

Pediatric infectious diseases – Quo vadis 2015?

David Nadal

Division of Infectious Diseases and Hospital Hygiene, University Children's Hospital of Zurich, Steinwiesstrasse 75, 8032 Zürich, Switzerland

Abstract

In modern medicine the discipline pediatric infectious diseases is an essential medical specialty. The challenging and complex tasks in the next years include meticulous consolidation and careful extension of existing activities aiming at conducting high level research, offering high standard teaching, and providing high quality patient management. This can only be accomplished by exquisitely dedicated individuals with extraordinary communication and integrative skills following painstaking continued training and formation. Potential careers in the discipline can be envisioned not only in academics, but also in government, public health, and industry, whilst less likely in private practice.

Introduction

The discipline pediatric infectious diseases has evolved to an essential medical specialty and faces major challenges in the years to come. One of the most important tasks of pediatricians has always been the management of patients with communicable diseases. The main reason for this is the higher frequency of infectious diseases in infants and young children compared to older children and adults due to the limited adaptive immunity repertoire and thus increased susceptibility to common pathogens. Therefore, pediatricians are considerably involved in the diagnosis, treatment and prevention of infectious diseases. In consequence, every pediatrician must be considered also an infectious disease specialist. This, in turn, has been a downside for the development of pediatric infectious diseases as a medical discipline recognized on its own in many countries. Nevertheless, the multiple technical advances in the recent years have led to substantially improved prevention and treatment success rates in many pediatric disciplines, and a plethora of these success rates are linked to the integral role of pediatric infectious disease specialists providing profound knowledge, expertise and quality assurance. Accordingly, pediatric infectious disease specialists

nowadays play a pivotal role both for community pediatrics and for clinical pediatrics in highly specialized medical centers.

This chapter attempts to summarize the current different activities of pediatric infectious disease specialists, to delineate their interactions with other medical disciplines and to speculate on the near future goals and development of this specialty with the widest scope compared to all the specialties in medicine.

Current activities of the pediatric infectious disease specialist

Similarities, overlaps and differences in relation to infectious diseases in adults

Pediatric infectious disease specialists are based mainly in hospital settings and have very similar activities in clinics, teaching and research compared to their counterparts in adult medicine. The four disciplines microbiology, epidemiology, immunology, and pharmacology build up the essential basis for both pediatric and adult infectious disease specialists. Nevertheless, despite several overlaps that are beneficial for constructive professional interactions, the position of the pediatric infectious disease specialists differ from those of specialists for adult infectious diseases. These differ not only in relation to the basic training in pediatrics and internal medicine, respectively, but also in relation to distinct focuses in the clinics obviously mandated by many age-related uniqueness of patients in the pediatric age (Tab. 1). Etiology, epidemiology, pathogenesis, management and prevention of infectious diseases in children may substantially differ from those in adults.

One important example of the uniqueness of pediatric infectious diseases is the need to deal with infections in newborns. Newborns have distinct pathophysiological characteristics, which mainly relate to the immature immune system. Another example of uniqueness comes from the age-related and more frequent contacts to potential infectious sources or index cases in nurseries, day-care centers or schools. These contacts lead to increased risks to preferentially acquire respiratory or gastrointestinal infections. Similar reasons account for higher frequency of outbreaks of infectious diseases in children compared to adults. Infants and toddlers are often the source of infections within a household, for health care workers or medical personnel as well as for nursery employees and teachers. Infections represent the reason for up to 60% of the hospitalization of children. Etiological diagnosis of these infections may be hampered by the limited volumes of biological samples including blood or cerebrospinal fluid available from young children, often affording rather tedious, and to this-age-group-adapted, diagnostic approaches. Moreover, most of the hospitalized children are prescribed one or more antibiotics [1]. In this context it needs to be underscored that the pharmacokinetics and pharmacodynamics of antimicrobial substances are

Table 1. Specific clinical tasks of the pediatric infectious disease specialist [4]

– Integrative discipline
– Provision of primary care and consultative services to patients from all pediatric disciplines
– Implementation of quality assurance programs in hospitals and other health care settings, e.g., infection control, hospital epidemiology, antimicrobial management programs
– Engagement in preventive efforts through implementation of vaccine strategies and other means; play a significant role in public health programs at all political levels
– Conduction of research seeking cures for new diseases as well as preventive measures, such as new vaccines
– Teaching and leadership in academic health institutions

rather different in children compared to adults. This may afford the use of distinct preparations or dosages in children. In addition, pharmacology and toxicology of antimicrobial drugs in newborns and specifically in preterm or small-for-date babies are rather special. Accordingly, in pediatrics special knowledge in the distinct uniqueness of newborns and other age groups, other disciplines and on nosocomial infections in neonatal and pediatric nurseries and intensive care units is warranted. Finally, vaccinations make up a larger proportion of the preventive measures in pediatrics than in adult medicine, and this is mirrored by the extraordinary success of general immunization campaigns in children [2].

