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Prediction and prevention of allergic disease in at risk children

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Abstract. – **Allergic asthma and rhinitis, atopic dermatitis (AD), urticaria and gastrointestinal allergy, are common diseases of infants and children. Their phenotypic expression varies widely, being very mild in some cases, severe and frustrating in many, but even life-threatening in others. Specific IgE to foods and positive challenge test to a number of food allergens are frequently present in children with these disorders. Cow's milk (CM) appears to be the most common offending food both in gastrointestinal and in cutaneous manifestations of atopic disease. It was recently estimated that 14% of children suffer from AD and about 25% from more or less adverse reactions to CM. Babies of atopic parents are at high risk of developing atopic diseases. The main goal of modern medicine is prevention of chronic and severe diseases. Food allergy (FA) and AD may negatively interfere with the child's life and his physical and physiological development. We stress that few diseases like AD, although not being lethal, are causes of invaluable physical and emotional suffering either for children or their parents. Indeed, severe AD confronts doctors with one of their most demanding challenges: too long has this condition been neglected. Sensitization to foods occurs more commonly early in life, however it may even occur prenatally. The possibility of preventing such disorders in predisposed children has stimulated the investigators' imagination since the beginning of this century, when atopic diseases were not so common. However, the possible influence of early diet on later FA has received much attention only in the last decade.**

Prevention of FA might be achieved by altering the dietary factors, which are responsible for the sensitization and for the phenotypic expression of the disease. As the crucial expression of allergic disease results from an intricate interrelationship between the atopy-prone genetic constitution and the encountered environment, prevention of IgE-mediated disease could potentially be approached by selectively interfering with the major forces, genetic and environmental, that appear to be responsible in concert for the ultimate phenotypic expression of atopy.

Key-Words:

Cyclosporin A, Bioequivalence, Microemulsion, Pharmacokinetics, Immunosupression.

Introduction

Several reports show that the incidence, prevalence and severity of atopic disorders is steadily increasing especially in the last 20 years[1-5]. In a recent study Burr et al[2] report that the prevalence of the more important allergic diseases of children is more than doubled between 1973 and 1988. Therefore atopic diseases (bronchial asthma, allergic rhinitis (AR), allergic conjunctivitis, AD, allergic urticaria, and FA) represent a major health problem in industrialized countries. As regards the reactions to CM, in a study on 1749 babies followed-up from birth to three years of age, Host e Halken have found that only 39 children had allergy to CM (CMA) (2,2%)[3].

It is been long known that atopic diseases are polyfactorial, and that their phenotypic expression appears to be regulated by genetic, and modulated by environmental factors, both affecting the development of atopy. Thus the ultimate expression of allergic disease results from an intricate interrelationship between the atopy-prone genetic costitution and the environment[6-15].

Prevention of IgE-mediated disease could potentially be met by selectively interfering with the major forces, genetic and environmental, that appear to be responsible in concert for the ultimate phenotypic expression of atopy. The offsprings of atopic parents are especially prone to develop atopic disease, con-

sequently they are defined "high-risk" (HR) babies[16-19]. The first weeks of life are extremely important for the expression of the allergic phenotype, because the mucosal and immune systems of newborns and young infants may be particularly vulnerable to a variety of environmental influences that should be avoided. Hence the preventive programs devised for such neonates should begin since the very moment of their birth and be continued as long as necessary.

Genetic Factors

The first study on the inheritance of asthma and AR dates back to Cooke e Van der Veer in 1916. In a monumental work the familial aggregation of atopy and its genetic inheritance was underlined[20]. Family history (FH) positive for atopic disease is the genetic predisposition to IgE mediated hypersensitivity reactions, and is certainly the prerequisite to define a neonate "HR"[21]. Children with a parental history of atopic disease are at a higher risk for the development of atopic symptoms. In addition these children develop atopic symptoms earlier than those with negative FH[22]. It has been found that if one parent is affected, the chances of an offspring being affected vary between 20 and 40%. If both parents are affected the figure increases to 40-60%, and 50-80% if both show the same allergic manifestations. The risk of atopy in children with an allergic sibling vary between 25 and 35%[14,23,24]. A baby with a negative FH still has about a 5-15% risk of developing atopy. Also the severity of atopic symptoms appears to be genetically modulated[14], as well as the levels of total and specific IgE antibodies[25].

