CORRESPONDENCE

Which is the principal early-life infection-related risk factor for asthma?

To the Editors:

In a previous issue of the *European Respiratory Journal*, KUSEL *et al.* [1] reported very interesting 10-yr results of their prospective birth cohort study. Originally, 263 children at risk for asthma and allergy were recognised pre-natally and recruited as newborns, and 198 (75.3%) attended the 5-yr [2] and 147 (55.9%) the 10-yr follow-up study [1]. The drop-out rate of 44% is understandable but needs evaluation. The data were collected very carefully during the first year including diaries completed by parents and home visits with sampling for virus detection by PCR during all acute infections [2]. Respiratory infections were classified as upper (URI) and lower (LRI), and both URIs and LRIs further as wheezy and nonwheezing.

At age 10 yrs, 18.4% of the 147 children had current asthma and 20.4% persistent wheeze [1]. During the first year of life, 35.8% had experienced at least one LRI with fever and/or wheeze. The figure was 26.5% for febrile LRI and, likewise, 26.5% for wheezy LRI. Atopy determined by skin-prick tests to a panel of two food and five inhaled allergens was present in 31 (21.1%) infants at age 6 months, and in 63 (42.9%) and 56 (38.1%) children at age 5 and 10 yrs, respectively.

In adjusted analyses, children who had wheezy or febrile LRI at age <12 months and were atopic by age 2 yrs were at increased risk for asthma or persistent wheeze at 10 yrs [1]. Wheezy LRI associated with human rhinovirus (HRV) was a risk factor for asthma and persistent wheeze only in children with atopy onset after 2 yrs. However, wheezy LRI associated with respiratory syncytial virus (RSV) was not a risk factor in either group formed by atopy onset [1].

The authors highlight the waning of the association between wheezy LRI at age <12 months and asthma or persistent wheeze ascertained at 10 *versus* 5 yrs [1]. Instead, they stress the role of the severity of early-life respiratory infection, which in their study was estimated by fever and LRI *versus* URI.

We have prospectively followed up, over 25 yrs, 83 children who were hospitalised for bronchiolitis at age <24 months with chest radiographs taken on admission in all cases. An interstitial infiltration was found in 46 (57%) children. Follow-up studies were performed at 4.5–6.0, 8.5–10.0, 14.0–16.0, 18.5–20.0 and 26–28 yrs, and we found no evidence for an association between current asthma at any time and the severity of bronchiolitis, assessed by radiological infiltration [3]. In addition, asthma was consistently more common in these two wheezing groups than in the 44 children hospitalised for pneumonia alone.

The multivariate analyses used by KUSEL *et al.* [1] were adjusted for sex, breastfeeding, pet ownership, older siblings, tobacco

smoke exposure and daycare attendance. Atopy at age 6 months was not, but atopy at age 2 and/or 5 yrs was, a risk factor for both asthma and persistent wheeze at 10 yrs. Atopy was taken into account in the analyses by performing stratified analyses in relation to atopy onset by and after 2 yrs.

However, this modelling does not answer the question of whether the severity (fever in the present study) of respiratory infection in infancy is a risk factor for later asthma or persistent wheezing independently of the associated virus or the presence of wheeze. In addition, there might be certain time windows for the virus-specific or nonspecific influences of infections to airways or to immunity even within the first 12 months of life. Perhaps such modelling would be worth trying here, and grouping might be realistic. Only 9.3% of infants with LRI had both wheeze and fever. Febrile LRI did not recur in any child and wheezy LRI recurred in only 14 children. No data were presented on fever and wheeze URIs, which may, of course, be both confounding and disease-modifying factors.

In our post-bronchiolitis studies, HRV bronchiolitis (or non-RSV bronchiolitis in older studies) increased the later asthma risk compared with RSV bronchiolitis, with some waning of the effects of both viruses from 7 yrs of age onwards [4], in line with the waning between 5 to 10 yrs in the present study [1]. In addition, RSV and HRV seem to have different effects on lung function presenting at least at 7 and 12 yrs of age. RSV bronchiolitis was associated with a more restrictive and HRV with a more obstructive pattern of subnormal of lung function [5].

As the authors summarised, severe LRI in infancy is a major risk factor for asthma and persistent wheeze at age 10 yrs in high-risk children [1]. However, the specific roles of different viruses in early life need further attention, as does the question of whether the severity/fever is an independently significant risk factor. Lung function results, which hopefully have been obtained and will be reported in the near future, may shed more light on both open questions.

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Linezolid: safety and efficacy monitoring

To the Editors:

We read with interest the recent *European Respiratory Journal* article by SINGLA *et al.* [1], which described the treatment outcome of 29 (pre-)extensively drug-resistant (XDR) tuberculosis (TB) patients from Delhi, India. All patients received linezolid as part of their anti-TB regimen. The high percentage of favourable treatment outcomes in the study led SINGLA *et al.* [1] to conclude that “Linezolid could have played a key role”. However, in our opinion, conclusions on the role of a single agent, such as linezolid, are difficult to draw from a series of cases without controls, in which every patient received linezolid in addition to an injectable antimycobacterial agent and a fluoroquinolone. Indeed, the important role of later-generation fluoroquinolones is addressed, but neither drug sensitivity testing (DST) nor drug concentration monitoring for linezolid was performed. Therefore, linezolid treatment itself could even be subtherapeutic [2].

SINGLA *et al.* [1] conclude that “an aggressive, comprehensive management programme using linezolid along with other drugs can favourably treat significant number of patients”. Although we concur with this statement, a closer look at the management programme applied in this study suggests that the programme might not be too aggressive or comprehensive. For instance, no directly observed therapy (DOT) was applied, nor did the patients receive nutritional or good psychosocial support. Compliance was only assessed indirectly by checking empty blister packs. Since noncompliance could lead to treatment failure and increase of resistance against the few drugs that are still effective in (pre-)XDR-TB treatment, we would strongly advise to abandon DOT only in exceptional cases where compliance is highly probable [3]. Therapeutic drug monitoring (TDM) can be recommended to ensure adequate drug exposure during treatment. In rural areas, dried blood spot analysis may enable TDM by offering an affordable tool for drug concentration measurement in a centralised laboratory using stable, easy-to-obtain samples [4].

The very low incidence of major adverse events (AEs) of 10.3% reported by SINGLA *et al.* [1] is in contrast with findings in literature, where 41.2% of 85 multidrug-resistant/XDR-TB patients treated with linezolid experienced major AEs [5]. The authors provided no explanation for low AE incidence found in their study. Perhaps the fact that temporary discontinuation of linezolid was scored as a minor adverse event, along with the

absence of DOT, resulted in a lower score of AEs in the study by SINGLA *et al.* [1]. Unfortunately, the authors provided no information on the manufacturer of the linezolid. Only the low cost of linezolid of less than US\$1 per tablet is mentioned, compared with approximately US\$80 per tablet in the Netherlands. It is well established that counterfeit drugs pose a great threat and counterfeit drugs sometimes contain little to none of the claimed drug [6]. Although there is no evidence that the administered drugs in this study were counterfeit, it also cannot be excluded based on the information provided by SINGLA *et al.* [1]. This, combined with the absence of DOT and TDM, could very well be a reason for the low incidence of major AEs as observed in the study by SINGLA *et al.* [1].

In our opinion, only a randomised controlled trial of linezolid *versus* a placebo, in addition to an adequate background regimen using DST and TDM, will provide comprehensive results on efficacy and safety of linezolid as potential drug for (pre-)XDR-TB treatment regimen.

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