# Oral food desensitization: the BACH proposal for the very gradual reintroduction of a food

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**Purpose of review**
The common treatment of IgE-mediated food allergy is to avoid the offending item and educating patients on appropriate emergency measures. Recently, attempts to gain food tolerance with oral administration of increasing doses of the offending food have become frequent. Desensitization procedures are risky and safety is a priority. Their success depends on the individual allergic characteristics and the modality of food administration.

**Recent findings**
Most schedules adopted in the desensitization protocols are empiric and not regular, as requirements of safety would require.

**Summary**
Some oral food desensitization schedules were compared in order to verify whether the increments between doses were regular. Through a mathematic formula adopted by the musicians to tune instruments in the 17th Century, including Bach, I describe a method to calculate an increment factor by which a schedule of food administration that ensures an absolutely constant increment between doses can be achieved. This method can prove useful for every situation in which a gradual dose increment is needed (food, drugs in an experimental setting, specific immunotherapy with inhalants or venom insect allergens). All calculations can be done also without a computer, and this is particularly important if modern technologies are not available, such as in developing countries.
I propose calling this method '**B**uilding an **A**llergen-augmentation **C**urve **H**armoniously (**BACH**)'.

**Keywords**
food allergy, method to calculate gradual increment factor, oral food desensitization, schedule for oral desensitization protocol, vaccine safety

## INTRODUCTION

Recently, IgE-mediated food allergy has been receiving growing attention in the clinical literature [1] and it has been shown that few food sources as cow's milk, hen's eggs, wheat, soy, peanuts, tree nuts, fish, and shellfish are accountable for the vast majority of food allergic reactions [2]. Until now, avoiding the offending item (passive approach) and patients' tutoring on the emergency measures to be taken in case of accidental ingestion represented the common management for food adverse reactions [3]. Lately, successful attempts to induce food tolerance by means of oral administration of increasing doses of the offending food (active approach) have become more frequent [4]. Other approaches are controversial or experimental and cannot be tested on humans at present [5].

## SAFETY AND PROBABILITY OF SUCCESS OF THE FOOD DESENSITIZATION PROTOCOLS

The limit of the desensitization procedures with foods is mainly the issue of safety. Indeed, if we could freely administer the offending food without the fear of inducing severe – or even fatal – allergic reactions that prevent us from increasing the doses, we would be able to desensitize many more of those suffering from food allergy. In order to overcome this problem, at least in part, our group

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## KEY POINTS

- The increment between doses in a desensitization protocol with a given food should be gradual and constant.
- The gradual and constant increase between doses improves safety.
- By increasing the safety, we increase the effectiveness of the oral desensitization procedures.
- A table with the increment factor between doses is provided. It makes developing a schedule for the regular incremental administration of a food an extremely easy exercise.
- The method is also useful for creating regular schedules for all kinds of specific immunotherapy or when we need to increase the drug dosage in a clinical or experimental setting.

adopted the strategy of administering oral $H_1$-antihistamines throughout the whole desensitization protocol [6], similarly to that suggested in hymenoptera desensitization protocols [7]. More recently, some authors [8,9▪] pretreated children receiving rapid oral milk desensitization protocol with anti-IgE monoclonal antibodies (omalizumab). In this way, the authors attempted to reduce or eliminate (specific) serum IgEs in order to prevent – or at least cushion – IgE-mediated allergic reactions and meet the safety requirements in a procedure that is not risk free [10]. Overall, the reaction rate in this study was relatively low, given the rapidity of the protocol, but the lack of a control group does not allow us to draw any conclusion about the effectiveness of this pretreatment in reducing the side-effects.

Generally speaking, the outcome of a desensitization protocol mainly depends on two variables: the individual allergic characteristics (i.e. to say the 'strength' of the allergy) and the modality of food administration during the desensitization protocol.

As regards the individual characteristics, we compared the results of the work of our own group [6] and the work of Longo *et al.* [10]. Both studies dealt with cow's milk allergic children even if the two populations were quite different as the children in the Longo *et al.* study were older (5–17 versus 5–10 years) and presented higher cow's milk-specific IgEs. Indeed, the main difference between the two studies was in the fact that in our study the patients had severe allergic symptoms with only occasional anaphylaxis, whereas in the study by Longo *et al.* all enrolled children had anaphylaxis. As a consequence, regardless of the schedule used, the outcomes of the two studies were different. In our study, in fact, 71.4% of the children achieved the daily intake of 200 ml of cow's milk over a 6-month period, 14.3% of children could tolerate 40–80 ml/day of whole cow's milk, whereas 14.3% failed to be desensitized. None of them required emergency treatments. In the study by Longo *et al.*, instead, only 36% of children became completely tolerant, whereas 54% could take limited amounts of cow's milk (5–150 ml), and 10% were not able to complete the protocol because of symptoms. Intramuscular epinephrine was necessary in four children and two required treatment in the emergency department.