There was general agreement that in the individuation of HR neonates, not only a careful FH, but also the measurement of IgE levels in cord blood (CBIgE) are crucial. Several studies have demonstrated that CBIgE levels after some favourable data[26-28], lack of sensitivity and have a poor positive predictive value[29-31]. Lilja et al[32] have shown that some blood sampling techniques can influence quantitatively the determination of IgE levels. These workers, comparing three different techniques (aspiration from the umbilical vein, capillary collection at 4-5 days of life, and gravity collection) in at risk babies, have concluded that the first two techniques are less contaminated with maternal blood than gravity collection and should therefore preferred in studies related to the prediction of allergic diseases[32].

Prenatal Factors

Antibodies to CM, egg and wheat have been detected in both the amniotic fluid and cord blood. Since the mothers had no antibodies to these allergens, it follows that the antibodies had been synthesized by the fetus[33,34]. It has been demonstrated that the fetus of about 22 weeks of gestation is capable to respond to several allergens, both foods and inhalants[35-37]. Such antenatal sensitization could suggest the necessity, in atopic families, to avoid food antigens in the diet of pregnant and nursing mothers. It was consequently recommended to atopic women not to ingest also during pregnancy excessive amounts of offending foods such as egg, CM, peanut and fish[38-42]. Recent studies failed to show any preventive effect of total abstention from CM and egg from gestational week 28 to delivery between offsprings of mothers on the above dietary manipulations and children for whom no prevention was adopted[41,42].

Perinatal Factors

In the very first months of life many allergens may enhance sensitization and also trigger an allergic reaction in a sensitized child. The month of birth seems to be a predisposing factor in atopy sensitization: a significantly higher incidence of sensitization to pollens in children born in March-May and to mites in children born in September-October has been shown by several investigators[43-45]. In Western countries the birth in September and October is accompanied with the highest incidence of sensitization to Dermatophagoides pteronyssinus (Der p), while children born in spring present with a higher incidence of pollen allergy[46-48].

Environmental Factors

Among the environmental factors favoring the development of atopic disease, *cigarette smoke* plays by far the primary role[49]. Evidence is already accumulating that there is a connection between parental smoking habits and atopic symptoms in children, notably the daily exposure in their own house: in a recent study 58% of allergic children with severe asthma (aged 12-45 months) was exposed to passive smoking compared with 37% of not allergic babies[50]. Epidemiologic studies show that cigarette smoke can decrease the IgG, IgA and IgM serum levels[51]. Several authors studying the relationships between cigarette smoking and serum IgE antibody levels have reported higher IgE concentrations in adult smokers and their offsprings compared to nonsmokers and to controls, respectively[14,51-53]. It has been consistently been found that environmental tobacco smoke exposure is associated with morbidity, increased cough, wheezing respiratory illness, bronchospasm, airway responsiveness, and increases in the number of emergency department visits[54-57]. The odds ratio for wheezing children of smokers was 1,36, and it was higher in babies under the age of two[57]. Several are the mechanisms through which tobacco smoke could exert its morbid effects in infants exposed[57,58]. Indoor cigarette smoke has also been proposed as increasing the risk of a direct action on the immune system with an increase in CD4+ cells and changes in CD4+/CD8+ ratio[59]. In HR babies were evident the effects of parental smoking on IgE serum levels from their birth to three years of age: the IgE concentrations were higher in children from households with smoking parents, and there was a significant difference at 9 and 36 months[52]. Longitudinal studies have evaluated the influence of parental smoking on IgE levels in cord blood and the subsequent development of allergic disease in the first years of life[60]. Maternal smoking appears to have an effect primarily important on IgE production during the fetal life, also carrying the risk of a later development of infant allergy[61]. The bulk of studies that have examined the relationship of maternal cigarette smoking to wheezing symptoms and asthma episodes in infancy have found a positive association: in children of a mother smoking only 10 cigarettes/day there is a higher risk of subsequent asthma and a reduced pulmonary function at one month of age[62-65].

