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Pediatric Cardiology

A National Survey on the Pediatric Cardiologist's Clinical Approach for Patients with Kawasaki Disease

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Abstract. In 1994, the American Heart Association (AHA) published the most recent guidelines for long-term cardiovascular management of Kawasaki disease. Since then, recent publications have shed new light on different diagnostic, prognostic, and management issues. We sought the opinion of pediatric cardiologists practicing in U.S. fellowship programs on the subject by means of a multiple-choice survey. Two questions addressed therapy in the acute phase, each preceded by a statement from related literature. Ten duplicate questions addressed the long-term cardiovascular management in five sets of paired questions; each question was first given in reminiscence of a clinical situation and then preceded by a statement from particular publications representative of new information that has become available since the publication of the 1994 AHA guidelines. All questions were provided in the same mailing. Replies were received from 97 participants practicing at 29 institutions. For the acute illness, 21% of respondents do not use high-dose aspirin, and 50% support reassessment of current guidelines. Universal intravenous immune globulin (IVIG) administration is followed by 97%, among whom 20% agree that evaluation of selection criteria is needed. For long-term management, 60–75% advocate regular follow-up of risk level I patients, and 80% favor periodic follow-up, with stress imaging (34–40%), for risk level II. For risk level IV more respondents favor stress echocardiography as opposed to nuclear imaging, in consonance with recent literature. For risk levels III and IV, 36–40% perform coronary angiography on a regular basis, whereas 60% do so when coronary symptoms are present or when stress imaging suggests myocardial ischemia. Finally, 19–25% of respondents do not routinely advise healthy lifestyle to patients free of coronary artery lesions. In conclusion, the guidelines for conventional therapy in the acute phase and long-term cardiovascular management need to be revised.

Key words: Kawasaki disease — Coronary — Management — Survey — Guidelines

Kawasaki disease (KD) is characterized by a generalized microvasculitis, with its highest impact on the coronary artery system. In the United States, it is regarded as the leading cause of acquired coronary artery disease in children [6]. The long-term cardiovascular sequellae, however, remain under continued scrutiny. In this respect, the American Heart Association (AHA) issued practice guidelines in 1994 [6]. Since then, multiple publications have shed new light on the long-term cardiovascular effects as well as on related investigational and therapeutic modalities. The objective of this survey was to measure the degree of compliance of academic pediatric cardiologists to the current recommendations and to determine the trend in the management of KD in view of the new published data. We therefore polled the opinion of pediatric cardiologists practicing in fellowship programs in the United States by means of mail survey.

According to Paridon et al. [27] 37% of risk level I patients and 67% of risk level II patients had reversible exercise-induced myocardial perfusion defects as identified by ^{99m}Tc-Sestamibi. Although Paridon et al.'s multicenter study lacked appropriate controls, it was supported by Muzik et al. [20] and Hamaoka et al. [11]. Evidence of Coronary artery (CA) thickening was documented by Sugimura et al. [32] and Suzuki et al. [35] in risk level II patients evaluated by intracoronary ultrasound. Furthermore, a significant reduction in nitroglycerine- or acetylcholine-induced vasodilatation was well documented