The second variable conditioning the outcomes is the type of the desensitization protocol. Generally speaking, to date, two main types of desensitization protocols have been used: rush – in which the final dosage of the food is achieved in a few days [10–17] and 'long term' – in which the final dose is achieved after months [6,18–23,24▪,25–33]. Some studies [10,34] have adopted mixed rush-slow protocols.

As expected, rush protocols are more risky, but overall, they are not comparable, as they deal with several different foods such as cow's milk [10,11,14], tomato [12], peanut [13,16], and hen's egg [15]. Moreover, the majority of these studies are anecdotal as they concern only single [11–13] or a few cases [14]. In some studies [10,16], the rush phase is preliminary to a longer lasting phase.

Most of the long-term studies [6,18–23,25–28] starting with very low doses of the offending food attempt to reach the highest doses (or the maximum tolerated dose) of the food. Because of the length of these protocols, they are performed at home and not in a more protected setting. For this reason, safety is a priority. If we look at the schedules of these studies, we can note that the increment between doses is not as regular as safety requires. In order to clarify the method used in our own protocol [6], we will give an example and then analyze the three slow protocols.

By way of example, let us imagine that a starting dose of 10 ml of cow's milk has to be doubled in 10 days to reach a final dose of 20 ml. The simplest way to do this would seem to be to add to the first dose of 10 ml, 1 ml of cow's milk each day, in order to reach the dose of 20 ml on the 10th day. This schedule (represented as a curve in Fig. 1a, left side) is only apparently gradual. Indeed, if we look at the increment factor between doses (i.e. to say the percentage of increment), we note that they are different for each day, with the first increment being 10% (from 10 to 11 ml) and the last increment 5.3% (from 19 to 20 ml) (Fig. 1a, right side). From the safety point of view, it is reasonable to think that the risk of an adverse event is more probable the first day

