MANAGEMENT OF PATIENTS WITH BRONCHIECTASIS

Almonzer Mhanna MD

Bronchiectasis is a chronic and often progressive disease of the bronchi and bronchioles in which persistent inflammation and/or infection leads to permanent airway dilation and a characteristic chronic, productive cough.

N Engl J Med 2002; 346: 1383–1393.

Bronchiectasis is clinically distinguished between cystic fibrosis (CF) and non-cystic fibrosis bronchiectasis (NCFB), due to inherent differences in pathophysiology and treatment approach, and is typically characterised separately in clinical trials

there are no US-specific guidelines for managing BE (the exception is BE related to CF), But There are many guidelines for the management of BE in other countries and regions, including in the UK ,Australia/New Zealand and Europe. Unfortunately, many of them are based on low-quality or limited evidence

BTS guideline

British Thoracic Society Guideline for bronchiectasis in adults FREE

Adam T Hill [1], Anita L Sullivan [2], James D Chalmers [3], Anthony De Soyza [4], J Stuart Elborn [5], R Andres Floto [6, 7], Lizzie Grillo [8], Kevin Gruffydd-Jones [9], Alex Harvey [10], Charles S Haworth [7], Edwin Hiscocks [11], John R Hurst [12], Christopher Johnson [7], W Peter Kelleher [13, 14, 15], Pallavi Bedi [16], Karen Payne [17], Hashem Saleh [8], Nicholas J Screaton [18], Maeve Smith [19], Michael Tunney [20], Deborah Whitters [21], Robert Wilson [14], Michael R Loebinger [14]

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European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino, Pieter C. Goeminne, Melissa J. McDonnell, Stefano Aliberti, Sara E. Marshall, Michael R. Loebinger, Marlene Murris, Rafael Cantón, Antoni Torres, Katerina Dimakou, Anthony De Soyza, Adam T. Hill, Charles S. Haworth, Montserrat Vendrell, Felix C. Ringshausen, Dragan Subotic, Robert Wilson, Jordi Vilaró, Bjorn Stallberg, Tobias Welte, Gernot Rohde, Francesco Blasi, Stuart Elborn, Marta Almagro, Alan Timothy, Thomas Ruddy, Thomy Tonia, David Rigau, James D. Chalmers

European Respiratory Journal 2017 50: 1700629; **DOI:** 10.1183/13993003.00629-2017

Thoracic Society of Australia and New Zealand (TSANZ) position statement on chronic suppurative lung disease and bronchiectasis in children, adolescents and adults in Australia and New Zealand

Anne B. Chang, Scott C. Bell, Catherine A. Byrnes, Paul Dawkins, Anne E. Holland, Emma Kennedy, Paul T. King, Pamela Laird, Sarah Mooney, Lucy Morgan, Marianne Parsons, Betty Poot, Maree Toombs, Paul J. Torzillo, Keith Grimwood

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Heterogeneity in bronchiectasis is reflected with different aetiologies, different clinical symptoms, different severities of disease, and diverse clinical courses, inflammatory profiles and microbial communities

Given the heterogeneity of bronchiectasis, the bronchiectasis paradigm has shifted in recent years towards a “treatable trait” approach, so Treatment of bronchiectasis, broadly speaking, takes on three main categories: the improvement of mucociliary clearance, preventing and treating infection, and reducing associated inflammation ,also keep in mind that evaluation of the Comorbidities ((such as cardiovascular disorders, GERD, psychological illnesses, pulmonary hypertension, COPD, Asthma)) and treat them as part of bronchiectasis treatment is paramount, In order to reach the main goals that include reducing symptoms, improving HRQoL, preventing PEx and hospital admissions, preserving lung function, and, ultimately, prolonging life.

Identifying and treating the underlying cause

The first step in bronchiectasis management is to identify an aetiology that may be treatable or influence management.

>>>Of the broad spectrum of causes of noncystic fibrosis bronchiectasis, only a few respond to direct treatment (eg, Certain immunodeficiencies, NTM infection, ABPA, Alpha 1 AT , Autoimmune inflammatory conditions such as RA or IBD, Aspiration).

>>>>All CF patients should undergo CFTR genotyping to determine if they carry a mutation that makes them eligible for CFTR modulator therapy

Airway clearance :

international guidelines recommend all patients with bronchiectasis receive instruction in airway clearance techniques taught by respiratory physiotherapists .

