

TOWARD EUROPEAN GUIDELINES FOR PKU: HOW TO SPEAK A COMMON LANGUAGE?

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ABSTRACT

Background: Because phenylketonuria (PKU; OMIM 261600) is a rare disease, international collaboration is needed to collect enough patient data to determine outcome and prognosis, and to establish international guidelines, which are currently being developed. This necessitates the use of a common language.

Objective: The aim of this study was to examine whether consensus exists about the concepts of “compliance,” “off diet,” and “lost to follow-up.”

Methods: A survey of 10 multiple-choice questions was conducted among 68 professionals attending a workshop on the development of European guidelines for PKU management during the 5th European Phenylketonuria Group Symposium in 2013. Consensus was considered to exist if an answer was given by the majority (>50%) of responders.

Results: Fifty-three percent of the participants considered “>75% of requested number of blood samples” as optimal compliance. Sixty percent reported “<50% of requested number of blood samples” as poor compliance. Fifty-six percent of the participants considered “>75% of requested number of outpatient visits” as optimal compliance. For the other 5 questions regarding compliance, no consensus was realized. Sixty percent of the responders defined the combination of “patient does not take a protein substitute” and “is not in good metabolic control” as “off diet.” There was no consensus for the definition of “lost to follow-up.”

Conclusions: Consensus was clearly lacking regarding the surveyed concepts, with only 4 of the 10 questions achieving consensus. A score table is proposed for the definition of poor, fair, and good compliance, independent of age and sex. Other concepts, such as the definition of the severity of phenylalanine hydroxylase deficiency, need to be determined.

INTRODUCTION

Phenylketonuria (PKU, OMIM 261600) is a rare disease; therefore, centers and countries have to cooperate to collect enough data from their patients to determine outcome and prognosis, and to establish guidelines. However, such cooperation necessitates the use of common definitions in a comparable way. There is a need for consistent terminology in PKU care to compare results and develop guidelines.^{1,2} We investigated the possibility of consensus about concepts of “compliance” (or lack of it), “off diet,” and “lost to follow-up” to be able to speak the same language while European guidelines are being developed for PKU.

METHODS

In 2008, a meeting on the concept of “diet for life” was initiated. Two months in advance of that meeting, the 10 participants (dietitians, pediatricians, and a psychologist

experienced with PKU treatment and research) received an open-ended survey on their use and interpretation of definitions of “compliance,” “off diet,” and “lost to follow-up.” The results of the survey were discussed during the meeting to ensure there was no misunderstanding about the questions and possible answers. Based on their input, a multiple-choice questionnaire was developed that was tallied with voting machines during the workshops on European guidelines at the 5th European Phenylketonuria Group Symposium in March 2013. The consensus workshop was 1 of 4 different workshops and was run twice. The target audience for the symposium was professionals working in the field of pediatric and adult inherited metabolic disorders, either as health care professionals or researchers, all over the world.

The survey included 10 multiple-choice questions about the concepts of “compliance,” “off diet,” and “lost to follow-up.” Eight of these questions regarded compliance

with metabolic control (phenylalanine [Phe] concentrations), frequency of blood sampling, use of protein substitutes, and frequency of outpatient visits. All questions were developed to be independent of age or sex and independent of the national or center-based guidelines the participants followed. Each question had 3 to 5 possible answers.

Consensus was considered to exist if an answer was given by the majority (>50%) of responders. Statistics were descriptive due to the aim and nature of the study.

RESULTS

A total of 84 professionals participated in the workshop. Of these, 54 were physicians (64%), 14 were dieticians (17%), 8 were industry related (10%), and 8 had another profession (researcher, patient organization) or their profession was unknown. The 16 participants of the last groups mentioned were excluded from the analysis. Participating and treating professionals originated from centers in Belgium, Brazil, Canada, Germany, Estonia, France, Israel, Italy, Latvia, Kazakhstan, Poland, Portugal, Romania, Saudi Arabia, Slovakia, Spain, the Netherlands, Turkey, and United Kingdom, with about 80% hailing from European countries. The PKU experience of the participants ranged from <5 to >20 years.

