Cardiol Young 2004; 14: 465–469

ISSN 1047-9511

Letters to the Editor

Dear Sir,

We have read with interest the articles published in the Journal concerning rheumatic fever (Mota C. Rheumatic fever in the 21st century. Cardiol Young 2003; 13: 491–494 and Ozkutlu S, Hallioglu O, Ayabakan C. Evaluation of subclinical valvar disease in patients in rheumatic fever. Cardiol Young 2003; 13: 495–499). We agree that rheumatic fever is far from being eradicated, even in the well-developed western countries, and that the epidemiologic features have changed, no longer being related to unfavourable socio-economic conditions, and with a more frequent carditis that may be difficult to detect. In the same period as the one analysed by Ozkutlu et al., specifically for the winter season over 1999 and 2000, we observed a remarkable increase in the incidence of new patients with rheumatic fever presenting to our Institution in Northern Italy, noting 17 cases instead of the usual 4–5 cases seen each year over the previous decade. Half of them were diagnosed late due to diagnostic difficulties encountered by family doctors. These patients had more severe lesions than the group diagnosed at earlier stages. In contrast to what is stated by Otzkutlu et al., however, our cases with mild mitral valvitis presented murmurs that could be mistaken for "innocent" murmurs, but were properly defined when auscultated by an experienced cardiologist. Our criterion for significant mitral regurgitation as judged using colour Doppler was a jet reaching one-third of the height of the left atrium, while Ozkutlu et al. considered as a cut-off of a jet extending 1 cm from the mitral valvar annulus, this criterion being less restrictive. It would be interesting to know the grades of mitral or aortic lesions in cases of patients deemed to have "innocent" murmurs in the experience of the Turkish group. We agree that Doppler echocardiography is fundamental for the recognition of mild lesions, but we feel that the family doctors should be aware of the fact that rheumatic fever still poses a significant problem, and that an early diagnosis allows a better prognosis. Our data also indicate an improvement in valvar lesions at follow-up in this new cohort of patients with rheumatic fever.[1]

Vlasta Fesslova, MD
Centro Cardiovascolare Istituto Policlinico
San Donato Milanese
Milano, Italy

Maria Bardare
Department of Pediatrics
Istituti Clinici di Perfezionamento
Milano, Italy
Tel: +39 02 52774 511; Fax: +39 02 52774 459
E-mail: cardiologiafetale@grupposandonato.it

Reference

1. De Sanctis M, Fesslova V, Mannarino S, Salice P, Sersale G, Corona F, Bardare M. A possible comeback of rheumatic fever in Northern Italy. Ital J Pediatr 2003; 29: 217–221.

Reply

Dear Sir,

I thank Dr Fesslova for her comments, which highlight important remaining questions about the approach to rheumatic fever. It is a fact that this intriguing disease continues to present a daunting challenge. Among the problems which still need to be addressed are the diagnostic difficulties, along with our incomplete understanding of the factors responsible for the changes in epidemiology, specifically the reason for its disappearance and reappearance. After a marked decline, the sudden resurgence of focal epidemics in civilian populations through the 1980s in the United States of America, and the more recent episode of a sixfold increase during a period of 7 months over the average annual incidence of 4–5 cases seen in Northern Italy, as described by Dr Fesslova et al., highlight these ongoing difficulties. As has been pointed out, many physicians are unfamiliar in these situations with the varied presentations of rheumatic fever. This fact in itself could result in late diagnosis, with all its consequences. Even in the areas where rheumatic fever is highly prevalent, however, the identification of mild carditis can present problems on some occasions for those involved with the clinical diagnosis, even when they are experienced cardiologists. The more accurate description of the morphological and functional abnormalities of the cardiac segments by Doppler echocardiography, and the contribution of this technique in identifying the subclinical valvitis, have emphasised the potential difficulties in diagnosing mild valvar lesions by auscultation. In our experience, many patients have no murmur. Even when a murmur is audible, its character is similar to that

of the innocent murmur heard in healthy children, these characteristics being well described by Ozkutlu et al. Taking into consideration the lack of a specific diagnostic test, besides the unknown pathogenesis, we must continue to recognise that, unfortunately, the diagnosis of rheumatic fever is still dependent on the impression gained by the physician from a set of nonpathognomonic signs and symptoms.