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elsewhere [15, 35, 39]. For risk level IV, stress testing is recommended in the 1994 AHA guidelines, leaving the choice of nuclear versus echo imaging to the discretion of the managing cardiologist. The diagnostic value of electrocardiogram (ECG) stress testing was similarly discredited by Armstrong et al. [1] and Suzuki and Kamiya [34]. The preferred testing modalities (stress echocardiography and stress perfusion scan) [13, 26, 31] were compared by Dahdah et al. [5]. Accordingly, despite improved myocardial perfusion at peak exercise, patients with persistent coronary artery aneurysm may have segmental wall motion abnormalities during exercise stress testing [5]. Despite the availability of a variety of diagnostic techniques, however, coronary angiography remains the gold standard to detect anatomical changes such as aneurysmal and stenotic lesions. In this respect, Kato et al. [16] reported an increasing incidence of CA stenosis in patients with persistent CA aneurysm. Early stenosis approached 10% within 18 months of the acute onset of the disease and 23% in the following two decades. These facts evoke the necessity for repeated coronary angiography in risk levels III and IV in order to detect newly developed CA stenosis. From a remote long-term perspective, Dhillon et al. [8] proposed that abnormalities of systemic endothelial function are present many years after resolution of acute KD, even in risk level I. Similarly, Sugimura et al. [33] stated that patients in risk levels II and III had poor coronary artery dilatation, which may be a risk factor for atherosclerosis. Recently, pathology features of atherosclerosis were documented in CA specimens obtained from former KD patients [36]. Therefore, healthy lifestyle practices become of primary importance. Needless to say, the criteria used in most centers to identify abnormal CA dimensions [28, 37] were recently revised by Oberhoffer et al. [23], providing more updated reference tables and placing more patients in the abnormal CA category according to De Zorzi et al. [7]. Finally, regarding the treatment in the acute phase of the disease, aspirin (ASA) proved beneficial in the 1970s but later IVIG proved superior [4, 10, 18, 19, 25]. Therapy targets the acute symptoms and reduces the risk of CA injury and the ensuing sequellae. The historical use of a high-dose, antiinflammatory ASA regimen maintained its weight in the subsequent era [4] to be later revoked in two meta-analysis studies by Terai and Shulman [38] and Durongpisitkul et al. [9]. Furthermore, Ichida et al. [14] discredited the necessity of high-dose ASA when they reported CA involvement in 27% of patients treated with high-dose ASA versus 20% and 23% in those who received moderate- and low-dose ASA, respectively. As the convergence of opinions acknowledging the limited use of high-dose ASA is emerging, other investigators are attempting risk stratification for the development of CA vasculitis [2, 3, 14, 17, 21, 22, 24]. In 1995 and in 1999, Sato et al. [29, 30] demonstrated the validity of a scoring system proposed by Harada et al. [12]. In short, patients who did not receive IVIG according to Harada's scoring system did not develop CA aneurysms.

Materials and Methods

Participants

The list and addresses of all U.S. pediatric cardiology fellowship programs were obtained from the directories of the National Training Programs and the American Board of Pediatrics. Phone calls to all programs were initially made in order to obtain the list of faculty members. Forty programs including 350 pediatric cardiologists were identified.

Survey

Questionnaires were mailed via regular mail to all participants, who were instructed to provide one answer per question (see the appendix). A self-addressed, prepaid postage answer sheet was provided to encourage compliance. A follow-up phone call was made 2 or 3 weeks later in case of no response. Another copy of the questionnaire was forwarded, when necessary, by mail, fax, or e-mail. On the answer sheet, participants were also asked to state their number of years in practice as pediatric cardiologists, and a space was provided for optional open-ended comments. Confidentiality was pledged in the questionnaire, which also did not ask for institutional statistics or personal data regarding any individual participant or patient. An identifying number was used for tracking purposes and to detect potential duplicate replies. The study was approved by our institutional review board.

Questionnaire

Twelve questions in the survey addressed the general approach to clinical scenarios in the acute and long-term management of KD patients at different risk levels (Table 1) as described in a special report published by the AHA in 1994 [6]. Questions 1–10 explored the long-term management of the disease and were given in five sets of paired questions. Each question was first given in regard to a clinical situation. Subsequently, the same question was preceded by statements from particular publications we considered to be representative of new information that has become available since the publication of the 1994 AHA guidelines. Questions 11 and 12 were independent and examined therapeutic management during the acute phase of the illness. Because the management in the acute phase does not derive solely from the cardiologist's opinion, these two questions were not duplicates. A statement from related literature was provided directly within each question. The questions were categorized as follows:

Risk level I (Questions 1 and 2): According to current AHA guidelines, no follow-up is necessary for this category of patients beyond the subacute phase of the disease.

Risk level II (Questions 3 and 4): In this category, follow-up is optional. Questions 1–4 examined the current trend in the follow-up of risk levels I and II in comparison to the AHA guidelines.

Table 1. Classification of Kawasaki disease patients according to the American Heart Association

Risk level	Definition
I	No coronary artery changes at any stage of illness
II	Transient coronary artery ectasia that disappears during the acute illness
III	Small to medium solitary coronary artery aneurysm
IV	One or more giant coronary artery aneurysms, or multiple small to medium aneurysms, without obstruction
V	Coronary artery obstruction

Risk level IV (Questions 5 and 6): Although the follow-up of risk level IV is unequivocally recommended, the tests to be performed are left to the discretion of the cardiologist. Questions 5 and 6 inquired about the preferred method of evaluation for this category of patients.