Viral infections in the pediatric age frequently trigger asthmatic attacks[66] in addition to favoring and exacerbating AD lesions[67]. Their cytopathic effect on gut mucosal membranes might increase the permeability of intestinal wall, thus favoring antigen penetration[67]. Supportive data show the necrotizing action with which several influenza and parainfluenza (types 1-3) virus can typically damage the bronchial mucosa, denuding it of the epithelial lining, thus facilitating the aeroallergen penetration[68,69]. Viral respiratory infections trigger wheezing, transient airway responsiveness[66], high IgE levels, RAST positive responses, and histamine release from leukocytes after infectious episodes[69]. In the classic study done by Frick et al, in 11 children out of 13 the allergic sensitization was precipitated by recurrent airway infections[70]. Recent data support the hypothesis that measles infection[71] and/or delayed hypersensitivity to tuberculin[72] are associated with reduced asthma prevalence ("hygiene hypothesis"), while from an immunological standpoint, frequent infections in early infancy causing high IL_{12}, IL_{18}, and IFN-y production would lead to downregulation of Th2 responses and detrimental circumstances for allergen sensitization[73].

The significance of the early *exposure to inhalants* in the atopy development (Figure 1), stresses the prerequisite of reducing, where feasible, the level of environmental allergenic load of the child in the first years of life[22,74]. Some determinants of asthma are modifiable,

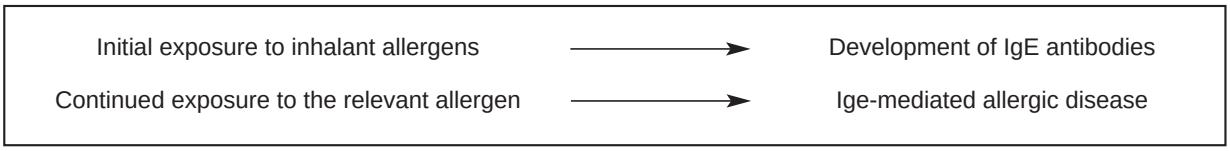

Figure 1. Effects of inhalant allergens.

and are the target for preventive measures, such as house dust mite (Der p)[74]. The HR babies should strictly avoid contacts with pets: it has been documented that sustained exposure to indoor allergens postnatally may be a determinant of subsequent atopy[22]. Platts-Mills et al[75] have shown that there are house dust mite allergen concentrations critical for the sensitization and asthma development. They have demonstrated that levels of Der p l >2 µg/g of dust increase the risk of sensitization, symptomatic asthma, and bronchial hyperreactivity. Although the asthma phenotype may not be fully manifest until later childhood, in a prospective study on 13 children followed-up from birth to 11 years of age, 12/13 had asthma at age 11, which was significantly related to the exposure to >10 µg of Der p 1 during the first two years of life. Sporik et al concluded that "we believe that increased exposure to dust mites and other indoor allergen may be a factor contributing to the recent increases in the morbidity and mortality associated with asthma[76]".

Dietary Factors

Early exposure to food allergens is associated with an increased risk of sensitization, since the offending foods represent the more common cause of allergic symptoms in the first months of life, when increased uptake of allergens exists, and the intestinal barrier is more permeable to macromolecular absorption.

The immune mechanisms suited to the antigen exclusion and elimination are physiologically immature, thus permitting to food antigens to penetrate the gut barrier[77]. It is therefore increasingly apparent the immune protection of the vulnerable neonate insured by breast milk[77-79]. Several prospective observational studies confirm the protective value of human milk in the extrauterine environment and in the following critical period, and as an effective tool in preventing the early development of symptoms of sensitization[77-79]. The phenotypical expression of atopic diseases has been a target for preventive medicine since 1936 when Grulee and Sanford recommended dietary intervention in newborns[80]. Moreover, additional studies have shown a lower incidence of AD in breast-fed babies compared to bottle-fed infants, however other studies failed to show a clear-cut effect of breast-feeding, supplemented or not with other formulas, on the later occurrence of allergic disease[81].