Relation to community pediatrics and to hospital pediatrics

Pediatricians in private practice and, in some countries or regions, also general practitioners, are in charge of the management of children with common and frequent infectious diseases [3]. The quality of this management benefits highly from the continued access to and availability of a pediatric infectious disease specialist during the medical formation and training as well as throughout private practice activities. Pediatric infectious disease specialists provide important recommendations on the use of microbiological and other diagnostic tests, application of antimicrobial drugs, and measures for infection control, which may substantially differ in children compared to in adults. Furthermore, infectious disease specialists possess the required expertise for the establishment of standards of care for frequent communicable diseases and relevant guidelines for the community. Pediatric infectious disease specialists are involved in the care of both outpatients and inpatients [4].

The impact of the pediatric infectious disease specialist within a hospital can easily be deduced from the number of consultations related to infectious disease or infection control issues requested by both experienced

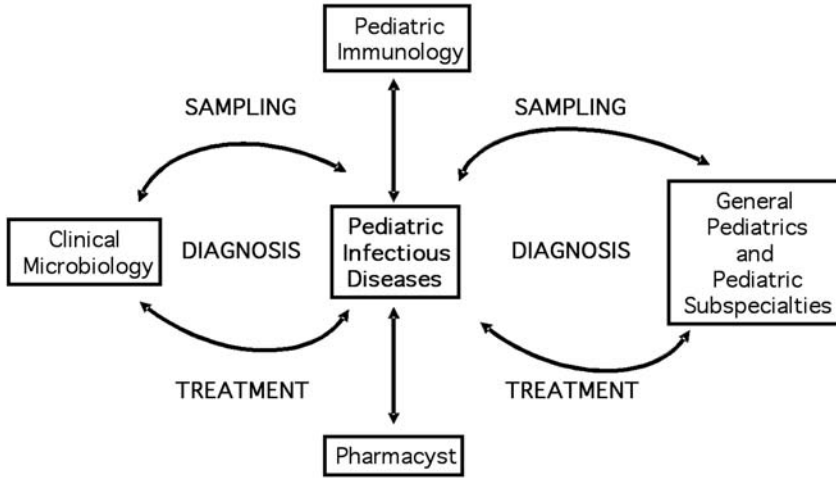


Figure 1. Communication pathways of pediatric infectious diseases.

and non-experienced physicians within or outside the hospital. Bedside consultations and phone consultations both play an important role [5]. The multiple interactions result, e.g., in a more considerate selection of diagnostic measures and assays, more judicious and less costly use of antimicrobials, and reduction of formal consultations and hospitalizations [6] (Fig. 1). Much of the shared knowledge originates from pediatric infectious diseases research programs, as they substantially contribute to the development of improved diagnostic, treatment and prevention means as well as to the understanding of pathogenesis and epidemiology of infectious diseases. The multifaceted roles of the pediatric infectious disease specialist clearly improve the quality of patient care and teach physicians who are involved in primary health care [4].

Integral and integrative behavior

Specialty in pediatric infectious diseases is the paradigm of an integral and integrative discipline providing paramount professional help, advice and support to other pediatric disciplines and to disciplines from adult medicine. Obvious examples are consultations for patients with underlying conditions including congenital heart disease, cystic fibrosis, primary or secondary immunodeficiencies such as due to HIV infection or iatrogenic immunosuppression following allograft transplantation, or tumors. Many of these patients nowadays survive beyond the pediatric age and need to undergo the difficult process of transition to medical care for adults [7]. Thus, close

interactions with colleagues from adult medicine taking over the care of these patients before, during and after the transition process are indispensable to ensure satisfaction and compliance of the patients with often heavy burdens in addition to the burdens of adolescence.

Infectious disease specialists have a considerable number of skills at their disposal [8]. Experienced infectious disease specialists, for example, often reduce the use of expensive diagnostic measures even in the most complex patient situations, apply intravenous antimicrobial treatment also to outpatients and switch from intravenous to apt oral medication on time. Hence, infectious disease specialists increase the satisfaction of patients while ensuring management quality at lowest possible expenses.