Risk for atherosclerosis (Questions 7 and 8): These questions addressed the cardiologist's practice regarding dietary restrictions and healthy lifestyle practice in risk levels I and II.

Coronary angiography (Questions 9 and 10): These questions evaluated the timing of coronary angiography in case of persistent coronary aneurysm (i.e., in risk levels III and IV).

Immune globulin therapy (Question 11): This question addressed the use of IVIG in all patients with suspected KD as stated in the AHA recommendation versus the selective use of IVIG as seen in the Japanese literature.

Aspirin therapy (Question 12): This question addressed the preference for high-, moderate-, or low-dose ASA in the acute phase of KD.

Data Analysis

Demographics were presented as descriptive data and compared using the Student-*t*-test. For each question, responses were presented as percentages. Individuals providing no or multiple responses to a specific question were excluded from analysis of that question. McNemar's test was used to assess the difference in opinion before and after exposure to selected conclusions of recent studies that had a bearing on the specific scenarios (duplicate questions 1–10). A two-sided statistical p value of less than 0.05 was considered significant.

Results

The survey was conducted between January and September 2000. Of the total 350 targeted pediatric cardiologists, 42 were unreachable upon the second contact, which lowered the number of participants to 308. Of these, 97 (32%) pediatric cardiologists replied from 29 (73%) of the 40 fellowship programs. There was no significant difference in the number of years in practice between respondents and nonrespondents (13.2 ± 10 vs 13.6 ± 10.5). With the exception of 18 individuals, the majority of respondents (81.5%) provided a single answer per question. Replies to the questions are summarized in Table 2.

Risk Level I (Questions 1 and 2)

Despite the 1994 AHA guidelines of no follow-up, 61% of respondents provide follow-up. There was a significant increase in the proportion of those who would follow this category of patients after consideration of the findings of Paridon et al. [27] ($\chi^2_1 = 12.0$, $p < 0.001$). Likewise, there was a threefold increase in the proportion of those who would conduct stress tests in symptomatic individuals ($\chi^2_1 = 5.1$, $p = 0.023$).

Risk Level II (Questions 3 and 4)

Sixty percent of respondents comply with the AHA recommendations; however, two thirds prefer the follow-up option. After consideration of Paridon et al.'s [27] findings, there was a significant change in opinion in favor of periodic stress testing ($\chi^2_1 = 5.1$, $p = 0.023$).

Risk Level IV (Questions 5 and 6)

Most participants (98%) chose stress testing along with periodic rest echocardiography. After consideration of the findings from Dahdah et al. [5], the proportion of those electing stress echocardiography increased significantly from 31% to 44% ($\chi^2_1 = 11.1$, $p < 0.001$).

Risk for Atherosclerosis (Questions 7 and 8)

Despite a lack of clear recommendations pertaining to KD and atherosclerosis, 75% of participants recommend a healthy lifestyle to all their patients irrespective of a history of KD. After consideration of the statement drawn from Dhillon et al. [8] and Sugimura et al. [33], there was a modest but significant decrease from 25% to 19% in the proportion of respondents omitting regular advice for healthy lifestyle in case of no CA lesions ($\chi^2_1 = 4.16$, $p = 0.03$).

Coronary Angiography (Questions 9 and 10)

Respondents were evenly divided with respect to indication for coronary angiography; 36% perform coronary angiography on a regular basis and 40% follow the AHA recommendations by performing the catheterization mainly in the setting of abnormal

Table 2. Participants' opinion distribution[a]

