Towards a Personalised Approach to Managing Influenza Infections in Infants and Children – Food for Thought and a Note on Oseltamivir

Barbara Rath[1]*, Franziska Tief[1], Katharina Karsch[1], Susann Muehlhans[1], Patrick Obermeier[1], Eleni Adamou[1,2], Xi Chen[1], Lea Seeber[1], Christian Peiser[1], Christian Hoppe[1], Max von Kleist[2], Tim Conrad[2] and Brunhilde Schweiger[3]

[1]*Department of Pediatrics, Division of Pneumonology-Immunology, Charité University Medical Center, Berlin, Germany;* [2]*Department of Mathematics and Computer Science, Free University, Berlin, Germany;* [3]*National Reference Center for Influenza, Robert Koch Institute, Berlin, Germany*

Abstract: Acute respiratory infections represent common diseases in childhood and a challenge to infection control, public heath, and the clinical management of patients and their families. Children are avid spreaders of respiratory viruses, and seasonal outbreaks of influenza create additional disease burden and healthcare cost. Infants under the age of two and children with chronic conditions are at high risk. The absence of pre-defined risk factors however, does not protect from serious disease. Immunisation rates remain low, and physical interventions are of limited value in young children. Children with influenza may be contagious prior to the onset of symptoms, and school closures have been shown to have a temporary effect at most. The timely detection of influenza in at-risk patients is important to prevent hospital-based transmission and influenza-associated morbidity and mortality. Guidelines issued by professional associations and public health agencies need to be translated into everyday clinical practice. Antiviral therapy should be initiated early and monitored closely, including virologic and clinical outcomes. The duration of treatment and the decision to readmit children to schools and kindergartens should be adjusted to the individual child patient using evidence-based clinical and virologic criteria. This article presents lessons learnt from a quality management program for infants and children with influenza-like illness at the Charité Department of Paediatrics in collaboration with the National Reference Centre for Influenza at the Robert Koch Institute, in Berlin, Germany. The Charité Influenza-Like Disease (ChILD) Cohort was established during the 2009 influenza pandemic and encompasses nearly 4000 disease episodes to date.

Keywords: Antiviral, children, diagnostics, influenza, management, oseltamivir.

1. INFLUENZA-LIKE ILLNESS – A COMMUNICATION CHALLENGE

Acute respiratory tract infections are among the most common reasons for physician visits in infancy and childhood [1-3]. Parents seek urgent care in emergency rooms and outpatient clinics, often with the concern that they are losing control over the situation [4]. Patients presenting to referral and tertiary care centres are often more severely affected.

Parents are usually eager to learn the reason for their child's respiratory problem. This is a critical moment in parent-physician communication to explain the differences between bacterial and viral illness as well as the multiplicity of viruses that may trigger "the flu". Once an influenza diagnosis has been established, parents as well as children may respond very differently. Some may be relieved that "this is just a virus", others may remember threatening news headlines regarding death rates during past epi-/pandemics [5].

Managing influenza infections in infants and children creates a communication challenge. In lay language, the term "flu" is often used synonymously with "the common cold". The importance of distinguishing one from another is often unclear to the patient. Lay perceptions of disease severity associated with "a real flu" as opposed to "a common cold" may vary significantly [6-8]. Individual risk behaviours [9], risk perceptions[10], and factual knowledge regarding influenza may also depend on the ethnic and cultural background of the patient and their family [11-13].

A number of studies have shown that effective communication strategies during a primary visit for acute respiratory infections will reduce re-consultation visits and antibiotic prescription rates throughout the course of illness [14-16]. A study of more than 500 paediatric outpatients in England and Wales demonstrated that even a "When should i worry?" information booklet for parents was effective in increasing parent satisfaction (www.whenshouldiworry.com) [17].

Once infants and children are diagnosed with influenza, healthcare professionals play a significant role with respect to benefit/risk communication [16]. Parents may be overly relieved or concerned, or just confused, depending on the information they have received. Additional unimmunised family members with known risk factors may have been exposed to the child including younger siblings, pregnant mothers, relatives with chronic illness or aging grandparents [18-20].

