EUROPEAN PROTOCOLS FOR THE DIAGNOSIS AND INITIAL TREATMANT OF INTERSTITIAL LUNG DISEASE IN CHILDREN: ON-LINE SUPPLEMENT

1. **Andrew Bush MB BS (Hons) MA MD FRCP FRCPCH FERS**

Professor of Paediatrics and Head of Section (Paediatrics), Imperial College; Professor of Paediatric Respirology, National Heart and Lung Institute; and Consultant Paediatric Chest Physician, Royal Brompton Harefield NHS Foundation Trust, London, UK.

2. **Steve Cunningham MBChB, PhD**

NHS Lothian and University of Edinburgh.

3. **Jacques de Blic MD**

Pediatric Pulmonary Department, Hôpital Universitaire Necker Enfants Malades, Paris, France; Université Paris Descartes , Paris, France

4. **Angelo Barbato MD**

Department of Women's and Children's Health, University of Padova, Italy

5. **Annick Clement MD**

Assistance Publique-Hôpitaux de Paris, Hôpital Armand-Trousseau, Pneumologie pédiatrique, Centre National de Référence des Maladies Respiratoires Rares, Paris, France

6. **Ralph Epaud MD**

Centre Intercommunal de Créteil, Service de Pédiatrie; INSERM, U955, Equipe 5; Université Paris-Est, Faculté de Médecine, Créteil, France

7. **Meike Hengst MD**

Children's Hospital of Ludwig, Maximilians University, Munich, Germany

8. **Nural Kiper MD**

Pediatric Pulmonology, Hacettepe University Faculty of Medicine, Ankara, Turkey

9. **Andrew G Nicholson DM FRCPath**

Professor of Thoracic Pathology, Imperial College & Royal Brompton Harefield NHS Foundation Trust, London, UK

10. **Martin Wetzke MD**

Department of Pediatrics, Pediatric Pulmonology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany

11. **Deborah Snijders MD**

Department of Women's and Children's Health, University of Padova, Italy

12. **Nicolaus Schwerk MD**

Pediatric Pulmonology and Pediatric Lung Transplantation, Hannover Medical School, Clinic for Pediatric Pneumology, Allergology and Neonatology, Hannover, Germany

13. **Matthias Griese MD**

Lung Research Group, Children's Hospital of Ludwig, Maximilians University, Munich, Germany

on behalf of the chILD-EU collaboration

Correspondence: Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.

- **Tel: -207-351-8232**
- **Fax: -207-351-8763**
- **e mail:- a.bush@imperial.ac.uk**

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Delphi Consensus of Approaches to the Management of Children with Interstitial Lung Disease

We conducted a two round Survey Monkey questionnaire Delphi consensus of paediatric pulmonologists in Europe, North America and Australasia. The aim was to gauge current practice and treatment expectation. Clinicians were identified from national paediatric respiratory society groups The survey referred to children with proven or highly suspected interstitial lung disease.

