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Protracted bacterial bronchitis is a precursor for bronchiectasis in children myth or maxim?

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Editorial

Protracted bacterial bronchitis is a precursor for bronchiectasis in children: myth or maxim?

Introduction

"… from present knowledge, it seems justifiable to state that with better social conditions and prophylactic care much irreversible bronchiectasis can be prevented while with judicious treatment and skilled surgery many can be cured. Even with simple treatment the progress of most cases can be arrested, some showing considerable improvement and a few being clinically cured …."

Elaine Field in 1949 [1]

Although protracted bacterial bronchitis (PBB) was only first recognised as a clinical diagnostic entity in 2006 [2], astute clinicians described PBB-like conditions decades ago and postulated they were part of a pre-bronchiectatic state [1, 3]. The link between PBB and bronchiectasis was formally proposed a decade ago [4], and this paradigm is now increasingly accepted [5, 6]. Is this link (or spectrum) a myth or maxim?

Data from days gone by

While publications from days gone by did not refer to PBB as such, the condition clearly existed. Historically, astute clinicians described PBB-like conditions but did not define it as a clinical entity. Field's 1940s series on paediatric bronchiectasis described the concept of a pre-bronchiectasis state [1, 3] and advocated aggressive treatment (predominantly antibiotics) for prevention and cure of bronchiectasis. In the same era, Finke [7] opened his paper with the statement "The common background of chronic bronchitis and bronchiectasis is, in the majority of cases, non-tuberculous broncho-pulmonary infection". In that era, tools that are now widely available (e.g. flexible bronchoscopy and bronchoalveolar lavage (BAL) assessments) were non-existent. Almost 40 years ago, Taussig et al. [8] highlighted the various definitions of "childhood chronic bronchitis" doctors used, ranging from "productive cough for 3-months in a year" to "recurrent episodes of cough lasting for >2-weeks" and wheezing.

Further to the clinical associations described above, the BAL characteristics of PBB were also described with the advent of bronchoscopy prior to PBB being defined. Boogaard et al. [9] described chronic bacterial bronchitis in children with tracheobronchomalacia. Fayon et al. [10] found that ~13% of children undergoing bronchoscopy for "severe chronic asthma" had lower airway infection (defined as $>10^4$ cfu·mL^{-1} BAL with activated neutrophils). These features (infection and airway neutrophilia) are also PBB BAL features [11]. In the context that PBB is still often misdiagnosed as asthma [12], and that parents of children with PBB have often described wheezing illness [11, 13], some of the children in the study by Fayon et al. [10] probably had PBB and/or bronchiectasis.

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Recognising the link between protracted bacterial bronchitis and bronchiectasis creates an opportunity to understand the pathobiology of early suppurative endobronchial lung disease and prospects for the development of effective and early interventions http://bit.ly/2K3ikI6

What is PBB and is it real?

The original three criteria for PBB arose from clinical observations and now each criterion has been validated [11]. These criteria are: 1) the presence of chronic wet/productive cough; 2) bacterial infection in the BAL; and 3) cough resolved following 2 weeks of antibiotics [2]. Although not without initial controversy, PBB is now incorporated into many paediatric chronic cough guidelines [11, 14]. PBB is also accepted by the American College of Chest Physicians [14] and the European Respiratory Society (ERS) as a clinical entity through its incorporation into the ERS paediatric curriculum in 2012 and a task force document [15].

Subsequent to our original description [2], others (in the USA, China and Europe) [11] also described PBB. Currently, PBB is subclassified (PBB-clinical, PBB-micro, PBB-extended) [11] as it is not feasible to obtain lower airway cultures from every child with a chronic wet cough (>4 weeks duration), and the recognition that 4 weeks of antibiotics is required to resolve their cough in a minority of patients [14].