*Address correspondence to this author at the Department of Pediatrics, Division of Pneumonology-Immunology, Charité University Medical Center, Augustenburger Platz 1, 13353 Berlin, Germany; Tel: +49 30 450 666664; Fax: +49 30 450 566 931; E-mail: Barbara.Rath@gmail.com

2212-3989/13 $58.00+.00

For the physician, communicating the need to treat or not to treat with antiviral agents versus antibiotics poses an additional challenge [14, 21]. Many questions may arise regarding media reports of severe illness versus severe side effects. For questions remaining unanswered during the physician visit, social networking sites and the world wide web are commonly consulted by concerned patents and their children [22]. In addition, there has been increasing confusion surrounding the role of vaccines and non-pharmaceutical interventions (NPI) in preventing "the flu" [23-27]. Due to lack of time or confidence, the topic of influenza vaccination often remains unaddressed during doctor-patient encounters [26, 28]. At the same time, non-immunised medical personnel may feel particularly uncomfortable raising the topic when dealing with influenza patients [29].

Parents will want to know *which* virus *their* child is suffering from *now*. Traditionally, respiratory viral infections in children have remained unspecified and coded, diagnosed, and communicated as "a viral infection". Physicians who have highly sensitive and rapid diagnostic tests available, will be in a position to convey a personalised and specific message, followed by reassurance and specific instructions and recommendations.

2. EARLY DETECTION OF INFLUENZA

A number of lessons have been learnt during recent influenza epidemics and pandemics [14, 15]. During the peak of influenza season each year, paediatric emergency rooms are filled with patients displaying signs and symptoms of influenza-like illness [16]. Effective screening algorithms need to be in place for infection control purposes, as well as for the allocation of treatment modalities to those who are most likely to benefit [30].

Physicians should be aware of the need to achieve laboratory confirmation given the inaccuracy of clinical influenza diagnoses. Prospective studies have demonstrated that the positive predictive value of clinical influenza diagnoses in children remains below 40% [31, 32]. Influenza symptoms may be particularly vague in infants and small children, masked as gastroenteritis, bacterial sepsis (in neonates), bronchitis, syncope, seizures (febrile, afebrile) and other neurologic manifestations [33-36].

Highly sensitive and specific diagnostic capabilities are key, ideally to be applied at the point of care (POC) [37]. A personalised approach to the child patient requires accurate diagnostics. Active influenza surveillance in acute care settings will ultimately enhance patient safety. With an established diagnosis at hand, healthcare personnel, parents and visitors will likely be more aware of, and compliant with rigid infection control and social restriction measures [30].

Rapid tests have been disregarded widely during the pandemic due to concerns regarding the lack of sensitivity of laminar flow antigen assays in some studies [17]. Published sensitivities for rapid influenza diagnostic testing (RIDT) vary between 17% and 70%. Even the same test performed at different centres may yield different results indicating that the technique of nasopharyngeal sampling may play an important role [38, 39].

In infants and children, where viral loads are often higher than in adults, RIDT may yield acceptable positive and negative predictive values, as long as nasopharyngeal samples are obtained appropriately [37, 40]. The focus must therefore be placed on the establishment of integrated systems for POC testing using appropriate technologies and evaluation procedures [39, 41]. The value of RIDT in the respective setting should be established in comparison to culture or polymerase chain reaction (PCR) [37, 39, 42].

Conventional laminar flow tests have the disadvantage of occasional faint signals or signals with changing intensity over time. Reliance on test strip results that are legible only for a short period of time would be suboptimal in the busy emergency room setting. Innovative second generation fluorescent rapid tests have since been developed offering the benefit of increased sensitivities and standardised machine readings, thus limiting inter-rater variability [43].

Reports have shown that the effective use of RIDT may reduce the inappropriate use of antibiotics and unnecessary diagnostic procedures in children with influenza, while shortening the duration of stay in emergency rooms and hospital units [39, 44-46]. The timely detection of influenza infections in at-risk patients will also enable early treatment with antivirals at the time of their maximum efficiency [40]. A recent open-label observational study of real-life prescribing practice in infants with a clinical diagnosis of influenza suggested that physicians felt more comfortable treating influenza infections when laboratory confirmation was available [47].