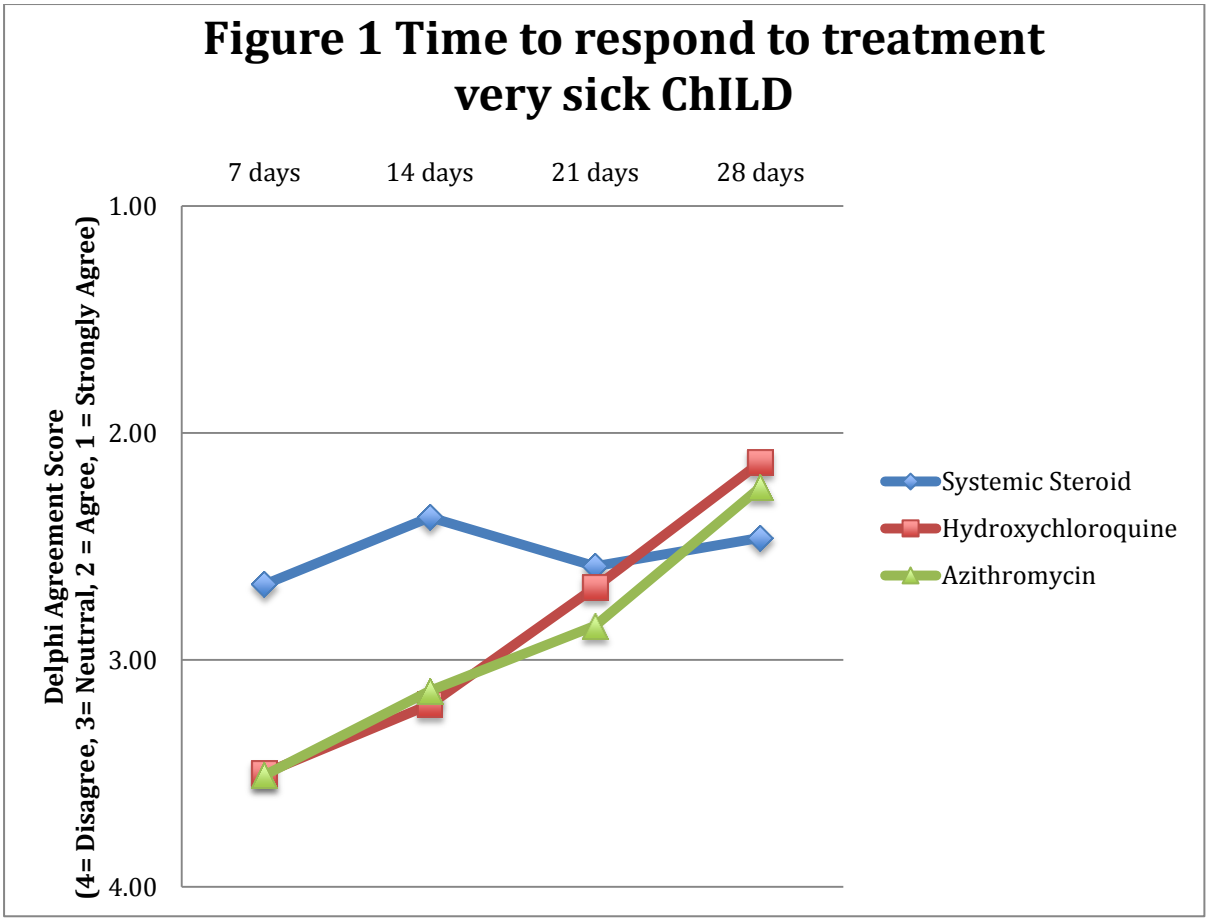
Survey 1

Survey 1: 8 scenario stems, total 75 responses on 1-5 scale (from strongly agree to strongly disagree). Data is presented for 144 responses (29 removed as fewer than 50% answers provided): Australia 14, Canada 3, France 5, Germany 15, Italy 1, USA 61, UK 37, Other 8.

(a) Scenario patient very sick and ventilated or close to ventilation with no known specific treatment.

Q1. Initial approach to treatment: Most popular systemic steroids alone (median 2, mode 1). Three other options median response 3 (Systemic Steroids with hydroxychloroquine, or azithromycin or both).
Q2. Both intravenous methylprednisolone (500mg/m2 or 10mg/kg) scored median response 2 (mode 1). Oral prednisolone (2mg/kg) scored median response 3. Three further options (daily oral prednisolone 1mg/kg, three days per month oral methylprednisolone at either 500mg/m2 or 10mg/kg) had median scores of 4. Some responders at larger centres expressed a preference for intravenous methylprednisolone at 30mg/kg (consistent with Rheumatology dosing).
Q3. Clinical response to treatment: Improvements in respiratory rate demonstrated progressive increase in agreement from 5% (neutral 3) to 10% (agree 2) to 20% (strongly agree 1). Improvements in heart rate produced more muted agreement as both 5% and 10% improvements produced neutral responses (3) and a 20% improvement agreement (2). Improvement in weight by 5% was neutral (3), but agreed as a response when 10% (2). Improvement in oxygen saturation were associated with better agreement; a 2% improvement was neutral (3), but a 5% increase caused agreement (2) and a 10% increase was strongly agreed as a sign of improvement (1). The loss of need for supplemental oxygen or mechanical ventilator support were both strongly agreed as demonstrating improvement (1).

Q4. Time to respond to treatment (Figure X). Systemic steroids were considered to work from 7 days, but hydroxychloroquine and azithromycin had 21-28 days for perceived benefit.



