The beginning of a new era: systematic testing for pathogens causing acute respiratory tract infections (ARI) in children

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The problem

On average, humans get sick ten times per year. About six times, the illness is due to an acute respiratory tract infection (ARI). Morbidity is especially high in children, since

- they usually encounter the offending organism for the first time in their life;
- the lack of immunity results in shedding of the offending organisms in high numbers of prolonged time as compared to adults;
- their airways are smaller than those of adults and thus the inflammatory response leads to a more significant narrowing of the airways resulting in more severe disease;
- on average, they have a high number of social contacts and also a more intimate contact with peers and caregivers alike resulting in a higher attack rate;
- they display an age-dependent lack of appropriate hygiene measures.

In poor countries, ARI are one of the leading causes of death (Table 1). Optimal medical management of ARI is, therefore, of the highest importance everywhere in the world. The utmost importance of ARI in children is in sharp contrast to the little knowledge we have about the etiology, epidemiology, and clinical consequences such as development of asthma following respiratory infections. While ARI are comparatively simple to diagnose clinically by investigating the history of the patient and by physical examination, clinical findings alone do not allow to identify the offending microorganism in an individual case. We regularly encounter the peak of the RSV season in the middle of the influenza season; and often – based on only partial knowledge of the epidemiological situation and the spectrum of diseases caused by both organisms –

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unspecific ARI reporting misleads the public and treating physicians alike: the lack of appropriate diagnostic tools for ARI and thus the failure to identify ARI-pathogens results in a failure to treat patients optimally. While we know that at least 70% of lower ARI are caused by viruses, “blind treatment” with antibiotics has become the standard of care in most cases of pneumonia and even in many cases of bronchitis in many institutions all over the world. More so, since we do not know the frequency of different ARI-pathogens, new and specific treatments are not developed.

What we currently know

From a principal point of view, ARI-organisms can be divided into:
- colonizers like *Streptococcus pneumoniae*; these are usually sensitive to betalactams, and
- non-colonizers including bacteria (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis* and *B. parapertussis*; usually sensitive to macrolides) and viruses (rhino-, entero-, metapneumo-, parainfluenza-, influenza-, adeno-, corona-, boca-, polyoma-, reo- and RS-virus; others).

With the rare exception where a blood culture turns out positive for *S. pneumoniae*, it is still impossible to date to prove that a pneumococcus is the causative agent of pneumonia. Definitive prove of such “colonizers” to be the etiology of lower respiratory tract infection (LRTI) would require lung puncture, in order to avoid contamination in the oral/pharyngeal cavity. For psychological reasons only, this procedure is hardly ever performed – although it is probably safe and indeed would definitely prove the etiology of the respective episode of ARI. In contrast to the situation with colonizing agents, detection of a non-colonizing ARI-pathogen in a nasopharyngeal specimen, especially in a child with first ARI-encounters, usually means that the pathogen detected in the upper airway is the cause of the LRTI.

Solutions

In their paper in this journal, Thomazelli et al. use eight separate PCRs to screen for the presence of ARI-pathogens. They then used fragment length analysis with GeneScan for definite identification of PCR-products. Studying patients from a large pediatric hospital for 1 year, they most commonly found RSV followed by metapneumovirus, parainfluenzavirus 3, adenovirus, and influenza virus. Dual infections were seen in about 7% of children.

These results are in accordance with our observation. Starting in 1996, we developed a multiplex-RT-PCR to detect nine and then 19 different ARI pathogens (work in progress). Over a 10 year period and examining more than 20,000 specimens to date, rhinoviruses are most commonly encountered in children hospitalized for LRTI. RSV causes only
half as many cases as rhinoviruses, and influenzaviruses are
detected in only about 7%. Clearly, these simple findings
should make us start developing effective interventions
against the most common ARI-microorganisms, not just
against influenza. Moreover, using multiplex-PCR as a rou-
tine diagnostic tool has reduced the use of antibiotics in our
institution; it has taught us the clinical course and the large
variability in the clinical presentation of ARI-organisms; and,
during epidemics, it has reduced the use of diagnostic inter-
ventions such as chest-x-rays or laboratory tests. In many
instances, specific therapies can be given, e.g. for myco-
plasma or influenza. Additional advantages are summarized
in Table 2.

We have created a “web based warning system”, where
we publish the number of each ARI-pathogen detected dur-
ing the preceding week, we predict the activity of each organ-
ism for the upcoming epidemiological season (July 1st to June
30th the following year), and we give general information on
ARI.

This allows pediatricians in Germany e.g. to tailor the use
of RSV-immunoglobulin: in uneven years, RSV-epidemics
start late and run with a high peak. This is followed by con-
tinuous RSV-activity the following (even) year, sometimes
even throughout summer, to reach again an early peak in
autumn/winter. Likewise, rhythms can be detected for
metapneumovirus and other paramyxoviruses, whereas
adenovirus, enterovirus and rhinovirus are detected through-
out the year.4

Current problems

Whenever new diagnostic tools come along, they need to
be validated and this is especially true for PCR based tech-
niques. Contamination must be avoided at all times from the
minute the specimen is taken; e.g. negative control samples
should occasionally be collected at the bedside of patients (like
sterile saline or buffer) to prove that medical staff did not shed
“their” pathogen into the patient specimen. Besides the use
of strict methods to avoid contamination in the laboratory,
validation of the multiplex-testing should be established for
each organism by comparison to current standard tech-
niques like cell culture.6

Whatever “test-system” is used, its limitations must be
kept in mind and need to be communicated to the treating
physicians.

The future

It is clear to us that systematically testing for ARI patho-
gens is the way forward. Technical problems will be solved
within a few years. More tests will become standardized and
validated. Currently, testing is too expensive for the indi-
vidual. We ask for € 396.- per test if ordered commercially
(www.arti-st.de). Therefore, today public health institutions
should use the method for local surveillance. It is in the inter-
est of the public to know, which microorganisms are respon-
sible for the highest morbidity (and perhaps even mortality)
in the population. Furthermore, the public must be interested
in emerging pathogens like H5N1. These can be included in
the multiplex test systems, and this alone should be worth
the systematic approach as compared to not meeting the chal-
lenges caused by ARI at all or with insufficient and systemati-
cally misleading methods. With new technical developments
on the horizon, the price for systematically testing for ARI can
be substantially reduced in the near future and “acute respi-
ratory infection – systematic testing (arti-st)” will then hope-
fully become the standard of care for each individual child.

References