Sensitization through breast milk. Babies exclusively breastfed are not infrequently affected by AD[82]: on the other hand, breast milk is not as antigen-free as it is usually thought, since minute amounts of food antigens ingested by nursing mothers can pass into the human milk[82,83], thus inducing in the child atopic manifestations[82]. Furthermore, IgE antibodies to different foods such as CM, egg, etc have been shown in fully breast-fed babies: however a recent study has demonstrated that sensitization through breast milk is very uncommon (0,042% of cases)[84]. Indeed small amounts of CM or egg allergens in the maternal diet might be transferred into the breast milk and act as a "booster dose", triggering an anaphylactic shock in the breastfed baby. According to our opinion this shock is frequently labelled as "allergy to breast milk" whereas it is due to hypersensitivity towards CM proteins, as elegantly discussed by Lifschitz et al[85]. In support of this assumption, it should be noted that human milk contains levels of β-lactoglobulin which were found always lower than the levels in CM[86]. In order to prevent an allergic sensitization through breast milk we have therefore suggested the avoidance of foods eliciting hypersensitivity responses during breastfeeding of an HR baby, especially CM, eggs, fish and peanut[87].

Occasional supplements in nurseries. Particularly sensitizing could be in addition the occasional supplements of CM which are often given even to breast-fed babies. Such little supplements of allergens, in a predisposed newborn, are more sensitizing than the higher doses[77]. The results of several studies examined by us support the hypothesis that CMA is significantly more common in children fed CM supplements in the "window period" compared with babies exclusively breastfed early in life[77]. Høst et al[88] support this hypothesis, since the authors have reported that only the 39 fully breast-fed babies who developed adverse reactions to CM, none of whom had symptoms at the first exposure to CM, *received supplements of CM in the nursery.*

Dietary manipulations during the first months of life. According to several studies, the protective effect of the exclusive breast feeding for the first six months of life could be explained by the delayed introduction of solid foods[89]. Consequently in HR babies, breast feeding reduces the incidence of allergic manifestations only if is exclusive and protracted, that is associated with a delayed weaning[18,77,87-90]. Saarinen e Kajosaari[89] have shown after a 17-year follow-up that breast feeding prevented FA with highly significant differences as well as respiratory allergy. Which are the plausible readings of such effects of human milk? In the first place breast milk provides the infants not only with homologous proteins which are not allergenic but also with a number of immunological factors which can prevent the absorption of macromolecules, and promote the natural maturation of gut barrier and of MALT (mucosa-associated lymphoid tissue). Breast feeding prolonged for the first six months of life can passively prevent the uptake of food allergens: secretory IgA and the other immunoglobulins present in human milk might accomplish a specific protection of the gastrointestinal mucosa still immature of the infants[77,89].

Tvpe and age of weaning. The role of type and age of weaning on the development of AD has been further shown by the longitudinal study of Fergusson et al[90] with a 10-year follow-up in a cohort of unselected children. An increased rate of eczema was associated in a highly significant way with the introduction of solid foods during the first 4 months of life, as well as with the number of different foods given at that age[90]. On the contrary, a prolonged (9 months) breast feeding[91] associated with introduction of solid food, may increase the prevalence of AD[90]. Hence, solid foods should be introduced one at a time, so parents or caregivers can identify and eliminate any food that cause a reaction.

Substitutes of CM. There is no agreement on the most suitable formula if the mother cannot breast feed. We stress the remarkable positive effects of soy protein formulas (SPF) in HR babies[87,92-96]. SPFs are nutritionally adequate, and unquestionably less sensitizing compared to CM, also insuring a regular growth even if given from birth and during long periods of time[93]. Some studies have shown that SPF, or breast-feeding supplemented with SPF for the first six months of life significantly reduced the prevalence of atopic diseases[87,92-95,97], with some controversial results (ref in 93). In detail, Bardare et al[94] studied a large cohort of children and demonstrated that the HR infants whose parents complied with the prescribed diet (prolonged breast-feeding with SPF supplements, etc) were found to have a lower incidence of atopy during the first year of life (13.3%) than infants whose parents had ignored the dietetic manipulations (54.7%), or infants whose parents were offered no dietary recommendation (28.9%)[94]. Table I reviews the main properties of SPFs employed in atopic children[93]. A recent study reports a higher intake of isoflavones per bodyweight in infants fed some SPFs, however the incidence of hormone-dependent disease is low in nations where soy is a staple. In addition the small cohort size (7 babies) introduces the possibility of a type II error in the data[98].