New developments for the specialists in pediatric infectious diseases

An outlook into the future cannot be undertaken without careful consideration of the past and the current situation. Thus, recent changes in the spectrum of infectious diseases, progress in the field of vaccinology, advances in microbiology, and quantum leap in communication technology are likely to determine new developments and areas of activity for the pediatric infectious disease specialist. The variety of topics covered in the chapters of this book nicely mirrors the wide spectrum of pediatric infectious diseases and the most recent novel developments in the field.

The changing spectrum of infectious diseases

Several achievements including clean water, improved sanitation, vaccination and antimicrobial therapies have brought many important infectious diseases under control. Nevertheless, we have had to face the emergence of pathogens that are resistant to antimicrobials and of new pathogens that have not been previously detected in humans.

The principal diseases of the last decade can be segregated into three major groups: (i) infections against which significant progresses have been achieved; (ii) newly emerged infections; and (iii) infections on which we had no impact [9]. In industrialized countries, infections with HIV or hepatitis C virus (HCV) have been transformed from diseases with no cure to manageable chronic infections due to newly available treatment or prevention modalities. Most importantly, mother-to-child transmission rates in these countries have fallen from around 15–25% to below 2%, and where preventive measures are strictly applied, vertical transmission of HIV has virtually vanished [10]. This success story, however, evolved at the expense of intra-uterine and neonatal exposure to drugs with a considerable toxic potential [11]. Thus, pediatric infectious disease specialists need to conduct long-term surveys on the evolution of these children following exposure to antiretrovi-

ral drugs in a life period with highest vulnerability, especially of the central nervous system. Testing of blood products has not only virtually abolished transfusion-related HIV infections but also HCV transmission [12].

Poliomyelitis vaccination campaigns have been extremely effective both in industrialized and in non-industrialized countries. Globally, the number of poliomyelitis cases has been reduced by 99% from 350 000 cases in 1988 to less than 800 cases in 2002 [13]. The goal to eradicate poliomyelitis, however, seems to be hurdled by unprecedented reemergence of poliomyelitis due to “escape” variants [14] or due to outbreaks in communities reluctant to vaccination, mainly for religious reasons and in countries where there are governmental obstacles to vaccination campaigns [13]. The tasks waiting the pediatric infectious disease specialists are to promote vaccination at the individual, at the community and at the country levels. This will demand persuasion activities focusing on individuals and on politicians. Similarly, measles, rubella and mumps are three viruses against which we possess excellent vaccines, and thus could be eliminated given that the only host for these viruses is humans. We will eventually defeat these viruses only if pediatric infectious disease specialists succeed in convincing parents of the necessity of vaccination. Many parents are no longer familiar with the disastrous consequences of these viruses simply because of the decreased circulation of these viruses in the populations due to the fact that a large proportion has been previously vaccinated. But convincing just the parents will not be sufficient, physicians and politicians will need to be convinced too [15].

The general introduction of the conjugate vaccine against *Haemophilus influenzae* type b for infants and young children early in the 90s has resulted in a dramatic reduction of *H. influenzae* type b invasive infections including meningitis, epiglottitis, arthritis, and osteomyelitis [16]. More recently, conjugate vaccines against *Streptococcus pneumoniae* or *Neisseria meningitidis* type C have also been introduced in general vaccination programs, and it appears that we will again witness a success. Nevertheless, not all *S. pneumoniae* serotypes are represented in the vaccine and the serotypes against which the vaccine elicits immunity may be replaced by other serotypes. Furthermore, a universal vaccine against *N. meningitidis* type B is still lacking. Thus, the reduction of *S. pneumoniae* or *N. meningitidis*-induced disease will not be as impressive as for *H. influenzae* type b. In consequence, pediatric infectious disease specialists will have to explore modalities to improve surveillance and treatment of these prominent and potentially deadly bacterial infections. It goes without saying that more research on the elucidation of bacterial and host-related pathogenetic mechanisms is needed to cut the imminent danger from these pathogens [17–19].

We have also witnessed the emergence of an unprecedented number of infections. Most of these infections are of animal origin: avian influenza, severe acute respiratory syndrome (SARS), West Nile, Ebola, and variant Creutzfeldt-Jacob disease. Another unprecedented observation was the

increase in the prevalence of antibiotic-resistant bacteria and the reemergence of previously eradicated pathogens as agents of bioterror. Among the most feared and serious antibiotic-resistant bacteria are methicillin-resistant *Staphylococcus aureus*. Multiple antibiotic resistances are a problem also with *S. pneumoniae*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* [9]. A main challenge for pediatric infectious disease specialists in addition to the challenge faced by their adult counterparts in this context will be the availability of apt antimicrobials in apt formulations. This in turn will demand that pharmacokinetic, efficacy and safety clinical trials for new drugs are conducted in parallel for adults and different age groups of children, to acquire the needed antimicrobial armamentarium on time.