ERS and BTS suggest long-term (≥3 months) mucoactive treatment (e.g. nebulized hypertonic saline ,NS, manitol) in adult patients with BE if standard airway clearance techniques alone fail to control symptoms .

ERS :There is insufficient evidence to permit evaluation of the use of oral mucolytics such as carbocisteine for bronchiectasis

BTS: If carbocysteine is prescribed, a 6 month trial should be given and continued if there is ongoing clinical benefit.

Both Agreed on not to offer recombinant human DNase to adult patients with bronchiectasis (strong recommendation, moderate quality evidence)

Infection control

Infection is a key component of the pathophysiology and such a crucial treatable trait ,also , Frequent exacerbations are associated with increased hospitalizations, reduced quality of life, and increased mortality ,

One difficult issue is chronic infection with Pseudomonas aeruginosa, which has a propensity to persist in damaged airways

Long-term treatment with inhaled antibiotic ((eg, tobramycin, gentamicin , aztreonam, colistin))for adults with bronchiectasis

and chronic P aeruginosa infection or not infected with P aeruginosa in whom oral antibiotic prophylaxis is contraindicated, not tolerated, or ineffective

Long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis

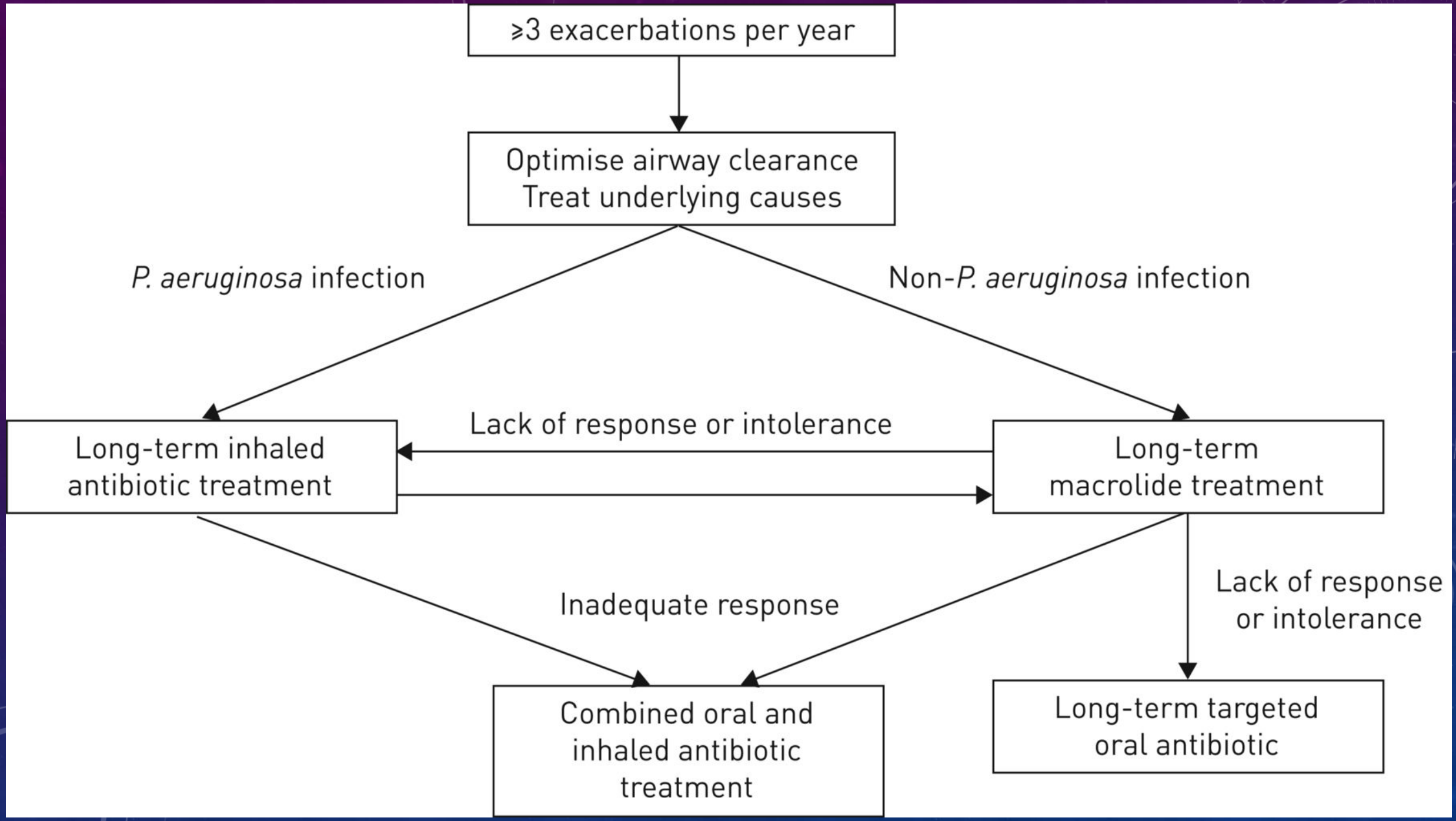
>>> and chronic P aeruginosa infection in whom inhaled antibiotic is contraindicated, not tolerated, or not feasible