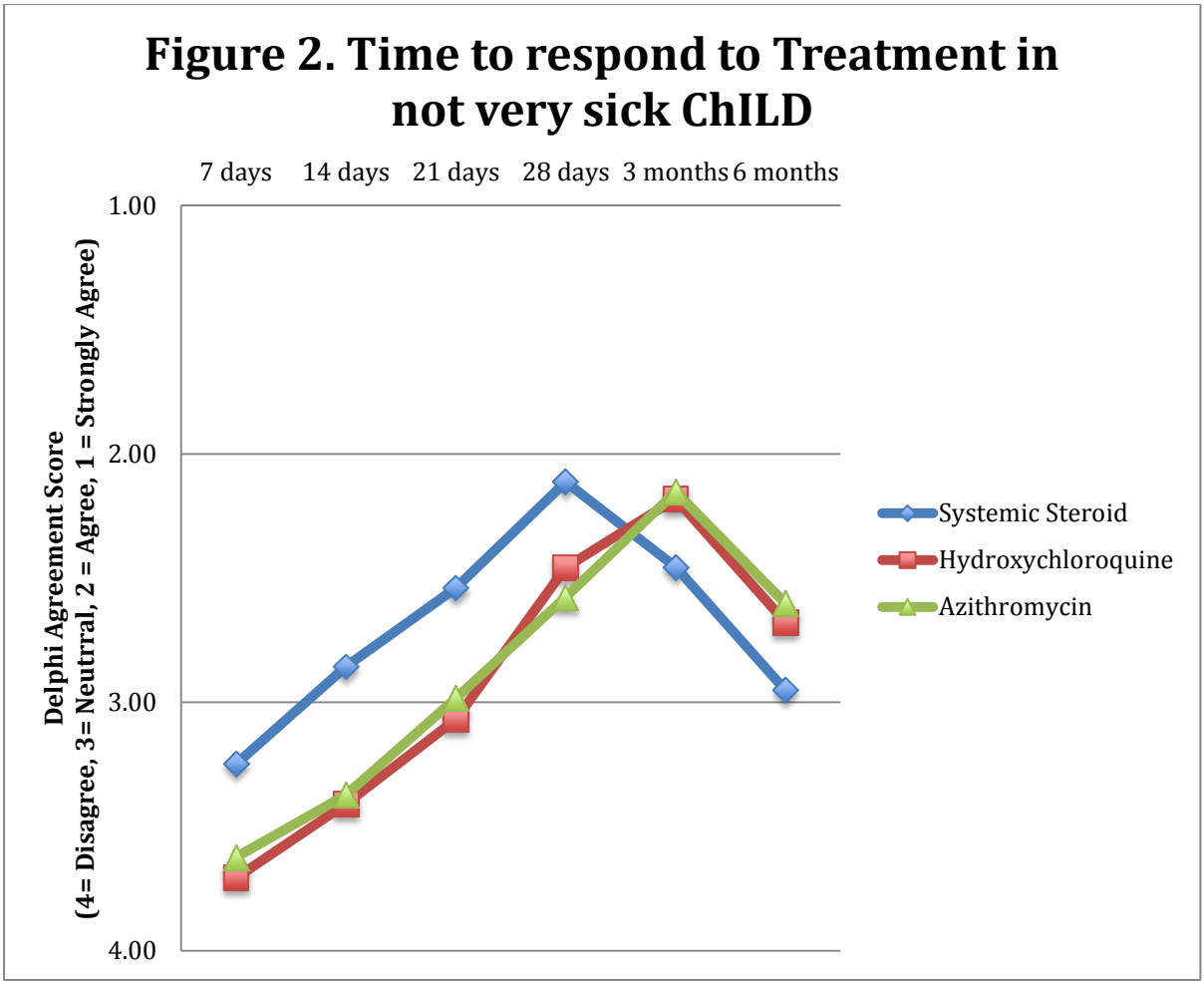
(b) Scenario patient not ventilated or close to ventilation, needing treatment but no specific treatment known. Similar stem questions repeated.

Q5. Initial approach to treatment: . As in infants who were more sick, most popular was use of Systemic Steroids alone (median 2, mode 1). Three other options median response of 3 (Systemic Steroids with hydroxychoroquine, or azithromycin or both). The responders did not significantly differentiate initial treatment response dependent on disease severity.

Q6. There was equal agreement for the use of either oral prednisolone 2mg/kg/day or intravenous methylprednisolone 10mg/kg 3 days per month (both agreement level 2). Oral prednisolone 1mg/kg and intravenous methylprednisolone 500mg/m2 both had neutral responses (3), and oral methylprednisolone at either dose disagreement (4).

Q7. Clinical response to treatment responses were identical to those provided in Q3. What clinicians consider a clinical pharmacological benefit are the same in different disease states in children with interstitial lung disease.

Q8. In less sick infants (Fig Y) clinicians considered steroids could take 28 days for maximal effect, with hydroxychloroquine or azithromycin upto 3 months.



Continental Differences

In Survey 1 there were roughly equivalent number of responders from North America and Europe. There were no major differences of opinion in responders from the EU and North America, with concurrence for all major findings above.

Many respondents considered that pulsed intravenous steroids have a lower side effect profile compared with daily oral steroids at a corresponding dose.