Unfortunately, during the last decade we had no impact on tuberculosis, malaria and worldwide HIV, the three leading killer infectious diseases which contribute to half of the global burden of mortality from infectious diseases. In fact, the absolute number of the epidemics has steadily increased. This may cause repercussions in industrialized countries. Thus, we pediatric infectious disease specialists who are in a privileged situation cannot neglect these unsolved medical problems, but rather need to increase our efforts to share our time, knowledge and expertise for the benefit of those who need it most. Vaccines against these three pathogens are, without a doubt, of paramount priority.

Finally, another important issue has come up recently: pediatric infectious disease specialists have to deal with aspects of biological terrorism against children (see the chapter by Kwang Sik Kim).

Progress in vaccinology

The development of several vaccines has been hampered by technical difficulties. Vaccines can be developed following the principles of Pasteur, i.e., isolating, inactivating and injecting causative microorganisms. Such development, however, is not apt for all pathogens, especially for those which cannot be grown in cultures, including HCV, papillomaviruses 16 and 18 and *Mycobacterium leprae* or for antigenically hypervariable microorganisms such as *N. meningitidis* type B, *N. gonorrhoea*, malaria and HIV [9]. In recent years, many obstacles in the engineering of vaccines have been overcome. Using “reverse vaccinology” [20], a process in which computer analysis, microarrays, proteomics and other genome-based systematic approaches are used to select genomic sequences of microorganisms, antigens likely to confer protective immunity can be identified. Candidate antigens can be expressed by recombinant DNA and be tested in animal models. Reverse vaccinology has enabled the production of vaccines against HCV, human papillomaviruses, and meningococci type B. These examples will be followed for other pathogens representing a threat to infants and children.

The pediatric infectious disease specialist will have to define priorities, and will have to conceive plans to test the safety and efficacy of these future vaccines, as well as the surveillance of the epidemiology of the targeted pathogens following the introduction of the vaccines on a larger scale.

A change in paradigm in vaccinology has come from the recognition that conquering the most difficult infections such as HIV and malaria may require the T cell arm of the immune system. Most vaccines available today work by inducing antibodies, and quantification of these antibodies is often used as a parameter for immunogenicity of and protection by a given vaccine. Unfortunately, protective antibody levels are not clearly defined for every available vaccine. Moreover, as in the example of HBV vaccine, the levels of specific antibodies may not be indicative for the status of protection. The level of specific antibodies may be below the limit of detection but vaccinated individuals may be still protected against HBV infection by the cellular immune responses. The effective stimulation of cytotoxic T cells can be obtained using engineered non-replicating viral vectors, such as modified vaccinia virus, replication-incompetent adenoviruses and DNA vaccines [9].

Another recent quantum jump has been that we – as other living organisms – possess a conserved “innate” immune defense against pathogens. The innate immune defense senses invading microorganisms or their components, and determines the type of adaptive immune response that will eventually result in protection. Toll-like receptors and NOD proteins are involved in this process. An improved knowledge of the pathways of innate immunity, their selectivity and their interactions is likely to improve the efficacy of vaccines, since certain compounds triggering innate immune defenses, e.g., unmethylated CpG, which mimics microbial DNA or lipopolysaccharide as a bacterial cell wall component, could be used as novel vaccine adjuvants to enhance immunity. The field of innate immunity is certainly one of the most promising fields for laboratory and clinic-based research in pediatric infectious diseases [21].

Advances in microbiology, immunology and genetics

Among the most important developments resulting in unprecedented insights into pathogenesis, susceptibility and diagnosis of infectious diseases are advances in microbiology, immunology and genetics. Important changes, with introduction of molecular biology techniques and laboratory automation, have increased the accuracy and velocity of microbiological diagnosis (Fig. 2), and new tools are still being developed [22]. The pediatric infectious disease specialist will considerably benefit from close collaborations with microbiologists both at the research and at the routine level. An equally symbiotic relationship between pediatric immunologists and geneticists will help establish the reasons for increased susceptibility to distinct patho-