As regards hydrolysate formulas (HFs)[99] we have reported anaphylactic symptoms in 5 children fed a partially whey HF[100], in 9 infants fed this same HF in the nursery and again at the weaning[101] and in 200 children aged one month-15 years[102]. We have investigated the sensitizing effect via breast milk of a partially hydrolyzed (whey proteins) HA (Hypoallergenic Formulas). The formula was given (400 ml daily) to 39 nursing HR mothers throughout the lactation period (six months). As controls served 39 HR mothers who consumed 400 ml of CM daily. There was no significant difference in the cumulative incidence of atopic diseases in the babies at one year of age according to the mothers' diet. However the prevalence

Table I. Main properties of SPFs.

- Not reacting with CM
- Lower allergenicity (IgE Abs) than CM
- Similar antigenicity (IgG Abs) to CM
- Nutritional adequacy similar to CM formulas
- Better palatability than highly HFs
- Less expensive than highly HFs

Table II. Allergenicity, antigenicity and cross-reactivity of HFs, SPFs and Rezza's diet.

	HFs			SPFs	Rezza's diet
	Casein	Whey			
	highly	partially	highly		
Antigenicity	-	+	+	+	+
Allergenicity	+	+	++	-	±
Cross-reactivity with IgE Abs to CM	+	+++	++	-	-

Adapted from 104.

of babies at 6 and 12 mos with specific IgE and with total IgE more than 2 SD of the normal values for age were significantly higher ($p = 0.02$) in the group of babies whose mothers received the HA. This preliminary study shows that this HF not only still contains peptides which are able to sensitize high risk babies via breast milk, but it seems even more sensitizing than CM[103]. Accordingly, none of the HA is non allergenic, therefore a SPT or a challenge test should be done before individual use with a fresh sample of the recommended HF or HA ready-to feed formula in order to evaluate its allergenicity[99]. Table II summarizes the possible cross-reactivities among the substitutes commonly recommended for infants with CMA, while Table III outlines the composition of an ideal CM substitute[104].

Instead we have obtained excellent results with the home-made meat-based formula in atopic children (Rezza's diet), both a diagnostic and elimination diet[104]. A major advantage of this diet is that can be tailored to the individual patient, that is vegetables, other types of fruit and meat, wheat flour and other nutrients can be added to the diet according to the age and weight of the child and the physician judgement. Rezza's diet has several advantages and indications compared to HFs (Table IV)[104].

There are also amino acid mixtures that may be used in extremely severe cases of CMA.

It is crucial however to consider the possible consequences in HR children of an inappropriate diet, such as failure to thrive, malnutrition, etc (Table V).

Effect of environmental measures. We have reported and commented several studies on atopy prevention[87,92,94-96] stressing that not only dietary measures should be gi-

Table III. Composition of Rezza's diet.

• Lamb meat	g 100
• Olive oil	g 40
• Rice flour	g 70
• Water until to	1 liter
• Calcium	mg 500

Adapted from 104.

Table IV.

A) Advantages of home-made, meat-based formulas (Rezza's diet)
• Adequate nutritional value • Hypoallergenicity • Pleasant taste • Not too expensive • Easily available • Adaptability to individual needs
B) Indications of home-made, meat-based formulas (Rezza's diet)
• IgE-mediated CMA - Vomiting - Diarrhea - Angioedema - Urticaria - Asthma • Atopic dermatitis • CM protein intolerance • Diagnostic elimination diets (oligoantigenic)

Adapted from 104.

Table V. Possible consequences of inappropriate diets.

- Failure to thrive
- Osteoporosis and hypocalcemia
- Anemia
- Hypoprotidemia
- Zinc deficiency
- Malnutrition of mother, fetus and infant

Adapted from 104.

ven, but also environmental measures. The analysis of the numerous studies till yet appeared shows that prevention is not accomplished without utilizing such measures and consequently cannot always protect also from respiratory allergy. Table VI reports the main environmental measures.