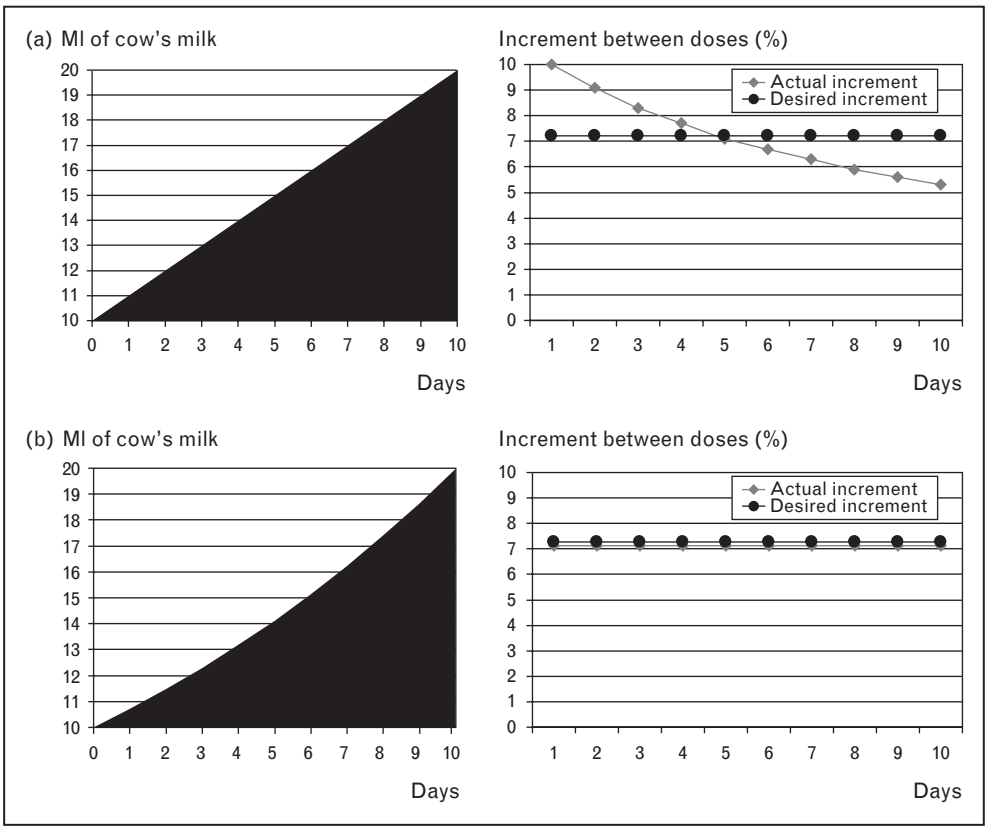


**FIGURE 1.** An example of how easy it is to construct an apparently gradual curve that is actually inaccurate. (a) If we were to start from a dose of 10 ml and reach a final dose of 20 ml in 10 days, the simplest way would seem to be to add 1 ml of cow's milk to the starting dose each day (10, 11, and 12 ml and so on up to 20 ml), thereby obtaining an apparently gradual increment of doses (left-hand side). But, if we look at the percentage increments between doses (right-hand side), they are not regular throughout the 10-day period. In fact, the first increment from 10 to 11 ml is 10%, but the last increment from 19 to 20 ml is 5.3%. The other increments are also different from each other. For safety reasons, would be desirable a constant increment between doses. (b) In this case, the increment between doses has been calculated by applying an increment factor that corresponds to the 10th root of 2 ($\sqrt[10]{2} = 1.071773$, as indicated in Table 1). The right-hand side of the figure indicates that the increment between doses is constant (7.2%) and the series of doses are different from example (a) as, in this case, the increment is regular (10, 10.7, and 11.5 ml and so on up to 20 ml) (see text and Table 1 for details).

(increment of 10%) than the last day (increment of 5.3%) and that a better way to redistribute the risk over the entire period would be to apply the same increment factor (7.2%) between all doses (Fig. 1b). Now, we will apply the same analytical method to two long-term studies. In the study by Patriarca *et al.* [18], the protocol foresaw the administration of 120 ml of cow's milk in 103 days, starting from a dose of one drop of cow's milk diluted 1 : 10. In the study by Staden *et al.* [24▪], the protocol foresaw the administration of 250 ml of cow's milk in a period of 67 days, starting with a dose of one drop of cow's milk diluted 1 : 100. On the left-hand side of Fig. 2a and b, we have plotted on a curve the daily amount of cow's milk administered during the two cited protocols. On the right-hand side of Fig. 2a and b, we have, instead, calculated the increments between doses in the protocols. It is evident that the schedule of cow's milk administration is not regular either in the protocol of Patriarca *et al.* [18] or in the protocol of Staden *et al.* [24▪], because the increment factor between doses is not the same as it should be. Other examples [10,14,23,26,35–37] of how an empiric schedule can present a nongradual increment are depicted in Fig. 3.

How can the problem of calculating exactly the increment factor between two consecutive doses be solved?

## HISTORICAL NOTES ON TUNING IN MUSIC

In the 17th Century, musicians in Europe had to face a problem like ours when it came to standardizing the tuning of various musical instruments (lute, violins, harpsichord, etc.) when they were played together, for example, in a duo or in a small orchestra. It is not easy for us today to understand this concept, but we can imagine that the sound of