Cleonice de C. Mota
Hospital das Clínicas
Universidade Federal de Minas Gerais
Faculdade de Medicina
Serviço de Cardiologia e Cirurgia Cardiovascular
Av. Prof. Alfredo Balena
110 – 5° Andar, 30130-100
Belo Horizonte
MG, Brazil
Tel: +55 31 3248 94 37; Fax: +55 31 3248 92 96
E-mail: cleomota@medicina.ufmg.br

Dear Sir,

My colleagues and I thank Dr Fesslova for her interest in our study. We have re-evaluated our data to try to answer her question, and we also commend her on the recent publication in the Italian Journal of Paediatrics. Only two of our 21 patients with innocent murmurs have mitral regurgitation of moderate severity. All the others have mild regurgitation. In one of the two patients initially with moderate regurgitation, the lesion has regressed and returned to within normal limits. The other patient still has moderate regurgitation and continues to be followed up. We agree with Dr Fesslova that Doppler echocardiography is an essential technique for the recognition of mild lesions.

Suheyla Ozkutlu, MD
Hacettepe University
Faculty of Medicine
Pediatric Cardiology Unit
06100 Sihhiye
Ankara, Turkey
Tel: +90 312 310 4258; Fax: +90 312 309 0220
E-mail: suheylaozkutlu@yahoo.com

Dear Sir,

Re: Recommendation for the use of palivizumab as prophylaxis against respiratory syncytial virus in infants with congenital cardiac disease.

The above article was published in your journal of October 2003.[1] We wish to express our disagreement with the recommendations. In our view, the evidence on which the recommendations are based is very weak indeed. Our disagreement is on a number of counts.

The authors recommend the use of palivizumab for the prophylaxis of respiratory syncytial virus infection in children with congenital heart disease. Unfortunately, the study on which this recommendation was based[2] does not provide any supporting data. Indeed, the study does not mention the rates of infection in either the treatment or control arms. Hence, it is impossible to determine if treatment has any effect on prophylaxis. Instead, as indicated in the title of the paper, it only claims to reduce hospitalisation following infection by the respiratory syncytial virus in such children.

The evidence on which the recommendation for treatment of children with heart disease is based relates to only one statistically significant finding, namely, a relative reduction of risk in hospital admissions. They reported a "p" value indicating significance without looking at absolute figures concerning reduction of risk, or numbers needed to treat to save one episode. As our Table 1 shows, relative reduction of risk can sometimes appear misleadingly significant when looked at in isolation.

Even if one accepts the validity of relative reduction of risk for the end point, as they have done, it was still necessary to treat 22 children before one could be prevented from being admitted to hospital. Considering that at least 5 injections in each winter season are required, at a cost of £829.00 per injection, the authors are recommending that we spend over £90,000.00 to prevent one baby from being admitted to hospital. In the absence of any data suggesting any benefit after treatment in terms of death or serious morbidity, we believe that this is a questionable use of the limited resources available within the National Health Service. More robust evidence is therefore required before recommendations can be made for routine clinical use of this very expensive drug. This evidence should include a detailed assessment of the financial aspects of this treatment in the United Kingdom, particularly the ratio of cost to benefit.

In Table 2, we include our estimates, based on the data in the paper, of the cost of reduced admission to the intensive care unit, and decreased need for mechanical ventilation, which are the other secondary end

https://doi.org/10.1017/S1047951104214226 Published online by Cambridge University Press

Table 1. Four hypothetical studies each with an RRR of 50%.