The present survey showed consensus for 4 of the 10 questions. **Figure 1** presents the 8 questions on compliance, along with the corresponding responses. Fifty-three percent of responders considered ">75% of requested number of blood samples" as optimal compliance. Sixty percent reported "<50% of requested number of blood samples" as poor compliance. Fifty-six percent of the participants considered ">75% of requested number of outpatients visits" as optimal compliance. For the other 5 questions regarding compliance, no consensus was realized.

Forty-four percent of the responders reported ">75% of phenylalanine concentrations in target range" as optimal compliance. Thirty-one percent considered "<25% of the phenylalanine concentrations in target range" to be poor compliance, followed by 29% of participants reporting "<50% of phenylalanine in target range" and 28% of participants reporting "mean of Phe concentrations clearly out of target range." Forty-seven percent of responders reported "100% of requested amounts" as optimal compliance. Forty-three percent considered "<66% of requested amounts" to be poor compliance.

Forty-seven percent considered "<50% of requested number of outpatients visits" to be poor compliance.

Figure 2 presents responses to the questions on "off diet" and "lost to follow-up." Sixty percent of participants defined the combination of "patient does not take a protein substitute" and "is not in good metabolic control" as "off diet." In contrast, there was no consensus for the definition of "lost to follow-up", as the answers were almost evenly distributed.

DISCUSSION

The aim of this study was to determine whether consensus exists on definitions of some commonly used concepts in the day-to-day care of patients with PKU. Using a common language will facilitate the quality of patient care and collaboration with regard both to research and to defining international guidelines. This applies to all health care areas, not just PKU.³⁻⁸ To achieve our goal, we developed a multiple-choice survey that was conducted during 1 of the 4 workshops having a representative number of participants.

Consensus was achieved on only 4 of the 10 questions, which means there was a lack of consensus on 6 questions. On 2 questions, consensus was almost reached, with 47% of the participants in agreement (**Figure 1, E and H**). No clear consensus exists with regard to metabolic control, perhaps because there was no simple choice. An additional reason for lack of consensus might be the different use of classification (mean of Phe concentrations and a percentage of target range) in different centers. For the use of protein substitutes, the difference between the 2 largest groups was 10% (**Figure 1F**). Participants had to choose between 100% or >80% as optimal use. Although optimal should be close to 100%, this might have been viewed as unrealistic. Another reason for lack of consensus on this issue might be that it is difficult to control. On the one hand, everyone agrees about the importance of taking protein substitutes at the right amount and at the right time, but we also know that this is very hard to monitor, requiring new biochemical measures for more optimal oversight.

It should be stressed that we did not discuss the given answers by participants to achieve consensus. It is very possible that consensus could have been reached by real discussion.

To further simplify the use of the definition of compliance, we developed a simple structured score,