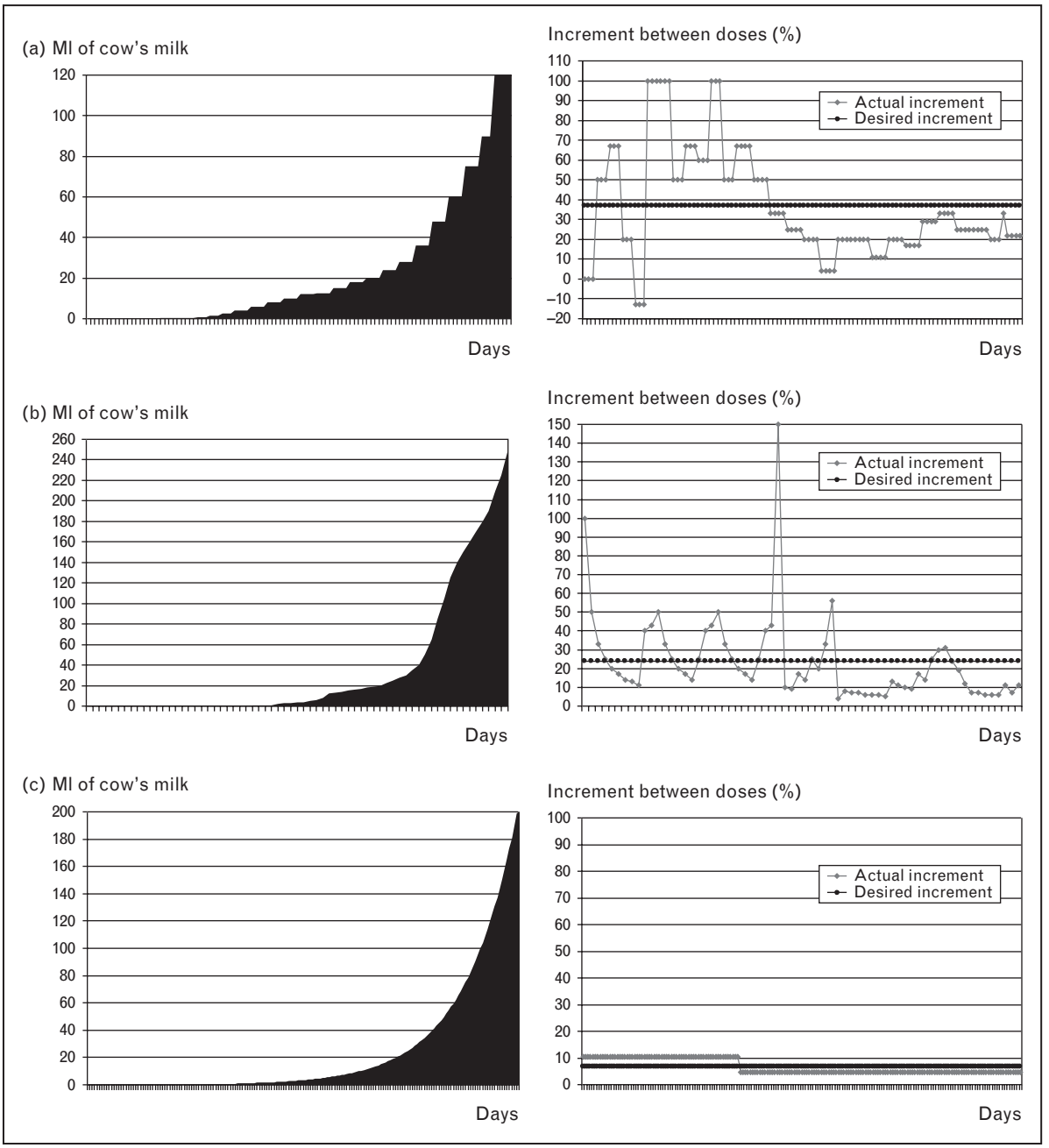


**FIGURE 2.** Analysis of the increment factors in three different oral desensitization schedules using the tool illustrated in Fig. 1. On the left-hand side, the amount of cow's milk (ml) administered daily according to the desensitization protocols adopted by Patriarca *et al.* (a – [18]), Staden *et al.* (b – [24▪]), and Meglio *et al.* (c – [6]) is plotted. On the right-hand side, the percentage variations between the previous and subsequent incremental doses of cow's milk are calculated. It is evident that in the studies by Patriarca and Staden, an apparent gradual schedule (a and b, left-hand side) corresponds to a high variability of the daily dose increments (a and b, right-hand side). Instead, in our own study, the schedule is gradual (c, left-hand side) and corresponds to constant daily dose increments (c, right-hand side) (see text for details).

two differently tuned instruments playing together is like listening to a perfectly tuned instrument accompanying an out-of-key singer.

To overcome this problem in western countries, the equal tempered tuning system was adopted [38]. By means of it, the distance between one note (e.g. the note 'C' with pitch at 262 Hz) and the subsequent higher 'C' that has a double frequency (pitch at 524 Hz) was divided by 12 identical (or 'equal') intervals. In this way, the frequency ratios between successive steps (i.e. to say between successive musical notes) was the same and the