Question/options	Opinion (%)	Opinion (%)	*p* value
Risk level I	*Question 1*	*Question 2*	
A. AHA recommendation (no follow-up)	39.18	24.74	<0.001
B. Follow-up Q 1–2 years (clinically ± ECG)	11.34	13.40	NS
C. Follow-up Q 3–5 years (clinically ± ECG)	27.84	34.02	NS
D. Follow-up only if subsequent heart disease	17.53	16.49	NS
E. Stress test only if symptomatic	3.09	10.31	0.023
Risk level II	*Question 3*	*Question 4*	
A. AHA 1st alternative (no follow-up)	20.62	17.53	NS
B. AHA 2nd alternative (clinical follow-up ± ECG Q 3–5 years)	44.33	40.21	NS
C. Follow-up periodically with ECHO	18.56	18.56	NS
D. Periodic stress echo or perfusion scan	15.46	22.68	0.023
Risk level IV	*Question 5*	*Question 6*	
A. Periodic ECG	2.06	0.00	NS
B. Periodic ECHO and stress ECG	15.46	11.34	NS
C. Periodic ECHO and stress ECHO	30.93	44.33	<0.001
D. Periodic ECHO and stress perfusion scan	44.33	39.18	NS
Risk for atherosclerosis	*Question 7*	*Question 8*	
A. No lifestyle restriction unless coronary lesions	24.74	18.56	0.03
B. Lifestyle restriction to all Kawasaki patients	9.28	13.40	NS
C. Lifestyle restriction to all patients	65.98	68.04	NS
Coronary angiography	*Question 9*	*Question 10*	
A. On regular basis	36.08	40.21	NS
B. Only if coronary symptoms	9.28	8.25	NS
C. Only if abnormal stress ECHO	20.62	21.65	NS
D. Only if abnormal stress perfusion scan	18.56	17.53	NS
E. Upon transfer to adult cardiology care	1.03	1.03	NS
Immune globulin therapy	*Question 11*		
A. Follow Red Book recommendations (treat all suspects)	76.29		NA
B. Follow Red Book, but selection criteria are needed	18.56		NA
C. Already use Harada's selection criteria	3.09		NA
Aspirin therapy	*Question 12*		
A. Follow Red Book recommendations (initial high dose)	26.80		NA
B. Follow Red Book and know colleagues using lower dose	12.37		NA
C. Follow Red Book and believe lower dose needs evaluation	49.48		NA
D. Already use initial moderate dose of aspirin	6.19		NA
E. Already use initial low dose of aspirin	4.12		NA

ECHO, echocardiogram; ECG, electrocardiogram; NA, not applicable; NS, not significant.
[a]Answer proportions (%) for each question represent the cumulative replies of participants who provided a single choice per question. Refer to the Appendix for full text of the questions and answers.

stress imaging. After exposure to the data from Kato et al. [16], there was an increased preference for performing coronary angiography on a regular basis; however, the change did not reach statistical significance. Thirteen participants provided two or three replies; of these participants, 3 changed their opinion in favor of regular coronary angiography. Analysis of the data after inclusion of these responses did not alter the results of the chi-square evaluation.

Immune Globulin Therapy (Question 11)

In respect to the use of IVIG, 76% of respondents indicated that they follow the *Red Book* recommendations [4] by treating all suspected KD patients. Only 3% would use Harada's criteria for the administration versus refraining from administration of IVIG, whereas 19% follow the *Red Book* but state that similar selection criteria need to be established.

Aspirin Therapy (Question 12)

Despite recommendation for universal use of high-dose ASA [4], 10% of participants use lower ASA posology and 12% are aware of colleagues who do so. Of the majority who follow the *Red Book* recommendations, 50% believe that the efficacy of an initial lower ASA dose needs to be evaluated in prospective clinical trials.

Discussion

In this survey, we were able to demonstrate that pediatric cardiologists practicing in fellowship pro-

grams either already take into consideration the recently published literature on KD or are willing to modify their practice accordingly. For instance, this is reflected by the preference to maintain regular contact with risk level I and II patients despite the 1994 AHA recommendations. With respect to the choice of stress testing, it was also apparent that stress electrocardiography was the least popular investigation. The major disagreement was between performing stress echocardiography or stress perfusion scan, where participants demonstrated their inclination to choose the most specific test according to the proposed information in our question. The same dilemma was also apparent when the question regarding the timing of coronary angiography was introduced. At the same time, we were able to expose some degree of disagreement with the AHA recommendations given that a significant number of participants proposed coronary angiography on a regular basis rather than based on abnormal stress imaging. From our survey, we could also conclude that a large proportion of participants advocate healthy lifestyle whether or not their patients have KD, a subject we believe should be addressed in future recommendations.