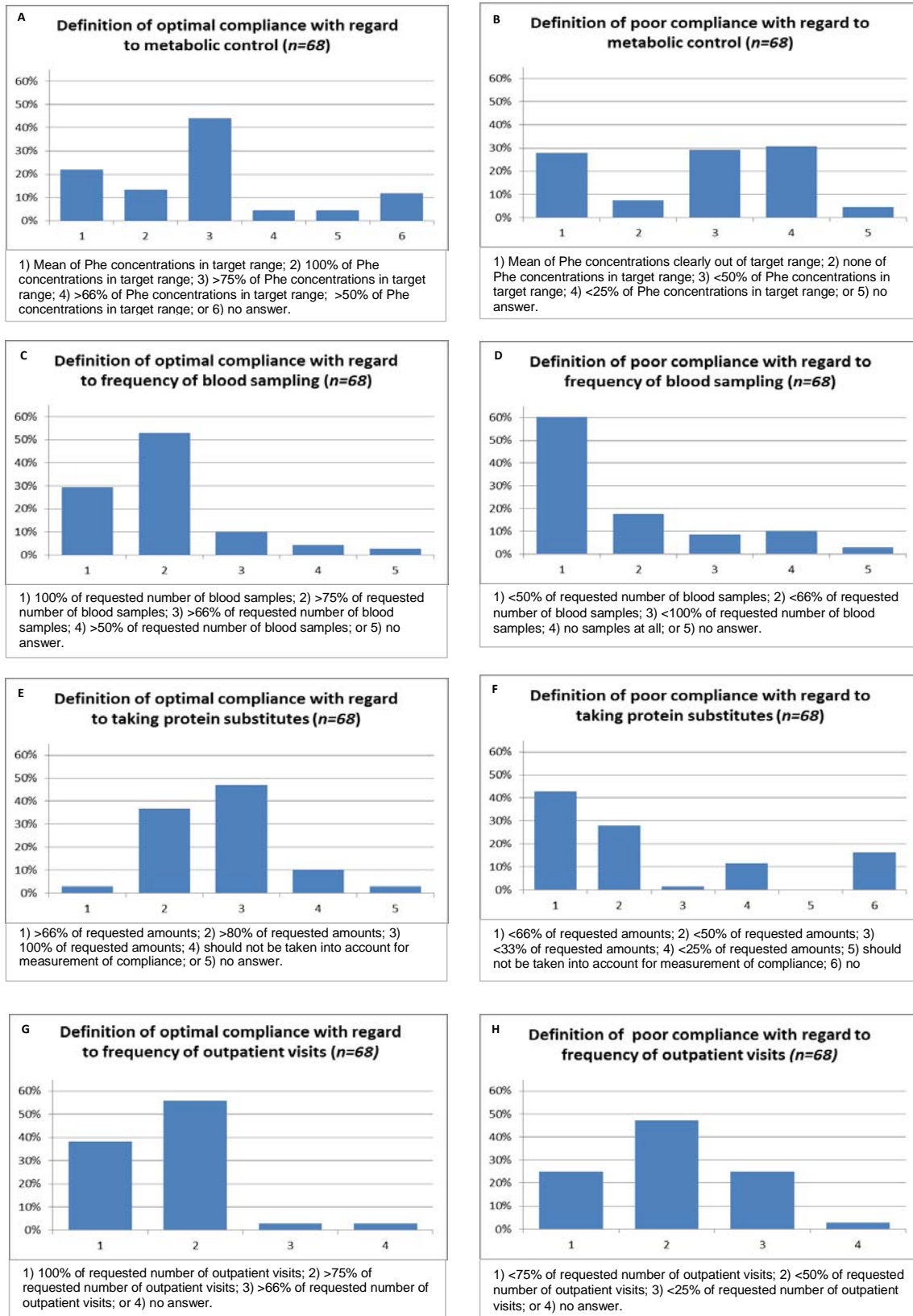
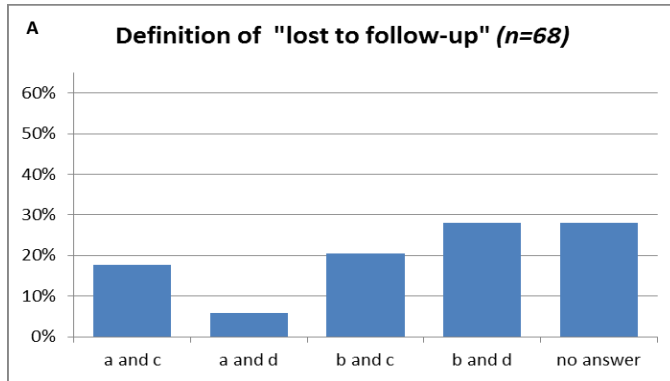
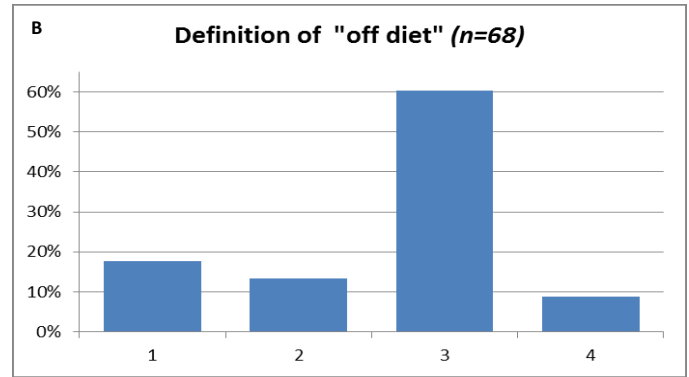