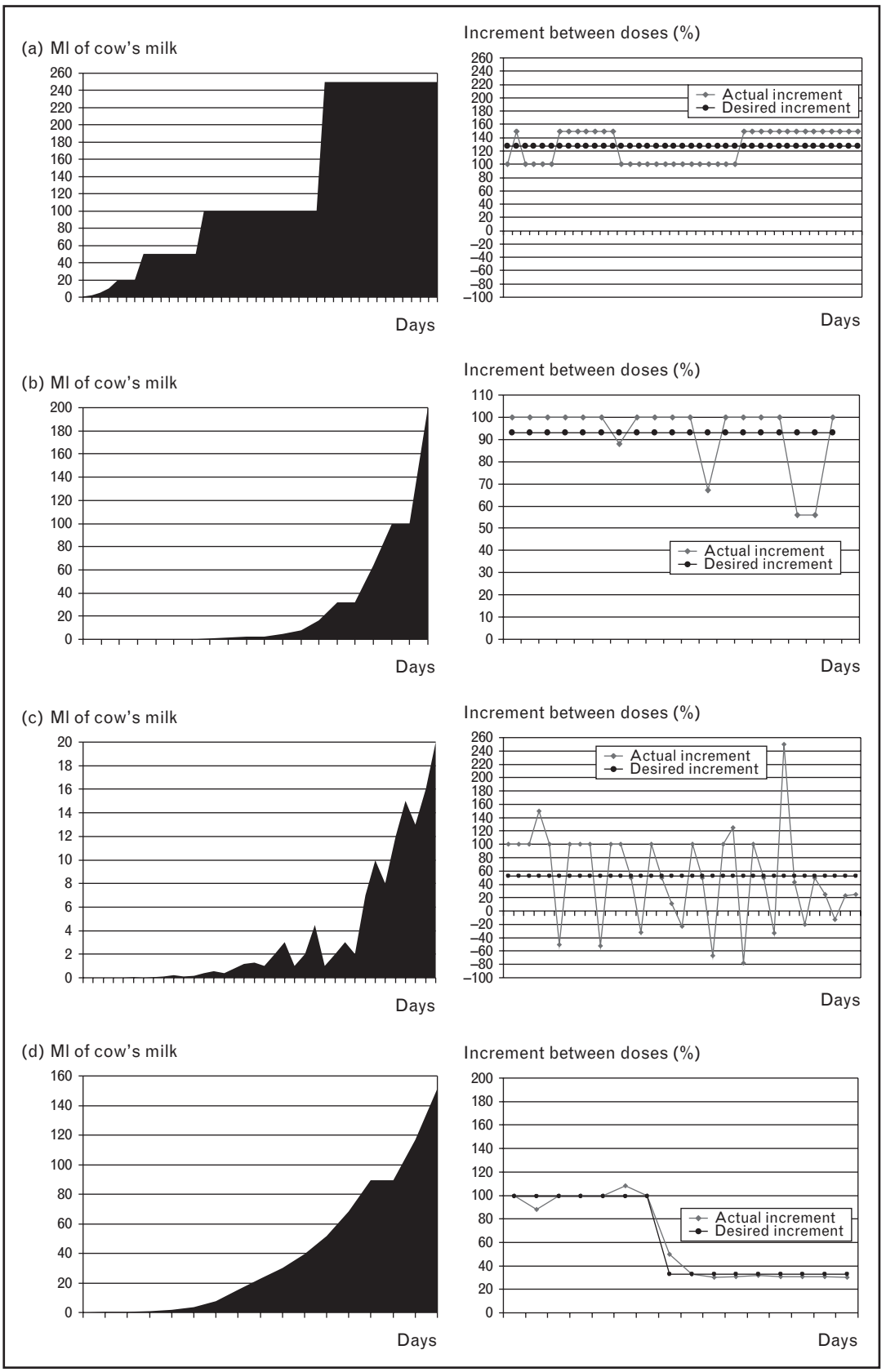


**FIGURE 3.** Some examples of how empiric schedules may differ from a hypothetical curve describing a gradual dose increment. (a) Morisset *et al.* [23]; (b) Martorell Aragonés *et al.* [14]; (c) Longo *et al.* (induction phase) [10]; (d) Skripak *et al.* [35]; (e) Zapatero *et al.* [26]; (f) Alvaro *et al.* [36]; and (g) Sanchez-Garcia *et al.* [37].