>>> in addition to, or in place of, inhaled antibiotic for adults with bronchiectasis and chronic P aeruginosa infection who have a high exacerbation frequency despite taking inhaled antibiotic

>>> not infected with P aeruginosa

Long-term treatment with oral antibiotic (selection based on antibiotic susceptibility and patient tolerance) for adults with bronchiectasis not infected with P aeruginosa in whom macrolides are contraindicated, not tolerated, or ineffective

If patients continue to have frequent exacerbations despite these interventions, a combination of nebulised and oral antibiotics can be helpful; and if this fails, cyclical intravenous antibiotics can be initiated on a case-by-case basis.


≥3 exacerbations per year
Optimise airway clearance
Treat underlying causes
P. aeruginosa infection
Non-P. aeruginosa infection
Long-term inhaled antibiotic treatment
Lack of response or intolerance
Long-term macrolide treatment
Inadequate response
Lack of response or intolerance
Combined oral and inhaled antibiotic treatment
Long-term targeted oral antibiotic

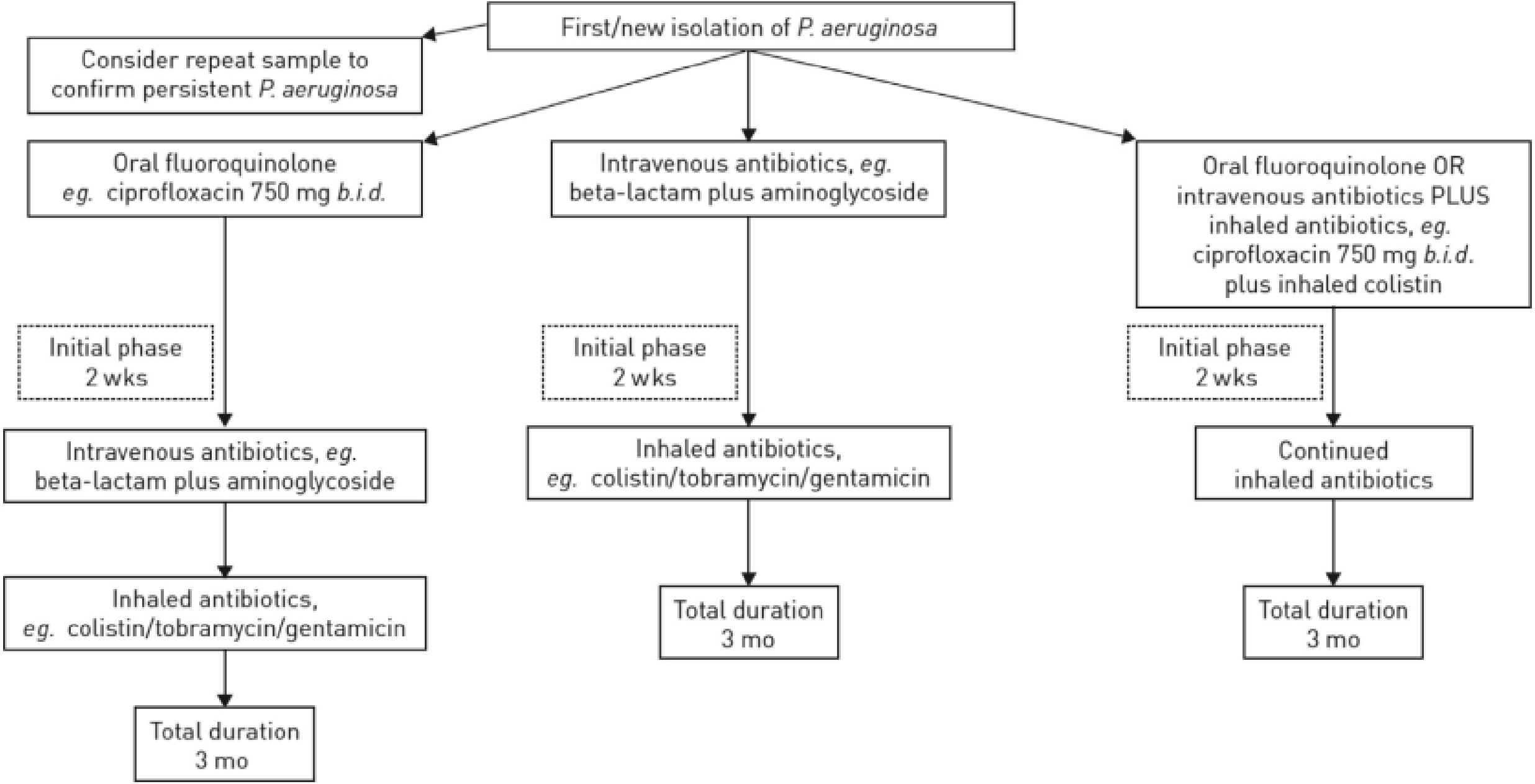
Eradication of new isolates of Pseudomonas (First growth of P aeruginosa)