	Study 1		Study 2		Study 3		Study 4	
	Treated group	Control group	Treated group	Control group	Treated group	Control group	Treated group	Control group
No. of patients	1000	1000	1000	1000	1000	1000	1000	1000
No. improved	3	2	10	5	50	25	500	250
RRR (%)	50		50		50		50	
ARR (%)	0.1		0.5		2.5		25	
NNT	1000		200		40		4	

Abbreviations: ARR: absolute risk reduction; RRR: relative risk reduction; NNT: number needed to treat to prevent one case occurring in the treated group

Table 2. Analysis of primary and secondary end points in the study.

	RSV hospitalisation		ICU admission		Mechanical ventilation	
	Palivizumab	Control	Palivizumab	Control	Palivizumab	Control
Total no. of patients	639	648	639	648	639	648
Outcome	34	63	13	24	8	14
RRR (%)	46		46		43	
ARR (%)	4.5		1.7		0.9	
NNT	22		59		108	
Cost/episode saved (£)	91,190.00		244,555.00		447,660.00	

Abbreviations: RRR: relative risk reduction; ARR: absolute risk reduction; NNT: number needed to treat to prevent one episode; RSV: respiratory syncytial virus; ICU: intensive care unit

points in the study. The figures for these are of even more concern, although the reduction of risk for these did not achieve significance.

Finally, the declaration of interest stated that a number of the authors were also investigators in the study. There is nothing in the declaration of interest to suggest that the authors benefited from the study, and we have no doubt of their integrity. Probity might have been better served, however, had the advisory group been completely independent. Perhaps the British Paediatric Cardiology Association should exercise more caution in the future in situations like this, where potential conflict of interest might exist.

Obed C. Onuzo
Department of Paediatric Cardiology
University Hospital of Wales
Cardiff, UK
E-mail: obed.onuzo@cardiffandvale.wales.nhs.uk

References

1. Tulloh R, Marsh M, Blackburn M, Casey F, Lenny W, Weller P, Keeton BR. Recommendations for the use of palivizumab as prophylaxis against respiratory syncytial virus in infants with congenital cardiac disease. Cardiol Young 2003; 13: 420–423.
2. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Connor EM, Sondheimer HM for the Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with haemodynamically significant congenital heart disease. J Pediatr 2003; 143: 532–540.

Reply

Dear Sir,

We thank Dr Onuzo et al. for their forthright criticism of our recommendations for the use of palivizumab in infants with congenital heart disease, and you, Sir, for the opportunity to respond.

The main thrust of the criticism appears to be that we have not considered the cost-effectiveness of this treatment, though we clearly state in our article that evaluation of cost–benefit is still required.

It cannot be denied that infection of vulnerable infants with congenital cardiac disease by the respiratory syncytial virus represents a threat to their well-being and survival. Paediatric intensive care

https://doi.org/10.1017/S1047951104214226 Published online by Cambridge University Press

units around the country prepare themselves each year for the influx during the autumn and winter months of children infected in this way, and every paediatric cardiology unit has experience of children undergoing prolonged intensive care, with some patients dying as a result of this infection.

There are a number of points raised in their letter that we will deal with in order.

