe pulmonary function for those not diagnosed early and asymptotically in CF cases born in 1987 or later suggests a potential cohort effect attributed to improved treatment strategies; observational studies following children born in the 1990s and treated during this latter period may therefore observe an even more pronounced beneficial effect for pulmonary function. Although strengths of this study include the use of the CFF National Patient Registry, biases inherent to observational studies (eg, survivor-

ship) are likely to be present.<sup>19</sup> Our exclusion of those diagnosed after 36 months and restriction of the cohort to those with pulmonary data at 6 to 10 years of age, potentially resulted in a sicker cohort, and may be evidenced by the low pancreatic sufficiency in this cohort. Although the EAD group included those diagnosed by NBS, they consisted predominantly of those diagnosed with CF via family history. Our attempt to control for geography partially controlled for treatment and physician knowledge in children diagnosed in states with NBS programs. Further limitations include that pulmonary measurements were not necessarily attained every year; there was, therefore, potential for delayed identification of achieving moderate-to-severe pulmonary status, possibly resulting in a more conservative estimate of risk for the overall period. Lastly, that pulmonary function measurements were recorded according to Knudson's equation rather than other appropriate equations (eg, Wang)<sup>20</sup> is not likely to affect the current analyses where the outcome is impaired pulmonary function rather than rate of decline.

The results from this large observational study suggest that early diagnosis of CF in conjunction with improved treatment may lead to better pulmonary function in childhood. Future large collaborative observational studies should demonstrate whether improved treatment and access to such treatment as a result of NBS, results in pulmonary benefits. Further studies should also include longer follow-up time past puberty for FEV<sub>1</sub> decline when measurements are stable.<sup>21</sup> Other modifiers of lung function will also need to be taken into consideration, such as exercise, passive smoking, and asthma.<sup>10</sup> Longer follow-up with careful timing of lung function measurements will also be needed to accurately assess the rate of decline in lung function. Until doing so, it is unclear how the delay in onset of pulmonary impairment indicated in these current data are to be considered

with the lack of delay of *Pseudomonas aeruginosa* acquisition previously reported.<sup>22-24</sup> There are currently many products in clinical trial that could alter the benefits of early intervention, such as the prevention of *P aeruginosa* infection with a *Pseudomonas* vaccine. The suggestive improvement seen only in the latter birth cohort underscores the importance of these types of analyses on the benefits and risks of NBS for CF children today. Further research is therefore needed to establish long-term beneficial effects of NBS on pulmonary function, especially in the face of improvements in care.

For policy decisions, these data should not be used alone, but taken in conjunction with the nutritional benefits observed in the Wisconsin trial and results from other studies. The results presented here support the 1997 Centers for Disease Control and Prevention workshop policy decision that states that each state considering CF NBS should do so under a controlled research protocol where participation is not mandatory and where informed consent is emphasized.<sup>25</sup> New evidence regarding early nutritional benefits, improved cognitive function or pulmonary function, or new evidence regarding the effectiveness of CF therapies would support a policy change.

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