The E R S guidelines recommend that adults with bronchiectasis and a new growth of P aeruginosa should be offered eradication treatment (offers 3 different antibiotic regimens), but not following new growth of other organisms.

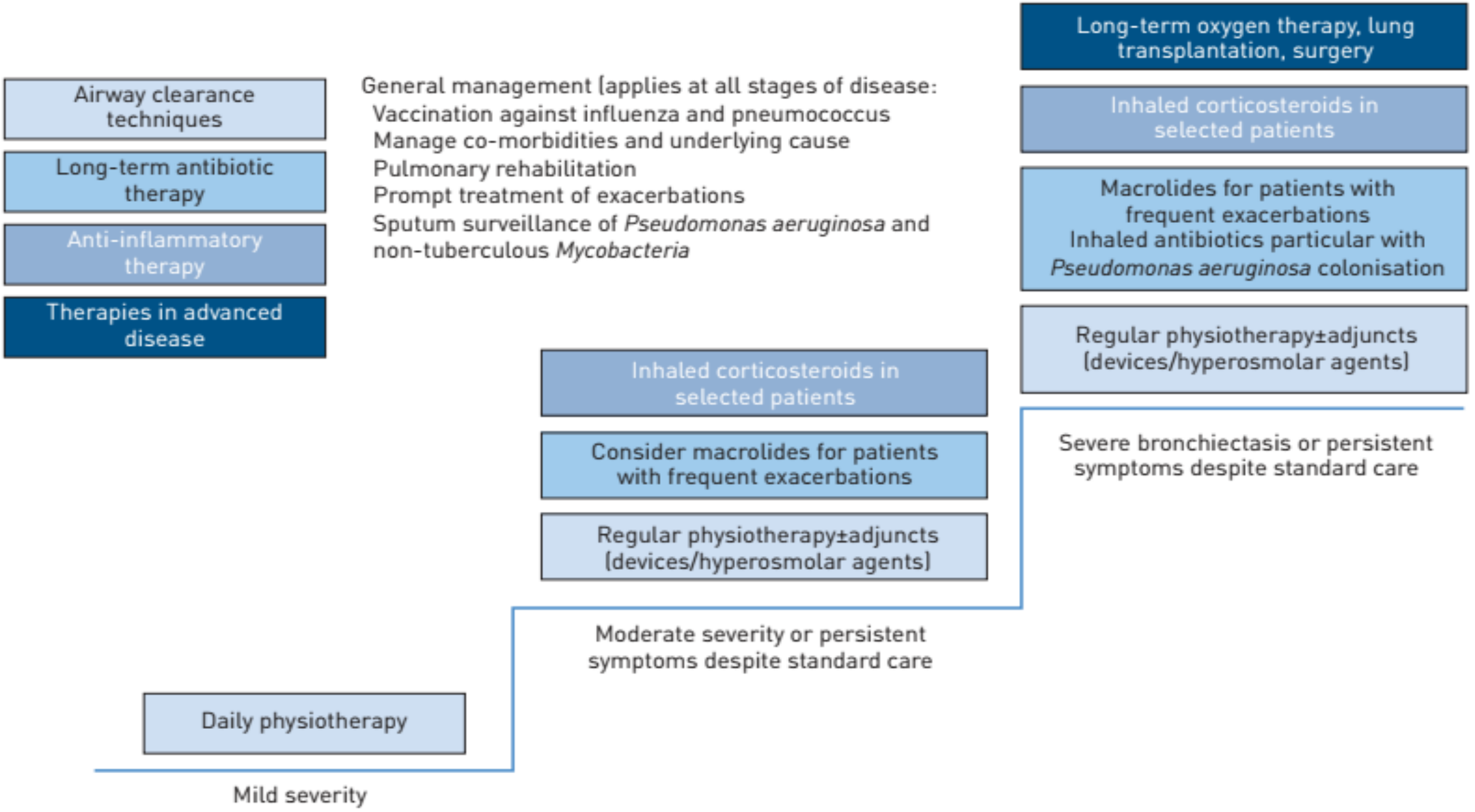
This is in contrast to the B T S guidelines that also recommend eradication treatment following a new growth of methicillin-resistant S aureus..