Biological plausibility

The pathognomonic chest computed tomography feature of bronchiectasis is abnormal dilatation of the airways, expressed as an increased broncho-arterial ratio (BAR) of >0.8 in children [5]. BAR increases with increasing severity of bronchiectasis [5]. That is, from a normal mean BAR of 0.5–0.6 in children [16], the gradual increase (other than for congenital forms of bronchiectasis, *e.g.* Mounier–Kuhn syndrome) occurs when the airway insults (usually infection and inflammation) are uncurtailed. Recurrent and/or persistent infection are part of the "vicious cycle" of airway
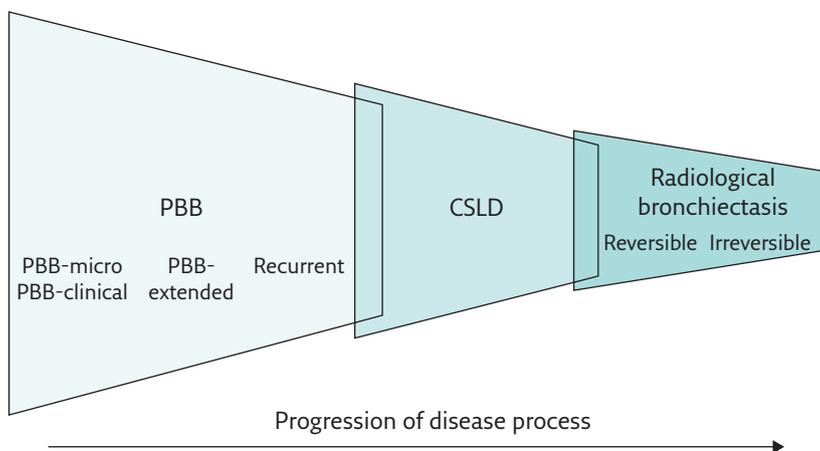

Figure 1 *Using the pathobiological model, PBB, chronic suppurative lung disease (CSLD) and radiographically confirmed bronchiectasis probably represent different ends of a spectrum with similar underlying mechanisms of airway neutrophilia, endobronchial bacterial infection and impaired mucociliary clearance. Untreated it is likely some (but not all) children with PBB will progress to develop CSLD and some will ultimately develop bronchiectasis, initially reversible and subsequently irreversible if left to progress. There is a degree of overlap between each of the entities. Reproduced from [11] with permission from the publisher.*

injury associated with bronchiectasis [5]. At some point during this process, lung injury is so advanced that the tissue changes become irreparable (irreversible bronchiectasis).

That PBB represents the early spectrum of chronic endobronchial suppurative disease, and irreversible bronchiectasis the opposite late end, is logical and biologically plausible (figure 1). Mild radiological bronchiectasis in children is reversible if treated early, thereby avoiding the later progressive decline in lung function [6]. Adults with bronchiectasis symptoms from childhood have worse disease and poorer prognosis (compared with adult-onset patients) [17]. Once bronchiectasis is severe (*e.g.* adults with established bronchiectasis), the pathobiology (*e.g.* airway microbiota [18]) is different. The following sections further illustrate this maxim with PBB and early bronchiectasis having shared clinical, bacterial, inflammatory and pathobiological features, that later diverge with increasing bronchiectasis severity.

Data linking PBB to bronchiectasis

Clinical

PBB and mild/early cylindrical bronchiectasis share clinical features and are indeed indistinguishable at first visit when bronchiectasis is not related to an underlying illness (*e.g.* immunodeficiency, primary ciliary dyskinesia). These common features are chronic wet/productive cough, reports of wheeze/rattles and the child appears otherwise well without digital clubbing [11, 13]. Chest radiographs generally show only perihilar changes [19], and spirometry is normal [11, 19, 20], as are respiratory system reactance and resistance measured by the forced oscillatory technique (unpublished data from the authors' research group). Also, both groups have impaired cough-specific and generic quality of life scores, which improve significantly with cough resolution [11, 20].

The chronic cough in most children with PBB resolves when treated with 2 weeks of an appropriate antibiotic (usually amoxicillin-clavulanic acid) targeting the common respiratory pathogens [11]. Some require a 4-week course [14]. When the child's chronic wet/productive cough does not resolve following 4 weeks of antibiotics, the adjusted odds ratio of having bronchiectasis (compared with children whose wet cough resolves) is 20.9 (95% CI 5.4–81.8). Recurrent PBB is a risk factor for future bronchiectasis (adjusted OR 11.5, 95% CI 2.3–56.5) [21]. Between PBB and bronchiectasis, lies the entity of chronic suppurative endobronchial lung disease (defined as the presence of symptoms and signs of bronchiectasis with the absence of radiographic evidence of bronchiectasis) [22], where intravenous antibiotics are required to resolve the child's chronic wet/productive cough. With advanced bronchiectasis

severity, additional features (*e.g.* digital clubbing, abnormal spirometry) may then appear [6].

