Journal of Cystic Fibrosis 14 (2015) 293 – 304

www.elsevier.com/locate/jcf

Review

Emerging bacterial pathogens and changing concepts of bacterial pathogenesis in cystic fibrosis

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Received 3 December 2014; revised 21 March 2015; accepted 22 March 2015
Available online 14 April 2015

Abstract

Chronic suppurative lower airway infection is a hallmark feature of cystic fibrosis (CF). Decades of experience in clinical microbiology have enabled the development of improved technologies and approaches for the cultivation and identification of microorganisms from sputum. It is increasingly apparent that the microbial constituents of the lower airways in CF exist in a dynamic state. Indeed, while changes in prevalence of various pathogens occur through ageing, differences exist in successive cohorts of patients and between clinics, regions and countries. Classical pathogens such as *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex and *Staphylococcus aureus* are increasingly being supplemented with new and emerging organisms rarely observed in other areas of medicine. Moreover, it is now recognized that common oropharyngeal organisms, previously presumed to be benign colonizers may contribute to disease progression. As infection remains the leading cause of morbidity and mortality in CF, an understanding of the epidemiology, risk factors for acquisition and natural history of infection including interactions between colonizing bacteria is required. Unified approaches to the study and determination of pathogen status are similarly needed. Furthermore, experienced and evidence-based treatment data is necessary to optimize outcomes for individuals with CF.

Keywords: *Stenotrophomonas maltophilia*; *Achromobacter xylosoxidans*; Methicillin resistant *Staphylococcus aureus* (MRSA); *Mycobacterium abscessus*; *Mycobacterium avium complex*; Microbiome

Contents

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http://dx.doi.org/10.1016/j.jcf.2015.03.012
1569-1993

1. Introduction

Cystic fibrosis exists as a changing disease. In the last four decades, median predicted survival has risen four-fold, with individuals born today expected to survive well into their fifth decade of life. In parallel to the changing epidemiology of patients, recent reports have highlighted the changes that are occurring within the spectrum of organisms causing infection in CF [1,2] (Fig. 1). While the driver of these changes is unknown, mechanisms postulated include: improved cultivation and identification, the selective pressure of antimicrobials, infection transmission and infection control practices, increasing prevalence of individuals with milder disease, and the survivor effect [1,3,4]. As respiratory disease continues to be the hallmark feature of CF and is primarily responsible for the attributable morbidity and mortality, understanding the spectrum and role of organisms involved in CF airways disease is of paramount importance.

Herein, we describe both the epidemiology and pathogenesis of those bacterial pathogens that have been considered emerging pathogens in CF for some time and/or whose clinical impact is increasingly apparent as well as those organisms/constellation of organisms that have only been recently described. We also propose a framework that may enable a better understanding of microbial pathogenesis of those organisms whose role in CF lung disease remains undefined.

2. Identification of microbial agents in CF

Historically organism identification in CF has been based on semi-selective cultivation designed to enrich selection for aerobic Gram-negative organisms and Staphylococci. Initially, many uncommon Gram-negatives were misidentified as *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex (*Bcc*), or merely reported as unidentified Gram-negatives. With the routine incorporation of technologies such as broad range 16S rRNA

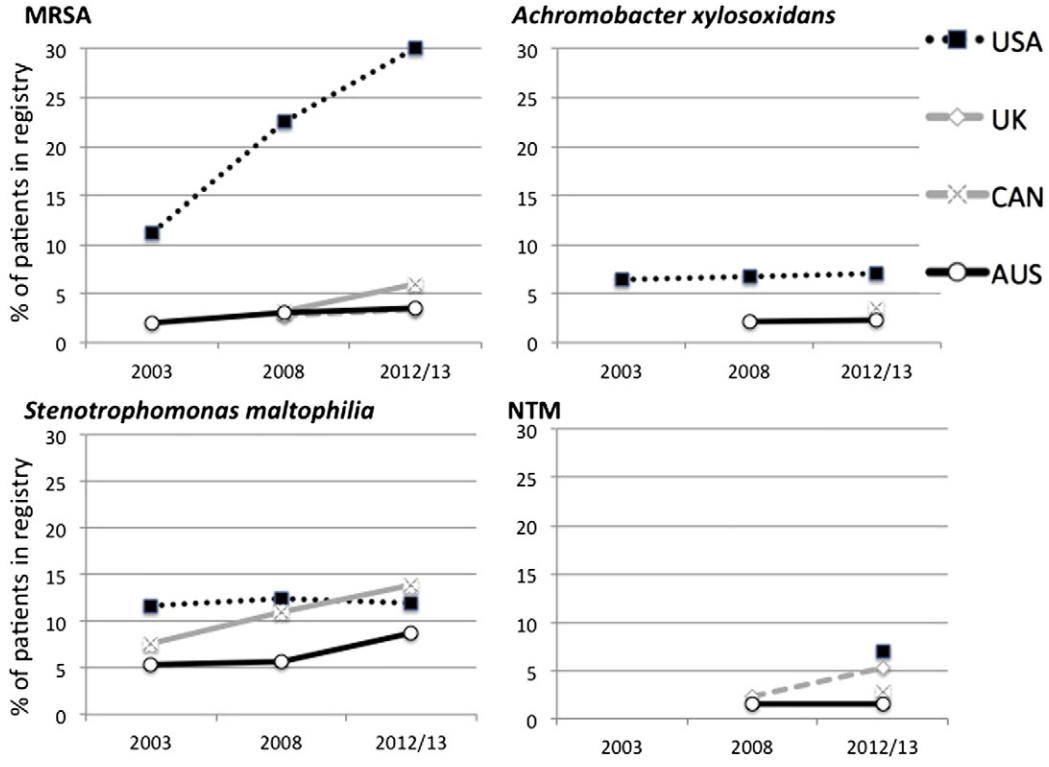

Fig. 1. Prevalence data of key emerging pathogens as a function of reporting country. These data demonstrate variably increasing prevalence of key emerging organisms over time, although, this is often country dependent. Inclusion and reporting criteria vary depending on registry (hence some data point not included), and generally represent at least one culture per calendar year and do not distinguish chronic infection from transient. Data adapted where available from 2003, 2008 and 2012 Australian Cystic Fibrosis Patient Registry, Canadian Cystic Fibrosis Patient Data Registry Report, UK Cystic Fibrosis Trust Annual Data Report and Cystic Fibrosis Foundation Patient Registry Annual Data Report and [122].