At the same time, adherence to therapy will likely improve with a laboratory confirmation of influenza infection prior to the onset of antiviral therapy [47]. Laboratory diagnoses of influenza at the POC will also allow the accurate monitoring of influenza infections (treated and untreated) in the respective hospital setting, and the distinction of "true" influenza infections from influenza-like illness due to other respiratory pathogens [48-51].

Clear guidelines and standard operating procedures need to be established, specific to each patient and setting, directing the clinical management of patients identified by positive or negative diagnostic tests. Agreement should be sought as to when antiviral therapy should be initiated, based on clinical suspicion, RIDT, or PCR. National and international guidelines provide structure and useful advice, even if some remain inconclusive with respect to treatment based on clinical suspicion versus laboratory confirmation [52-56].

3. INFECTION CONTROL - PROTECTING AT-RISK PATIENTS

The prevention of person-to-person transmission poses an additional problem during influenza season. Children are avid spreaders of influenza viruses, in schools and kindergartens as well as in the household setting. [57-59] School closures seem to incur massive indirect costs and provide only temporary help [60]. Physical interventions including respiratory masks and hand hygiene measures are of limited value in infants and children [61, 62].

Effective infection control is often perceived as additional workload imposed upon the hospital staff. Each time a

new case of influenza has been identified, isolation precautions need to be re-adjusted. Rooming-in care has become common practice in paediatric hospitals, posing an additional challenge to infection control [63]. Systems need to be in place minimising the time lag between the provision of the information of a new infection and the establishment of effective isolation precautions [64]. Parents and caretakers of hospitalised children with influenza, often affected by the same symptoms themselves, will need to be included in isolation precautions [62, 65]. Restrictive visitor policies may create additional emotional burden [66].

Efforts to prevent nosocomial transmission of influenza are particularly challenging during the busy winter months in paediatric hospitals. Influenza may cause significant mortality in hospitalised children, especially in chronically ill and immunocompromised patients. Oncology and neonatology units have reported significant outbreaks putting some of the most vulnerable patients at-risk [67]. Guidelines recommend annual immunisation of at risk patients as well as their household members (cocooning strategy), but patients belonging to risk groups are often insufficiently vaccinated [27]. The effectiveness of influenza vaccines may be reduced in severely immunocompromised patients, and the current influenza vaccines are not licensed for infants below the age of 6 months [27, 68-71]. Thus, timely diagnosis and initiation of antiviral therapy will remain crucial to these most vulnerable patient groups, who cannot be protected otherwise [72, 73].

4. UNDERSTANDING THE ROLE OF CO-INFECTIONS

While viral cultures remain the gold standard in the diagnosis of most viral infections, PCR technologies have been established as the mainstay of laboratory diagnosis. To maintain high levels of sensitivity and specificity with PCR detection of influenza, PCR primers should be adjusted regularly to the local epidemiology and circulating subtypes [74-77].

Different rates of co-infection of influenza with other respiratory pathogens have been reported. Numerous studies have been conducted to investigate the frequency of infections with other respiratory viruses [78-80]. Reported co-infection rates vary, depending on the number of viruses tested, the particular season and setting, as well as virologic method used. Newly developed multiplex platforms and automated techniques may help to save cost while increasing the number of pathogens tested simultaneously, but sensitivities may vary significantly [81-90]. The clinical impact of viral co-infections and the practical implications, especially with respect to the cohorting of patients testing positive for multiple viruses, remain unclear.

Occasionally, dual infections with several influenza viruses have been described, including influenza A/A, A/B and B/B dual infections [91-94]. These observations indicate that infections with one influenza subtype or type may not protect against other un-related strains, even though animal models suggested that seasonal H3N2 infection may protect against H1N1 infection via the nasal route [95]. These findings may have implications for the cohorting of influenza patients, but also for the development of quadrivalent and universal influenza vaccines [96-100].