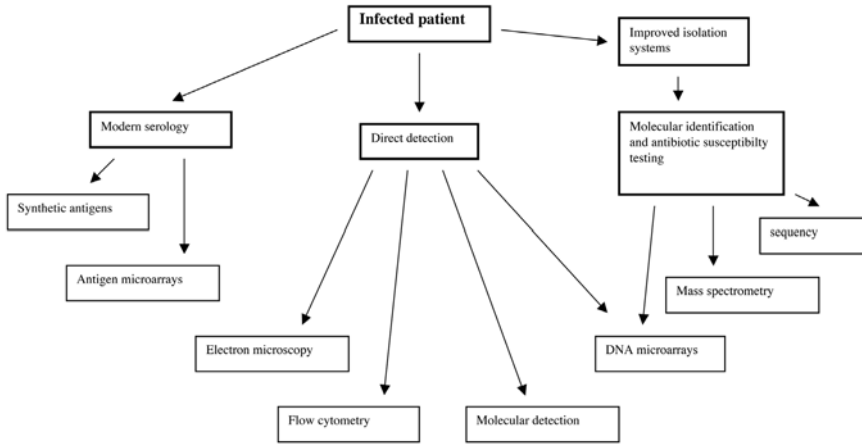


Figure 2. Modern techniques used to diagnose infectious diseases.

gens as, for example, mycobacteria or salmonella [23] and novel treatment modalities for immunocompromised children [24].

Increased intra- and interdisciplinary communication, interactions and networking

The sick child has the right to receive the best possible medical attention. This includes the caring physicians calling in specialists for consultations, and interdisciplinary consultations can be predicted to become a pivotal component of standard care for patients in the future. Who would dare to prevent a sick child from getting optimal remedial management?

Given the growing medical knowledge and the increasing complexity of modern medical care, pediatric infectious disease specialists can be anticipated to become highly solicited. Thus, intra- and interdisciplinary interactions will be more than ever crucial for pediatric infectious disease specialists in the years to come. Continued extensive communication, and close collaboration and partnership with other pediatric infectious disease specialists as well as with experts from pediatric immunology, clinical microbiology, pharmacy, epidemiology and all other pediatric subspecialties will build up the key for pediatric infectious disease specialists to ensure the indispensable optimal patient care, efficient teaching, and prosperous research. The most demanding challenge for pediatric infectious disease specialists will therefore be to comprehensively compile expertise, knowledge and cutting edge research for the ultimate benefit of the patient.

Whereas improved communication within the own hospital setting will help to cope with unqualified management of the sick child as much as pos-

sible, installment of a regular and frequent dialog with other centers will not only provide helpful suggestions from peers for the management of patients, but also facilitate and improve continuous education in the field and ensure exchange of ideas for independent and collaborative patient-related or laboratory-based research. The rapidly evolving communication technology has established excellent and affordable tools to allow for quick and reliable data and digital picture transfer as well as for audiovisual conferences at the national, international and intercontinental levels. Indeed, digital picture documentation of clinical and laboratory findings is advancing and will evolve.

The improved communication at the national and international level should pave the way towards standardized training curricula and the development of training quality evaluation programs. In countries where medical specialty units specifically devoted to pediatric infectious diseases await establishment, support from national and international professional societies will be required to promote the specialty, and communication networks will certainly contribute to expediting this process. The goal to install a pediatric infectious disease service at least in every large medical center is justified.

Networking will become more and more important to conduct multi-center studies devoted to the pathogenesis, diagnosis or management of less common infectious diseases to enable inclusion of sufficient patients in an appropriate time frame or to adequately respond to emerging infectious diseases [8]. Further, networking that also included experts other than pediatric infectious disease specialists will become increasingly essential to collect and exchange data pertinent to interdisciplinary managed patients as, for example, neonates, cystic fibrosis patients or transplant recipients, to optimize clinical research and management as well as issuing guidelines. Such guidelines will gain importance, e.g. in preventing misuse of highly expensive biologicals or drugs (<http://www.swiss-paediatrics.org/paediatrica/vol15/n6/palivizumab2004-ge.htm>).

Conclusions

The pediatric infectious disease specialist faces many challenging and complex tasks in the next few years. These tasks will include meticulous consolidation and careful extension of existing activities aiming at conducting high-level research, offering high-standard teaching, and providing high-quality patient management. These contributions to modern health care and medicine in general and pediatrics in particular can only be accomplished by dedicated individuals with extraordinary communication and integrative skills following painstaking continued training and formation. Potential careers in the discipline can be envisioned not only in academics, but also in government, public health, and industry, although less likely in private

practice. The diversity of issues and questions to be confronted makes the speciality of pediatric infectious diseases the speciality with the widest scope compared to all the specialties in medicine. Accordingly, commitment to pediatric infectious diseases will be extremely demanding. Since not all imposed tasks can be successfully completed by one person only, it will be of paramount importance to focus the activities and to carefully define priorities. Nevertheless, such demanding commitment will be fully compensated by manifold societal and personal rewards.

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