Analysis of preventive measures. The concept of existing foods which are forbidden and should not be eaten goes back to the Garden of Eden, and subsequently to suggestions of Hippocrates and Lucretius. CM could cause gastric upset and hives according to Hippocrates. Furthermore, the Roman poet Lucretius stated "one man's meat is another man's poison"[105]. Today, to suggest exclusive breast-feeding for at least six months and delayed weaning until after the 6th month, collides with practical problems (Eg for mothers who work), as well as with the widespread practice of early weaning. In keeping with this, it is to be noted that few young mothers understand something about breast-feeding physiology and on the contrary, most have very little awareness that early supplements can upset a developing balance. It will be a rather long time, if ever, before prenatal and postpartum educational efforts will be sufficiently widespread to modify this. In addition, our prevention programs described so far require profound modifications of both customs and mentality, sometimes a worry for the family, since they encompass suggestions not always easily accepted, measures that sometimes run into different habits and moods. For example the institution of an elimination diet during lactation may lead to an unbalanced maternal nutrient intake, also discouraging women from breast feeding[106].

As a consequence, dietary manipulations, suggested by our prevention programs, exclusive breastfeeding during the first six months of life, selected weaning after the 6th month, as well soy milk supplement when breast milk is not sufficient, in addition to representing a financial burden, commonly reasonable, can occasionally elicit misunderstandings in the family. It has been recognized, for instance, that in the first year of life of healthy children, CM provides almost the whole dietary supply of proteins, carbohydrates, and fat; its high nutritional value and low cost should be appreciated. For a 2-year old child, 500 ml of CM provide 100% of the daily requirement of Ca, 50% protein, 100% riboflavin and 24% energy. However, children with FA can avoid CM without nutritional loss if nutrients are provided by other foods such as meat, fish, vegetables and fruit. It is certain that postponing the atopy development leads to a lessening of the severity of the clinical manifestations, and even to atopy avoidance forever.

Table VI. Environmental controls suggested for HR infants and children.

- Absolutely no smoking in the house;
- Strict environmental controls for the elimination of house dust;
- No pets in the house;
- Avoidance of air pollution;
- Avoidance of lifestyle changes;
- Day-care centers attendance delayed to after 3 years of age

Adapted from 104.

Concluding Remarks

At present we cannot overlook that such dietary-environmental manipulations, that involve the whole family of the HR child, are suggested not for the treatment of an ongoing condition, but to reduce a statistic risk of disease. Although families of infants and children on mixed diets required intensive dietary counselling and training, nevertheless during the study we have noticed an active and aware collaboration from the families. The availability and the participation with which our suggestions were agreed to, al-

lowed us to get very encouraging results also for a correct treatment of CMA[105]. Based on the available evidence, the identification of the major risk factors for the onset of atopy in genetically predisposed babies, as well as the development of respiratory allergy in already atopic children appear to be the goals of primary and secondary prevention. The use of the well known drug the cetirizine *(ETAC* study) has been suggested to significantly decrease the risk of asthma in children with AD.

In conclusion, several studies show that preventing the onset of AD, CMA and FA with some dietary manipulations associated with environmental measures is at hand. However further studies are necessary to investigate the role of CM substitutes for the prevention of CMA in genetically atopic prone neonates. Finally it stems from foregoing, and we stress, that any preventive measure has to be *from birth and even earlier* if possible. Table VII reviews the possible causes of controversial results in studies on atopy prevention, and Table VIII examines the current philosophy on atopy prevention: a word of caution[106].

Table VII. Possible causes of controversial results in studies on atopy prevention (prospective versus retrospective where possible).

1. Selection criteria (atopic or non-atopic parents)
2. Methods used to diagnose the atopic disease (parental diagnosis, general practitioners, pediatricians, allergists, dermatologists)
3. Lack of supportive immunologic data
4. Lack of statistical analysis of data
5. Social demographic characteristics
6. Sex of babies
7. Drop-out rate
8. Small number of subjects
9. Exclusive nature and duration of breast-feeding
10. Dietary restriction in mothers (cow's milk, egg)
11. Age of solid food introduction
12. Type of solid foods
13. Maternal and child compliance
14. Attendance at day care facility
15. Environmental measures (smoking, dust, pets)

Table VIII. Atopy prevention: a word of caution.

• Lack of maternal compliance, eg smoking and dietary restrictions
• Dietary mistakes during nursing
• Delberate/accidental feeding hidden bottle at maternity ward "grandmother effect" eg egg feeding
• Sensitization via aerosol
• Cross-reacting allergens
• Strong adiuvant factors ?
• Effect of infections
• Overprotection of the infant
• Social isolation
• Feelings of guilt if symptoms do occur despite the efforts
• Economic consequence for the family

Adapted from 116.

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