Several preclinical and clinical studies are also addressing the incidence and impact of bacterial co-infection on disease severity and progression [46, 101-104]. It remains a challenge to distinguish bacterial co-infection from colonization in patients infected with influenza. While preclinical and clinical models are being developed to investigate molecular interactions at the bacterial-viral interface, the practical implication of positive bacterial test results in the clinical management of influenza patients remains to be determined. Large population-based studies are required to investigate the significance of viral-viral and viral-bacterial co-infections, and the clinical impact of antibiotic versus antiviral therapy in infants and children with different types and subtypes of influenza [30, 46, 101-104].

5. GETTING THE FULL PICTURE

One of the key challenges to the investigation of therapeutic interventions in paediatric influenza infections is the absence of a universal, standardised score for the assessment of disease severity in different age groups. Uniform criteria for the measurement of disease severity in children with respiratory infections are urgently needed for the evaluation of disease burden with influenza in children, as well as the effectiveness of antiviral therapy (including new drugs under development) and influenza vaccines in children [27, 30, 105-107].

Standardised, real-time disease severity scores would also be useful to monitor the progress of patients under antiviral therapy with neuraminidase inhibitors. Observer effects could be minimized and the duration of therapy adjusted to the individual patient [54, 55, 108]. Severely ill patients may require adjustment in the duration of treatment and the dosing of neuraminidase inhibitors (NAI) [56]. The impact of ECMO and hemodialysis/ filtration on NAI pharmacokinetics has been addressed by several investigators, but preclinical models and large-scale prospective studies are lacking [109-119]. Very little data are available on the pharmacokinetics and pharmacodynamics of influenza antiviral therapy in premature infants, neonates and small children under the age of one [33, 47, 120-129]. While oseltamivir has been licensed for infants older than 2 weeks in the United States, physicians and neonatologists in other parts of the world are restricted to off-label use, since the emergency-use authorisation for oseltamivir use in infants was lifted at the end of the 2009/10 pandemic [125].

In infants and children undergoing antiviral therapy, solid pharmacodynamic relationships need to be established allowing the individualised adjustment of dosing in those who are most at risk. Most importantly, standardised disease severity measures will provide an important tool for the direct comparison and meta-analysis of clinical trial data while improving the overall quality of clinical safety and efficacy data.

The establishment of sensitive and powerful disease severity measures, encompassing the entire spectrum from mild to severe disease, will help to direct evidence-based diagnostic and therapeutic decisions. Standardised disease severity scores may prove useful during the communication with parents and families. Ideally, disease severity scores

should be simple enough to be performed by parents at home, while providing an objective tool to assess the overall clinical improvement in their children [130].

6. MANAGING INFLUENZA INFECTIONS WITH ANTIVIRALS

The personalised management of influenza infections with antivirals starts with the assessment of the time point when the disease has started. While there is little doubt about the need to initiate antiviral therapy as early in the course of illness as possible, real-life situations often differ from the idealised environment established during clinical trials. In infants and young children, it is particularly difficult to determine the exact time of disease onset. The frequency and high prevalence of respiratory viral infections in this age group often creates confusion. While some parents may recall the onset of specific symptoms in their child, others may have more difficulty distinguishing one disease episode from another. Some children may have multiple caretakers who may or may not communicate well with each other.

Physicians working in acute care settings are in need of clear guidance on how to deal with historical reports of "tactile temperatures" when determining the duration of illness [131-133]. Physicians should be aware of differences in the perception of fever by parents from different cultural and socio-economic backgrounds [134]. While some physicians adjust for the body site where temperatures have been measured and/or exposures to antipyretics when determining body temperatures, others may not [135-137]. Non-respiratory presentations of influenza are common in infants and children and may delay influenza diagnoses and the onset of antiviral therapy [138].