Figure 1. Summary of responses to questions on compliance (Phe = phenylalanine).



a) No outpatient visits for 2 times the normal period; b) no outpatient visits for 3 times the normal period; c) no blood samples received for a period of 4 times the normal frequency; or d) no blood samples received for a period of 10 times the normal frequency.



1) Patient does not take a protein substitute notwithstanding (s)he is in good control; 2) patient is not in good control notwithstanding (s)he is using a protein substitute adequately; 3) patient does not take a protein substitute and is not in good control; or 4) no answer.

Figure 2. Summary of responses to questions about “lost to follow-up” and “off diet.”

giving a maximum of 2 points for good compliance with regard to “frequency of blood sampling,” “use of a protein substitute,” and “frequency of outpatient visit” (Table). As the authors unanimously believed that metabolic control was most important, it was granted double the points of the other issues, amounting to a total maximum score of 10. When compliance was poor, no points were granted; fair compliance was given half of the maximal points. Fair compliance was judged

applicable when compliance was neither good nor poor. Because we only found consensus for 3 of the 8 questions, we arbitrarily based the cutoff points on the answers given by the majority of the participants.

The other issues of “off diet” and “lost to follow-up” had different responses with regard to consensus. “Off diet” was clearly defined as “not taking a protein substitute and being out of metabolic control.” However, there was no consensus with regard to the definition of “lost to

Table. Compliance Score in Patients With Phenylketonuria, Independent of Age and Sex

Parameter	Poor	Fair	Good
Metabolic control	<25% of Phe levels in target range	25%-75% of Phe levels in target range	>75% of Phe levels in target range
Score	0	2	4
Frequency of blood sampling	<50% of requested number of blood samples	50%-75% of requested number of blood samples	>75% of requested number of blood samples
Score	0	1	2
Protein substitute	<67% of requested amounts at requested times	67%-100% of requested amounts at requested times	100% of requested amounts at requested times
Score	0	1	2
Frequency of outpatient visits	<50% of requested number of outpatient visits	50%-75% of requested number of outpatient visits	>75% of requested number of outpatient visits
Score	0	1	2
Total compliance score	<5	5-7	7-10

Phe, phenylalanine.

follow-up.” Most of the group did not answer this question, perhaps because it was too complicated or unclear. The same applied to 2 questions on compliance that >10% of the participants did not answer (**Figure 1, A and F**).

This is a first proposal toward definitions of the concepts of “compliance,” “off diet,” and “lost to follow-up” that are used in the routine care of patients with PKU. Defining other concepts might be helpful, considering for example the definition of the severity of PAH deficiency. Blau et al showed that the definitions reported for moderate and mild PKU and mild hyperphenylalaninemia (HPA) varied considerably not only between countries, but also between centers within a country, so there appears to be a need for a common definition for classification.⁹ This is important, as the decision on treatment also depends on the definition of mild HPA and mild PKU. Van Spronsen added that untreated Phe concentrations in blood have lost their power to successfully define various severities of phenylalanine hydroxylase deficiency—because of neonatal screening, patients now begin treatment before untreated Phe concentrations have achieved their full potential concentration.² The development of guidelines will need at least some consensus on such issues so that good clinical practice, sound (international) research, and international guidelines can be realized. Therefore, one of the aims of future meetings on guidelines should also be to achieve consensus about concepts like these.

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Conflict of Interest Statement

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