Our findings suggest that a review should be performed by the AHA Council on Cardiovascular Disease in the Young and also that updated guidelines are necessary. On the other hand, more elaborate prospective multicenter studies would compensate for the relatively limited number of patients in comparison to the extensive adult experience in CA disease. The role of the pediatric cardiologist, with joint effort from the adult cardiologist, may be very well defined in this area. A more critical point is the role of the pediatric cardiologist, which extends into a more complex dimension when determining therapeutic strategies in the acute phase of the disease. The nature of the disease dictates an integrated approach between the primary care physician, the immunologist, the hematologist, and the infectious disease specialist. Since the most feared morbidity related to KD regards the prevention of CA injury, we sought the opinion of the pediatric cardiologists, often considered primary consultants, on ASA and IVIG therapy. The low proportion of participants who do not deviate from the *Red Book* recommendations and the relatively higher proportion of those who propose evaluation of ASA therapy versus those who propose evaluation of IVIG therapy reflect a current trend toward discrediting the usefulness of ASA but not that of IVIG.

Limitations pertaining to this report need to be addressed. The response rate in this survey was 32% of individuals and 73% of U.S. fellowship programs. Indeed, the opinion of one respondent from a specific practice group does not necessarily reflect the opinion of the entire group. We therefore did not attempt to calculate the distribution of respondents within each fellowship program. Furthermore, the opinion expressed by the participants from our targeted academic pediatric cardiology programs may not be extrapolated to the entire pediatric cardiology community nor should it be considered a consensus on the subject. On the other hand, although no attempt was made to assess whether potential participants were interested in the subject of KD, it is possible that the respondents were a select group of interested individuals. Finally, our attempt to measure change of opinion before and after exposure to pertinent literature may have introduced a bias by reducing the contrast between "before" and "after." However, we were able to detect significant change in several important management parameters. The use of a few selected papers was intended to highlight the recent literature and hence, the need for a comprehensive review of the literature before any change in individual or institutional management policy is made.

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Appendix: Survey Questionnaire

Question No. 1:

What follow-up would you usually consider for a patient in the risk level I category?

A. Follow AHA recommendations (i.e., no follow-up required).
B. Follow-up every 1–2 years (clinical / ECG).
C. Follow-up every 3–5 years (clinical / ECG).
D. Follow-up only if subsequent cardiac disease suspected.
E. Follow-up with stress testing, only if symptomatic.

Question No. 2:
According to Paridon et al., 37% of patients with no previously demonstrated evidence of coronary artery lesions during any phase of the disease (risk level I) had myocardial perfusion defects with exercise testing. Based on the above findings, what follow-up would you usually consider for a patient in the risk level I category?

A. Follow AHA recommendations (i.e., no follow-up required).
B. Follow-up every 1–2 years (clinical/ECG).
C. Follow-up every 3–5 years (clinical/ECG).
D. Follow-up only if subsequent cardiac disease suspected.
E. Follow-up with stress testing, only if symptomatic.

Question No. 3:
What follow-up/tests would you consider for a patient in the risk level II category?

A. No follow-up beyond the first year unless cardiac disease is suspected (AHA recommendations, 1st alternative).
B. Clinically (±ECG) every 3–5 years (AHA recommendations, 2nd alternative).
C. Clinical evaluation (±ECG) and echocardiogram periodically.
D. Periodic screening for coronary artery disease with stress echocardiogram or myocardial perfusion scan.

Question No. 4:
According to Paridon et al. 67% of patients with transient coronary artery ectasia that disappears during acute illness (risk level II) had myocardial perfusion defects with exercise testing. Based on the above findings, what follow-up/tests would you consider for a patient in the risk level II category?

A. No follow-up beyond the first year unless cardiac disease is suspected (AHA recommendations, 1st alternative)
B. Clinically (±ECG) every 3–5 years (AHA recommendations, 2nd alternative
C. Clinical evaluation (±ECG) and echocardiogram perdiocally.
D. Periodic screening for coronary artery disease with stress echocardiogram or myocardial perfusion scan.

Question No. 5:
Along with clinical evaluation and ECG, what would you consider for a patient in the risk level IV category?

A. Periodic echocardiogram.
B. Periodic echocardiogram + ECG stress testing.
C. Periodic echocardiogram + stress echocardiogram.
D. Periodic echocardiogram + myocardial perufusion scan.