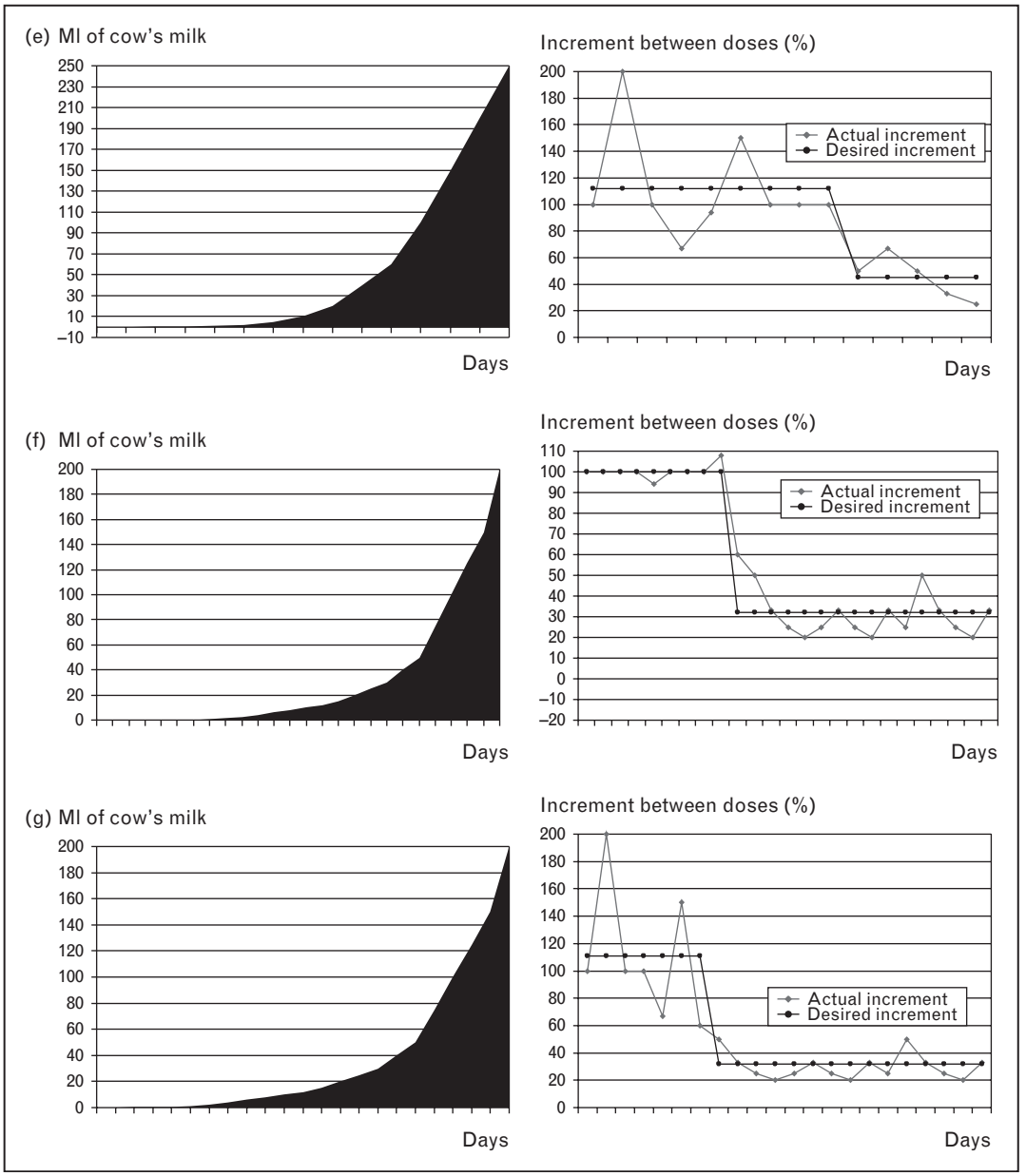


**FIGURE 3.** (*Continued*).

frequency of many notes were corrected, namely were 'equally tempered'. In other words, the temperament consisted of doubling the frequency of a certain note through 12 equal steps, being the increment factor of the frequency of consecutive notes constant.

The debate on equal temperament of musical notes started very early (Aristoxenus, 4th Century BC), but Vincenzo Galilei (1520–1591) (father of Galileo Galilei) was the first to study and apply in practice the 12-tone equal temperament, composing a set of dance suites for lute on each of the 12 notes of the chromatic scale ('Fronimo', 1584).

Other lute-playing countrymen of Galilei's such as Giacomo Gorzanis (1520–1575), Francesco Spinacino (15th Century–1507?) and Giovanni Maria Lanfranco (15th Century–1545) wrote music based on the equal temperament, but it seems that Simon Stevin (1548–1620) was the first to mention 'the twelfth root of two' as a way of calculating the exact interval between notes. Unfortunately, the calculation described in his study 'Van De Spiegheling der signconst' (*c.* 1605) was inaccurate.

The debate in the Baroque era involved several important musicians and theorists such as Girolamo Frescobaldi (1583–1643), Francesco Tartini (1692–1770) and others. But it was Andreas Werckmeister (1645–1706) who first coined the term 'well tempered', and to accurately and precisely describe a system known as the Werckmeister temperament

in his work 'Musical Temperament' (1691, original German title 'Musikalische Temperatur').