Survey 2

Survey 2: 9 lead statements requiring 11 individual responses. All results are presented descriptively. Data is presented for 114 responses (Consultant/Attending Pulmonologist) (12 removed as fewer than 50% answers provided): Australia 9, Canada 2, France 6, Germany 22, Italy 5, USA 30, UK 36, Other 5.

Survey stems provided consensus of opinion survey 1 and asked clinicians to choose as (a) Usual practice or (b) could happily use it if the consensus of the Delphi, or (c) Not usual practice and would not wish to use it even if the consensus of the Delphi. Doses were to be considered starting doses that could be varied at the discretion of the treating clinician.

Q9. In survey 1 large consensus to for both sick and less sick to judge the effect of systemic steroids before commencing additional therapies. Survey 2 confirmed this as usual practice in 76% (N=87). A remaining, 23% (N=26) agreed to approach even though not their usual practice One respondent (1%) did not wish to consider this approach.

Q10. In survey 1 large consensus for use of pulsed intravenous methylprednisolone for 3 days every 4 weeks at a dose of 10mg/kg/dose in those who were very sick. Survey 2 confirmed this as normal practice in 80% (N=91). A remaining 19% (N=22) agreed to approach even though not their usual practice One respondent (1%) did not wish to consider this approach.

Q11. In sicker patients use of oral prednisolone inbetween pulsed methylprednisolone a common comment in survey 1; In survey 2, the majority of respondents, 63% (N=72) favoured prednisolone at 1mg/kg/day, with 23% favouring prednisolone at 2mg/kg/day (N=26), and 14% (N=16) not wishing to use oral prednisolone between intravenous methylprednisolone even if it were the consensus of the Delphi.

Q12. In survey 1 in less sick ChILD there was no overall consensus between intravenous pulsed methylprednisolone or daily oral prednisolone 2mg/kg/day.
Initial preference was fairly evenly split with 46% (N= 47) responders using oral prednisolone alone, 45% (N= 46) methylprednisolone alone and 9% (N= 9) combining both.
When asked to consider the alternative strategy respondents were fairly flexible;
31 of the 54 (54%) respondents who had not chosen oral prednisolone would be happy to use it if that were the consensus, but 18 others would not consider using oral prednisolone even if it were the consensus. Of those whose first preference was not for methylprednisolone alone, 43 of the 56 (55%) respondents would be happy to use it were that the consensus of the Delphi; 8 others would not consider this approach even if it were the consensus. Finally those who did not identify combination of pulsed methylprednisolone and intervening oral prednisolone as their first preference, 42 of the 93 (45%) would consider using a combination of therapies were there consensus, whilst 34 would not wish to consider a combination even if that were the consensus.

Q13. In survey 1 a consensus was for hydroxychloroquine to be used in the treatment of ChILD. In survey 2, 89%, (N=100) of respondents used hydroxychloroquine at 10mg/kg and would be happy to continue to do so. 4% (N=4) used a different dose but could adapt if there were consensus, and 7% (N=8) did not use hydroxychloroquine and would not wish to do so.

Q14. Similarly for Azithromycin, in survey 2, a dose of 10mg/kg 3 days per week was favoured by 79% (N=89) of respondents, with a daily dose of 10mg/kg preferred by 12% (N=13). One (1%) respondent had a fixed alternative and 8% (N=9) respondents did not use azithromycin and would not wish to do so.

Q15. In survey 1 there was no consensus on the order of medication to follow initiation of systemic steroids. Respondents were fairly divided with the options provided in survey 2 with 38% (N=43) starting azithromycin first, 44% (N=49) commencing hydroxychloroquine first and 13% (N=15) commencing both at the same time. 4% (N=5) would not commence these medicines.

Q 16. In survey 1 there was no consensus as to whether Hydroxychloroquine could be used in the absence of systemic steroids. In survey 2 respondents were split between the 54% (N=61) who could use hydroxychloroquine alone (at 10mg/kg) and the 46% (N=51) who would not wish to do so even if consensus. There were no responses for option b.

Q17. Similarly for Azithromycin used as sole treatment for ChILD in the absence of systemic steroids the responses again were evenly divided by those who could consider Azithromycin as sole therapy in ChILD , 51% (N=57) for 3 days per week and 4% (N=4) for 7 days per week, or at an alternative dose 1% (N=1), and the 47% (N= 50) who would not consider Azithromycin as a sole therapy in the absence of systemic steroids and would not wish to do so even if consensus.

Continental Differences

In Survey 2 again there were no major differences of opinion in responders from the EU (N=73) and North America (N=32), with concurrence for all major findings above.