Question No. 6:
According to Dahdah et al., despite myocardial perfusion improvement with exercise, patients with persistent coronary artery aneurysm may have segmental wall motion abnormalities during exercise stress testing. Based on the above findings, what would you consider for a patient in the risk level IV category?

A. Periodic echocardiogram.
B. Periodic echocardiogram + ECG stress testing.
C. Periodic echocardiogram + stress echocardiogram.
D. Periodic echocardiogram + myocardial perfusion scan.

Question No. 7:
If a patient has no other risk factors for coronary artery disease: in general, would you place an asymptotic Kawasaki disease patient without coronary involvement on any restrictions?

A. No restrictions unless coronary lesions present.
B. Restrict smoking, saturated fat/cholesterol intake, and excess weight.
C. I formally advise all my patients on the above restrictions regardless whether they had a history of Kawasaki disease or not.

Question No. 8:
Dhillon et al. proposed that abnormalities of systemic endothelial function are present many years after resolution of acute Kawasaki disease, even in patients without detectable early coronary artery involvement. Sugimura et al. stated that patients with risk levels II and III had poor coronary artery dilation, which may be a risk factor for atherosclerosis. Based on the above findings, what restrictions would you recommend for a patient with Kawasaki disease as described in question No. 7?

A. No restrictions unless coronary lesions present.
B. Restrict smoking, saturated fat/cholesterol intake, and excess weight.
C. I formally advise all my patients on the above restrictions regardless whether they had a history of Kawasaki disease or not.

Question No. 9:
When would you consider coronary angiography for a patient with a history of Kawasaki disease and persistent coronary aneurysm?

A. On a regular basis (every 2–3 years, 3–5 years, etc.).
B. Only if clinical symptoms are suggestive of coronary stenosis/ischemia.

C. Only if stress echocardiogram is abnormal.
D. Only if myocardial perfusion scan is abnormal.
E. Upon transfer from pediatric to adult cardiology care (if otherwise not indicated).

Question No. 10:

Kato et al. reported an incidence of coronary aneurysm in acute Kawasaki disease of 25% (followed by resolution in ~50%). Early coronary stenosis was documented in 9.6% within 18 months of the acute onset of the disease. Among those who had persistent coronary aneurysms without stenosis initially, nearly 23% developed late coronary stenosis (2 and 17 years later). Based on the above findings, when would you consider coronary angiography for a patients with a history of Kawasaki disease and persistent coronary aneurysm?

A. On a regular basis (every 2–3 years, 3–5 years, etc.).
B. Only if clinical symptoms are suggestive of coronary stenosis/ischemia.
C. Only if stress echocardiogram is abnormal.
D. Only if myocardial perfusion scan is abnormal.
E. Upon transfer from pediatric to adult cardiology care (if otherwise not indicated).

Question No. 11

According to Sato et al. Harada's score is a reliable guideline for selecting patients for the indication of IVIG treatment. In this perspective would you:

A. Continue following the 1997 Red Book recommendations, i.e., treat all patients when diagnosis of Kawasaki disease is established or strongly suspected?
B. Continue following the 1997 Red Book recommendations, but see the necessity for establishing clinical/laboratory criteria, similar to Harada's, in order to select patients for IVIG therapy?
C. Already follow Harada's criteria (or other similar criteria) in selecting patients for IVIG treatment?

Question No. 12:

Terai et al. showed in a meta-analysis study that there was no significant difference in the prevalence of coronary artery aneurysm between initial moderate-dose aspirin (30–50 mg/kg/day) and initial high-dose aspirin (80–100 mg/kg/day) treatment regimens. In regards to aspirin (ASA) therapy, do you:

A. Recommend an initial high-dose ASA as per the 1997 Red Book recommendations?
B. Recommend an initial high-dose ASA as per the 1997 Red Book recommendations, and are aware of colleagues recommending initial lower dose ASA?
C. Recommend an initial high-dose ASA as per the 1997 Red Book recommendations, and believe lower dose regimens should be evaluated in prospective clinical trials?
D. Already recommend an initial moderate dose of ASA (30–50 mg/kg/day) instead?
E. Already recommend an initial low dose of ASA (3–5 mg/kg/day) instead?