- Although they express disagreement with the recommendations they do not clearly state the aspects with which they disagree.
- We refute the assertion that the recommendations are based on weak evidence. The study of Feltes et al.[2] was a double-blind, randomised, placebo-controlled trial. As such, it represents the highest level of evidence, short of a meta-analysis of several randomised-controlled trials. This provides us with evidence of both the safety and efficacy of this treatment.
- They say that we recommend the use of prophylaxis in children with congenital cardiac disease, whereas our recommendations largely concern infants and then only those with haemodynamically significant congenital heart disease, pulmonary hypertension and children with cardiomyopathy receiving treatment. We also state that consideration should be given to infants requiring admission for medical or surgical intervention during the season of infection with the virus, and children over the age of 1 with complex cardiac disease. In fact, it is clear that our recommendations will help the clinician justify more limited use of this expensive treatment. Our group were at pains to define patients who would not be regarded as likely to benefit from its use, as much as to identify those who likely would.
- We disagree that the study of Feltes et al.[2] does not provide data to support these recommendations. The study demonstrated that palivizumab recipients had a 45% relative risk reduction in hospitalisations for those infected by the virus. Though this does not tell us the rates of infection in the whole population studied, it strongly suggests that palivizumab has a positive impact on the burden of the disease in this group of vulnerable patients. The study does show reduction in stay in the intensive care unit, assisted ventilation, and death. To demonstrate significant reduction in these areas specifically due to infection with the virus, however, it would be necessary to perform a study on over 10,000 children with congenital cardiac disease so as to achieve an 80% power at the 5% level. For this reason, hospitalisation because of infection by the virus was the primary end point of the study.
- We note the criticism regarding the use of relative risk reduction as a statistical tool. We agree that it can be misleading when looked at in isolation. The incidence of hospitalisation because of infection by the virus in this group of 1287 patients, however, is clearly stated as involving 5.3% of the 639 patients who were treated, as opposed to 9.7% of the 648 who received placebo. The relative reduction in risk, and 95% confidence intervals, is clearly stated, along with the p value obtained using Fisher's exact test. It is self-evident that, in order to reduce the incidence from 10% to 5% (approximately), it is necessary to treat 20 patients so as to prevent one hospitalisation. These analyses undoubtedly should be part of the cost–benefit analysis that we stated were needed. Assessment of the number needed to treat analyses of the pharmacoeconomic issues from the payer's perspective, rather than society's. They do not include the costs of long-term consequences to an infant and their parents, including death from infection by the virus, or death or morbidity due to delayed correction or palliation of a cardiac lesion. As clinicians, we must be mindful of the wider implications of infection by the respiratory syncytial virus in our children, including mortality and morbidity. In this study, 6 of the 97 patients admitted to hospital died (6.7%), which illustrates the seriousness of infection by the virus in this group of patients.
- We believe that the costs as quoted by Dr Onuzo et al. are excessive compared to figures we have been quoted from our pharmacies. In addition, there are simple savings to be made by batching "at-risk" patients, so maximising use of each ampoule.
- Whilst we agree that we have responsibilites for judicious use of the resources available within the National Health Service, we refute the suggestion that we are recommending routine use of this expensive treatment. Our objective was to provide guidance to paediatric cardiologists and paediatricians faced with decisions regarding appropriateness of passive immunisation of individual patients under their care. It should be noted that palivizumab is being widely used in general paediatric practice for premature infants, infants with chronic lung disease, and those with immunodeficiency. It is approved for use by the Federal Drug Administration in the United States of America, and also for use in the European Community, both for these patients and for children with congenital cardiac disease.
- We are disappointed that Onuzo and his co-signatories have chosen to question our individual probity, as well as that of the British

https://doi.org/10.1017/S1047951104214226 Published online by Cambridge University Press

Paediatric Cardiac Association. The members of the working party were chosen because of their interest and expertise in the subject, and this inevitably included paediatricians and cardiologists who had contributed to that part of the study undertaken in the United Kingdom. Views were also sought from clinicians unable to attend the working group, as indicated in the acknowledgements. The authors of the letter are surely not suggesting that any participant in a commercially sponsored, randomised-controlled trial should be denied the opportunity to contribute to future recommendations in the area of their work and expertise?

Finally, we would suggest that professional bodies, including the British Paediatric Cardiac Association, have a duty to take an active role in the evaluation of new treatments that may benefit patients.

Barry R. Keeton
Wessex Cardiothoracic Centre
Southampton General Hospital
Southampton, UK
E-mail: keetob@suht.swest.nhs.uk
(Co-authors: Robert Tulloh, Michael J Marsh, Michael Blackburn, Frank Casey, Warren Lenney, Peter Weller)

https://doi.org/10.1017/S1047951104214226 Published online by Cambridge University Press