The next challenge is the monitoring of clinical signs and disease progression under antiviral therapy. Different physicians may be seeing the patient throughout the course of illness applying different criteria for the diagnosis of pneumonia and other complications related to influenza. In infants and children, radiological studies are often avoided to minimise radiation exposure. The Pneumonia Etiology Research for Child Health (PERCH) study aims to achieve standardization of pneumonia diagnoses in children [139]. The severity of extra-pulmonary signs and symptoms may be recognised and assessed differently depending on the level of awareness and experience of the physician in charge. Associated complications may be attributed to the drug by some physicians, and to the disease itself by others [138, 140-147].

The ultimate goal for the management of influenza infection with antivirals would consist of the application of evidence-based, objective clinical disease severity scores in combination with biomarkers measuring disease activity and the individual risk of severe disease outcomes, ideally at the point of care.

7. VIRAL LOAD KINETICS AND DRUG RESISTANCE

The most commonly studied surrogate marker for disease activity in infants and children with influenza is the amount of virus detected (semi-) quantitatively in the respiratory samples. Several studies have investigated the impact of viral load on disease severity and progression [148-156]. In the absence of shared standards for the measurement of disease onset, the duration of viral shedding cannot be compared easily between studies [157]. However, the lack of robust criteria for the classification of disease severity, each study may be measuring different disease outcomes.

Depending on the methodology used, the assessment of viral loads may be both expensive and time consuming. Different influenza subtypes respond differently to antiviral therapy, hence subtyping of influenza viruses may be required in addition to viral load measurements [122]. While current guidelines recommend oseltamivir treatment for an average duration of five days commencing within the first 48 hours of disease onset, specific patient groups may require individualised treatment modalities. WHO guidelines recommend that "…where the clinical course remains severe or progressive, despite five or more days of antiviral treatment, monitoring of virus replication and shedding, and antiviral drug susceptibility testing is desirable. Antiviral treatment should be maintained without a break until virus infection is resolved or there is satisfactory clinical improvement" [55]. According to CDC guidelines, treatment regimens beyond five days is recommended in severely ill or immunocompromised individuals with a risk of ongoing viral replication [54].

The question remains how "evidence of ongoing viral replication" should be determined on day 5 of therapy. Again, real-time assessments of disease activity in combination with virologic parameters are warranted to provide guidance to the clinician. Studies of virus load kinetics in infants, who commonly display high viral loads and prolonged shedding, also indicate that delayed viral clearance may be an early indicator of resistance development [122].

Systematic assessments of patient adherence with antiviral therapy should be combined with the coordinated surveillance and reporting of antiviral drug resistance, including systematic studies of household transmission of resistant strains [158-160]. The ideal scenario would thus include sensitive assays for the determination of antiviral drug resistance in conjunction with clinical guidelines on how to adjust therapy should drug resistance become evident [161, 162]. Affordable rapid tests are needed for the early detection of resistance development under therapy, allowing the timely adjustment of treatment plans in the affected patient [159, 160].

8. A PERSONALISED APPROACH

A personalised approach for the management of influenza infections in infants and children should always be directed towards the immediate needs of the young patients themselves and their caregivers. The best guidance for a personalised approach to the child patient can be found in the most common questions encountered in everyday clinical practice. A few examples – as food for thought - are provided below:

- What is the cause of my illness?
- How and when did I contract the disease?
- What is my risk with this disease?

- Is there a drug and will it be effective?
- What is my risk with this treatment?
- Am I getting better?
- Did I eliminate the disease?
- How can I prevent myself from getting sick again in the future?

CONFLICT OF INTEREST

Charité University received funding from Hofmann-La Roche Inc. and Quidel Inc. for clinical research on influenza and the evaluation of RIDT in infants and children. BR is principle investigator in clinical research supported by Hofmann-La Roche and Quidel Inc. BR is not in receipt of any personal funds or honoraria.

ACKNOWLEDGEMENTS

The authors kindly thank all members of the Charité Pediatric Infectious Diseases & Vaccines team. The authors further acknowledge the kind cooperation by colleagues at Charité University Medical Center, at Robert Koch Institute, and at Free University in Berlin, Germany.

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Received: April 01, 2013 **Revised: April 14, 2013** **Accepted: April 22, 2013**