

AN INTEGRATED APPROACH TO THE UNDERSTANDING OF *CHLAMYDIA* INFECTIONS: INTRODUCTION TO THE 2009 UPDATE

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SUMMARY

An integrated, multidisciplinary effort is needed to achieve a greater understanding of the immunopathogenesis of urogenital and ocular Chlamydia trachomatis infections to combat this infection successfully, to prevent long-term complications and to develop a vaccine. The contribution of molecular epidemiology and host-pathogen genomics to the understanding of diseases caused by C. trachomatis was explored in depth by the ICTI Consortium, which

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was first introduced in the Netherlands in December 2004 at the First Annual Amsterdam Chlamydia Meeting (AACM) and was the subject of a special Drugs of Today supplement published in 2006, entitled "An integrated approach to the understanding of Chlamydia infections". The ICTI Consortium formed the basis for a larger, European Union-funded international effort involving 20 centers, the EpiGenChlamydia Consortium. Major themes, including epidemiology, genetics and immunogenetics, biology and immunology, involving the chlamydiae species infecting humans, such as C. trachomatis, C. psittaci and C. pneumoniae, predominantly presented at the 4th and 5th AACM, are summarized in this second

Drugs of Today supplement, as well as timely mini-reviews of the advances made in the field.

INTRODUCTION

Chlamydia trachomatis infection is the most common bacterial sexually transmitted disease with 92 million new cases occurring worldwide each year. This infection is responsible for both the world's leading cause of blindness (trachoma) and its most prevalent sexually transmitted disease. In women it is associated with pelvic inflammatory disease (PID), ectopic pregnancy and tubal infertility. Complication rates can be as high as up to 20% after a single infection and in the case of PID up to 40% after multiple *C. trachomatis* infections.

THE 2009 UPDATE

An integrated, multidisciplinary effort is needed to achieve a greater understanding of the immunopathogenesis of *C. trachomatis* to combat this infection successfully, to prevent long-term complications and to develop a vaccine.

The contribution of molecular epidemiology and host-pathogen genomics to the understanding of diseases caused by *C. trachomatis* is the basis of the ICTI Consortium (Integrated approach to the study of *Chlamydia Trachomatis* Infection), which was first introduced in the Netherlands in December 2004 at the First Annual Amsterdam Chlamydia Meeting (AACM). The first international symposium inspired the publication of a special *Drugs of Today* supplement in 2006 (vol. 42, Suppl. A).

Later, the original, predominantly Dutch ICTI Consortium formed the basis of a wider international consortium of 20 institutes, the EpiGenChlamydia Consortium (www.EpiGenChlamydia.eu). This was possible due to funding obtained through the European Union Sixth Framework Programme for coordinated actions in functional genomics research, which was provided for a 30-month period (July 1, 2007 to December 31, 2009).

The first two articles in this supplement describe in detail this progress and the current status of the two consortia. A concise description of the achievements, goals, future directions and perspectives of the EpiGenChlamydia Consortium can also be consulted online on page 41 of the September 2009 issue of *The Parliament Magazine* (<http://www.e-pages.dk/dods/148/>).

This *Drugs of Today* supplement, which is to be presented at the final meeting of the EpiGenChlamydia Consortium in Amsterdam on November 15 and 16, 2009 and the Sixth Annual Amsterdam *Chlamydia* meeting on November 17, 2009, covers five major themes, namely epidemiology, genetics and immunogenetics, biology and immunology, the other chlamydiae species *Chlamydia psittaci* and *Chlamydia pneumoniae* infections in humans, and finally, bioinformatics and biomarkers.

This series of articles, including mini-reviews and manuscripts with original new data, provide a comprehensive overview of *C. trachomatis* infection in the clinical setting, in basic research, and in animal models of investigations that are ongoing in Europe, Finland, Russia, Africa and the United States.

Epidemiology

In the field of epidemiology, the importance of performing studies in developing countries is emphasized. Observations on *C. trachomatis* serovar distributions in Russia are presented and compared with those in the Netherlands. Clinical recommendations on the recent epidemics of lymphogranuloma venereum are also reviewed. This systemic sexually transmitted infection caused by the L serovars of *C. trachomatis* affects mainly HIV-positive men who have sex with men (MSM). On the most part, it is still unknown to specialists outside the field of genitourinary medicine. Proctitis is often the presenting symptom, and it can also be a cause of lower limb oligoarthritis and occasionally spondyloarthritis.

Genetics and immunogenetics

Trachoma, produced by *C. trachomatis*, is a priority health issue in many African countries. It causes unnecessary blindness and disability. The combined global efforts to eliminate trachoma will benefit from ongoing studies, such as those in the field of genetics and immunogenetics. The first study on heritability in twin-pairs from trachoma-endemic areas in the Gambia is reported. This key study found that host genetic factors contribute to 39% of the variation in lymphoproliferative responses to *C. trachomatis* (whole chlamydial elementary bodies) antigen, paving the way for studies to identify the genes responsible for this genetic predisposition.

A series of articles in experimental animals and humans using candidate gene approaches provides further evidence of a genetic predisposition. Different Toll-like

receptors (TLRs) and preliminary studies on genes involved in molecules important in the inflammasome pathway appear to play some role in the long-term complications of these infections. It is hoped that these studies will contribute to a better understanding of these genetic influences and also to the elucidation of preventive therapies for ocular and genital *C. trachomatis* infection by helping to identify protective mechanisms for rational vaccine constructions.

Earlier work with animal models had raised concerns about the adequacy of existing models. The challenge for the future, as described in this supplement, is to understand the importance of incorporating the preclinical assessments into the models in order to mimic the features of initial distribution and postinfection spread that take place in both previously uninfected as well as in currently infected women.

Biology and immunology

Advances in the biology and immunology of *C. trachomatis* continue to demonstrate its remarkable capacity to evolve by avoiding the innate and acquired immune response of the host. Over time, it has developed an effective host–parasite relationship that explains the common asymptomatic chlamydial infection. The ocular disease arises when hygiene conditions are poor, and when defects in the immune response exist long-term complications may occur. Recent concepts and observations open new paths of research involving the inflammasome, apoptosis and autophagic pathways. It is possible that knowledge of these pathways will help us understand the delicate survival mechanisms of *C. tra-*

chomatis in order to develop new strategies for treatment and prevention.

***C. psittaci* and *C. pneumoniae* infections in humans**

The economic and zoonotic consequences of *C. psittaci* infections have drawn new interest since there is evidence of zoonotic transmission from turkeys to humans, and several articles in this supplement describe recent data. *C. pneumoniae* infections in humans are also addressed. Current knowledge is reviewed and perspectives on how these bacteria may produce severe systemic diseases are considered, despite a lack of sufficient evidence showing that either the presence or the absence of *C. pneumoniae* antibody clearly identifies adults at increased risk of coronary events. Recent novel but scarce observations suggest that *C. pneumoniae* infection, through interaction with other environmental and genetic risk factors, may be associated with atherosclerosis and Alzheimer's disease.

Bioinformatics and biomarkers

Finally, the importance of bioinformatics and biomarkers is reviewed with the aim of opening up new and modern avenues of investigating these pathogens. The EpiGenChlamydia Consortium has been successful in making available a number of specific *Chlamydia* databases. The information they contain provides opportunities for understanding and identifying key processes and phenomena associated with the unique infection cycle of chlamydia. Bioinformatics may provide the tools necessary for a true breakthrough in the fight against chlamydial diseases: the development of a vaccine.