It is generally accepted that the most enjoyable and perfect example of this modern tuning system is the masterwork by Johann Sebastian Bach 'The Well Tempered Clavier' (1722), original German title 'Das Wohltemperierte Klavier', a collection of solo keyboard music pieces consisting of 24 preludes and fugues, one for all of the 12 major and 12 minor musical keys. In this opera, the composer advocated the equal tempered tuning system, so demonstrating the perfect equivalency between musical compositions, independently of the musical key chosen.

## HOW TO APPLY THE WERCKMEISTER TEMPERAMENT TO OUR WORK, AS BACH DID IN HIS?

As noted previously, the problem from the musical point of view was to double the frequency of a note in 12 equal steps, and Werckmeister found and calculated the increment factor by which the frequency of the previous note had to be multiplied in order to obtain the frequency of the next note. This increment factor was the 12th root of 2 ($\sqrt[12]{2} = 1.059463$), with 12 being the number of intervals by which the frequency had to be doubled. It is easy to note that the mathematical problem is identical to the case in which we might double a given dose of cow's milk in 12 days.

As a consequence, in our study [6], in order to solve the problem of the regular increasing dose of our desensitization protocol, we adopted the rules of the Werckmeister temperament used by Bach, with some modifications, in order to adapt it to our needs. Our protocol foresaw the administration of 200 ml of cow's milk in 6 months starting from the dose of one drop of cow's milk diluted 1 : 25. We decided to double the doses every 7 days until day 70 and, subsequently, to double the doses of cow's milk every 16 days in order to achieve a total daily intake of 200 ml in about 6 months. Accordingly, during the first phase (the first 70 days), the increment factor between two consecutive doses was the 7th root of 2 ($\sqrt[7]{2} = 1.104090$), with day 7 being the day on which we decided to double the dose. During the second phase (the last 110 days), the increment factor was the 16th root of 2 ($\sqrt[16]{2} = 1.044274$), with day 16 being the day on which we decided to double the dose. On the left-hand side of Fig. 2c, the daily amount of cow's milk administered during our protocol has been plotted, whereas on the right-hand side, a graph describing the increments has been created. It is evident that the increment was regular throughout the whole 6-month period of the protocol.

## APPLICATIONS

The application of this method allows the increment factor between doses to be calculated, so that the doses can be increased by the same percentage each time in an absolutely gradual and regular way.

Table 1 provides the increment factors for calculating how to double a given dose in 1 to 20 steps. In order to generate a schedule for gradual administration, we have firstly to decide the amounts administered in the initial and the final doses. Then, we must decide the number of steps required to double the dose (e.g. the dose may be doubled every 10 days or every 10 min). After that, we must refer to the table to find the increment factor by which the previous dose must be multiplied in order to obtain the next dose.

The examples described in detail in Table 1 make developing a schedule of a regular incremental administration of a food an extremely easy exercise. The transposition of these schedules onto a graph will give very gradual and regular curves.

It should be noted that this method is not only useful for oral food desensitization, but also in any situation in which one has to increase a given substance in a gradual and constant manner. It may therefore be applied when we need to increase a drug in a clinical or experimental setting, or when we perform specific immunotherapy with inhalants or with the more risky venom insect allergens.

Even if all calculations can be easily done on a computer (using a program such as Microsoft Excel), they can also be done on a calculator or even with pen and paper. This is particularly important in situations in which modern technologies are not always available, such as in developing countries.

## CONCLUSION

Recently, IgE-mediated food allergy has received growing attention and even if the standard treatment is to avoid the offending item and to educate patients on appropriate emergency measures (the passive approach), successful attempts to gain food tolerance by means of oral administration of increasing doses of the offending food (the active approach) have become more common. On the other hand, desensitization procedures with foods are risky and safety is a priority, especially for protocols that foresee the gradual food administration at home. In general, their success depends on two main factors: the individual allergic characteristics of the patient and the modality of food administration.

Most schedules adopted in the desensitization protocols are empiric and not regular, as safety requirements dictate. To demonstrate this, we

**Table 1. Increment factors between doses calculated with the aim of gradually and constantly doubling a given dose in 1 to 20 steps, following the requirements of the desensitization protocol**