Microbiology

In addition to clinical features, the lower airway microbiology of PBB and mild bronchiectasis are also similar [6, 11]. In both, *Streptococcus pneumoniae*, *Haemophilus influenzae* (mostly non-typable, NTHi) and *Moraxella catarrhalis* were the main bacteria detected in BAL specimens [6, 11]. Further, the lower airway core and satellite microbiota of children with PBB and bronchiectasis are similar based on bacterial 16S rRNA gene pyrosequencing and phylogenetic analysis [18]. This contrasts with adult data (with more severe disease) where the pulmonary microbiome is divergent from children with the same disease [18]. Also, with increasing severity of bronchiectasis, *Pseudomonas aeruginosa* infection becomes more common. Further, prospective studies found adenovirus was commonly co-detected with *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* in BAL samples from young children with PBB or bronchiectasis [23]. Upon genotyping, adenovirus in both conditions belonged predominantly to species C [23].

Pathobiology

Tracheobronchomalacia commonly coexists with PBB and bronchiectasis [11, 13, 24], but as data is limited to cross-sectional cohort studies, cause and effect is unknown.

The lower airway profile of PBB and bronchiectasis [5] is characterised by intense neutrophilic inflammation with marked pro-inflammatory mediator responses (*e.g.* interleukin (IL)-8, matrix metalloproteinase-9 and IL-1β) [25, 26]. Experimental and validation cohorts of children with PBB have significantly higher levels of gene and protein expression of IL-1β, α-defensin, IL-1 pathway members and CXCR2 than non-PBB disease controls [26]. The gene expression of the IL-1β signalling molecules pellino-1 and IL-1 receptor associated kinase 2 were significantly higher in those with recurrent (>3 episodes per year) PBB (*versus* those without) [26], of whom 85% eventually had bronchiectasis within 2 years [21]. Like clinical and microbial data, this also suggests a dose–response phenomena with PBB at one end and bronchiectasis at the other.

Further, concurrent experiments found that the pathobiological responses of lower airway specimens from children with PBB and bronchiectasis share similarities and significantly differ to controls. Impaired apoptosis and efferocytosis to NTHi [27] and gene expression levels of NTHi-stimulated BAL airway cells [28] from children with PBB were in between the values of controls and those with bronchiectasis.

The limitations: it looks the same but is it the same?

Although PBB shares many similarities with early bronchiectasis, cause and effect is unproven. Also, given the availability of computed tomography scans, there is currently only one prospective study, no animal models and human experimental evidence would be unethical to most. There is little doubt that the host response plays a critical role [6], but data from ~70 years ago [1, 7], supported by more recent data [6], dispels the opinion that bronchiectasis eventually develops in those predestined to do so and that PBB is unrelated. Nevertheless, there is little doubt that more in-depth studies and long-term cohort studies are needed. Clinically, some children with PBB also eventually have an asthma phenotype (recognised decades ago as wheezy bronchitis) and whether they then develop a chronic obstructive pulmonary disease (COPD)-like phenomenon remains speculative. Indeed, adults with COPD also share some similarities (*e.g.* NTHi infection, dysfunctional efferocytosis, and neutrophilic inflammation).

Summary

PBB is linked with, and highly likely a forerunner of, bronchiectasis. Untreated chronic wet cough (PBB) with ongoing bacterial infection and associated neutrophilic inflammation would lead to eventual airway damage (bronchiectasis). However, absolute proof is lacking and indeed is highly likely never to be proven. Nevertheless, the biological plausibility is convincing, supported by clinical, lower airway microbiology and pathobiological aspects. Recognising the link between PBB and bronchiectasis creates an opportunity for understanding the pathobiology of early suppurative endobronchial lung disease and consequently increases the prospects of developing effective and early interventions. Unless future data disproves the paradigm linking PBB with bronchiectasis [6], this link is a maxim.

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Conflict of interest

Support statement:

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