| Number of steps by which we want to double the dose (n) | $n^{th}$ root of 2 | | Increment factor between doses |
|---|---|---|---|
| 1 | $\sqrt[1]{2}$ | = | 2.000000 |
| 2 | $\sqrt[2]{2}$ | = | 1.414214 |
| 3 | $\sqrt[3]{2}$ | = | 1.259921 |
| 4 | $\sqrt[4]{2}$ | = | 1.189207 |
| 5 | $\sqrt[5]{2}$ | = | 1.148698 |
| 6 | $\sqrt[6]{2}$ | = | 1.122462 |
| 7 | $\sqrt[7]{2}$ | = | 1.104090 |
| 8 | $\sqrt[8]{2}$ | = | 1.090508 |
| 9 | $\sqrt[9]{2}$ | = | 1.080060 |
| 10 | $\sqrt[10]{2}$ | = | 1.071773 |
| 11 | $\sqrt[11]{2}$ | = | 1.065041 |
| 12 | $\sqrt[12]{2}$ | = | 1.059463 |
| 13 | $\sqrt[13]{2}$ | = | 1.054766 |
| 14 | $\sqrt[14]{2}$ | = | 1.050757 |
| 15 | $\sqrt[15]{2}$ | = | 1.047294 |
| 16 | $\sqrt[16]{2}$ | = | 1.044274 |
| 17 | $\sqrt[17]{2}$ | = | 1.041616 |
| 18 | $\sqrt[18]{2}$ | = | 1.039259 |
| 19 | $\sqrt[19]{2}$ | = | 1.037155 |
| 20 | $\sqrt[20]{2}$ | = | 1.035265 |

This table shows how to calculate the **increment factor** between doses in order to increment them by the same percentage and administer incremental quantities of any substance in a regular manner (i.e. foods, allergens for immunotherapy, and drugs in experimental settings). To do this, we have firstly to decide the amounts of the initial and the final doses; secondly, in how many steps we want to double the dose (this table considers from 1 to 20 steps – see left-hand column); thirdly, we have to find on the table the **increment factor** by which the previous dose has to be multiplied in order to obtain the following dose (see right-hand column).
Example 1 – We would need to start from 100 ml (day 0) and to double the dose to 200 ml in 10 days (=10 steps). In this case, we have to multiply the first dose (day 0 = 100 ml) by the **increment factor** that corresponds to the10th root of 2 ($\sqrt[10]{2} = 1.071773$, as indicated in the table) to obtain the second dose (day 1 = 107.2 ml). After that, we have to multiply the second dose by the same **increment factor** again in order to obtain the third dose (day 2 = 114.9), and so on up to the last dose (day 10 = 200 ml). We have used the **increment factor** that corresponds to the 10th root of 2 ($\sqrt[10]{2} = 1.071773$) because we decided to double the dose in 10 days. Had we decided to double the dose in 5 days, we would have used the **increment factor** that corresponds to the 5th root of 2 ($\sqrt[5]{2} = 1.090508$, as indicated in the table).
Example 2 – We would need to start from 1 ml and to finish with 128 ml. In this case, the first doubling of the dose takes the amount from 1 to 2 ml, the 2nd doubling from 2 to 4 ml, and so on up to the 7th doubling that takes the amount from 64 to 128 ml. If we decide to double the dose every 5 days (i.e. five equal intervals between every doubling), the whole period lasts 35 days (seven doublings for 5 days). At this point, we have to multiply the first dose (1 ml) by the **increment factor** that corresponds to the 5th root of 2 ($\sqrt[5]{2} = 1.148698$, as indicated in the table) to obtain the second dose (=1.15 ml). After that, we have to multiply the second dose (=1.15 ml) again by the same **increment factor** to obtain the third dose (=1.32 ml), and so on up to the 35th dose (=128 ml). We have used the **increment factor** that corresponds to the 5th root of 2 ($\sqrt[5]{2} = 1.148698$) because we decided to double the dose every 5 days. Had we decided to double the dose every 14 days, we would have used the **increment factor** that corresponds to the 14th root of 2 ($\sqrt[14]{2} = 1.050757$, as indicated in the table).

compared the oral food desensitization schedules adopted in certain studies to verify whether the increments between doses were regular. As expected, because these schedules were constructed using empiric methods, the increments between doses were irregular, with possible repercussions on safety and, ultimately, on effectiveness.

Drawing on a method used by the 17th Century musicians, such as Bach, to tune their instruments, I have described a new method that permits the

calculation of an increment factor between consecutive doses to achieve a schedule of food administration that ensures a constant and safer increment between doses. The transposition of this schedule onto a graph gives a very gradual curve.

This method can prove useful not only for food desensitization, but also in any situation in which a given substance must be increased in a gradual, constant mode, such as drugs in an experimental or clinical setting, or in specific immunotherapy (inhalants, venom, and insect allergens). It should be noted that as a table with several increment factors has been provided, all calculations can be done without a computer. This is particularly important in situations in which modern technologies are not available.

The proposal to call this method '**B**uilding an **A**llergen-augmentation **C**urve **H**armoniously (**BACH**)' is made.


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## Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 320).


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