using high-dose oral ciprofloxacin for 14 days. A repeat sputum sample should then be sent. If P aeruginosa isolation persists, a combination of intravenous and nebulised antipseudomonal antibiotics can be considered.

Eradication of chronic P. aeruginosa infection (present for years) is unlikely to be successful



Eur Respir J. 2017 Sep 9;50(3):1700629.)



The stepwise management of non-CF bronchiectasis.

Medical therapies to manage CF -lung disease

All patients with CF should undergo CFTR ((CF transmembrane conductance regulator)) genotyping to determine if they carry one of the mutations approved for CFTR modulator therapy

Inhaled airway clearance agents :
All patients should have an airway clearance regimen with the following:
For patients ≥12 years who are on elexacaftor-tezacaftor-ivacaftor (ETI) and who have normal or mildly reduced lung function, we suggest not using inhaled airway clearance therapies (nebulized dornase alfa [DNase] and hypertonic saline) (Grade 2B)
For most other patients, we recommend chronic use of nebulized dornase alfa (DNase) (Grade 1B) and suggest hypertonic saline (Grade 2B)

initiating chronic azithromycin therapy at the time of the first positive culture for Pseudomonas aeruginosa in patients as young as ≥6 months old (Grade 2C) and in the case of frequent pulmonary exacerbations

Based on a shift in understanding of bronchiectasis from a problem of impaired mucociliary clearance leading to bacterial infection, towards conceptualising the disease as an inflammatory airway condition , patients grouped by predominant biological mechanism or “endotype” ,and New therapies targeting inflammatory pathways have shown promising initial results

Since neutrophils are the predominant inflammatory cells present in the BE airways, it is appropriate to target them or their products. Yet, the observation of the presence of eosinophils in the airways of approximately 20% of BE patients may lead to the identification of a subset of patients who might benefit from corticosteroids and other biologic treatments

Previous attempts to develop therapies targeting neutrophils have focused on reducing neutrophil numbers, resulting in increased infections. New approaches that targeting metabolism could reverse neutrophil dysfunction (Immunometabolic reprogramming ie, blood neutrophils have been shown to display significantly delayed apoptosis, increased myeloperoxidase release, and impaired neutrophil phagocytosis and killing and increased neutrophil extracellular traps (NET) formation)

Many new experimental bronchiectasis therapies are under investigation

Brensocatib, an inhibitor of dipeptidyl peptidase 1 (DPP1) [dipeptidyl peptidase 1 (DPP1), an enzyme involved in the activation of neutrophil serine proteases so DPP1 inhibition prevents the activation of the neutrophil protease's elastase, cathepsin-G and proteinase-3 in the bone marrow without impairing other neutrophil functions], neutrophil elastase directly causes bronchiectasis inflammation and tissue damage.

The recently reported WILLOW trial showed a primary outcome that brensocatib significantly delayed time to exacerbation (134 days vs. 67 in placebo group), secondary outcomes showed reduced rates of exacerbations and significant drops in sputum neutrophil elastase levels. Brensocatib has now entered much larger, longer phase 3 trials (ASPEN)

Another approach to diminish neutrophilic inflammation is to directly cut the number of neutrophils entering tissues by preventing chemotaxis. CXCR2 is a chemokine receptor . Antagonism of CXCR2 has been shown to reduce lung neutrophil recruitment without impairing phagocytosis or oxidative burst.

AMPK(5' adenosine monophosphate-activated protein kinase) activation has already been shown to reverse phagocytic dysfunction and neutrophil extracellular trap formation in models of pulmonary disease. So can reverse metabolic reprogramming and are already in clinical use and/or development.

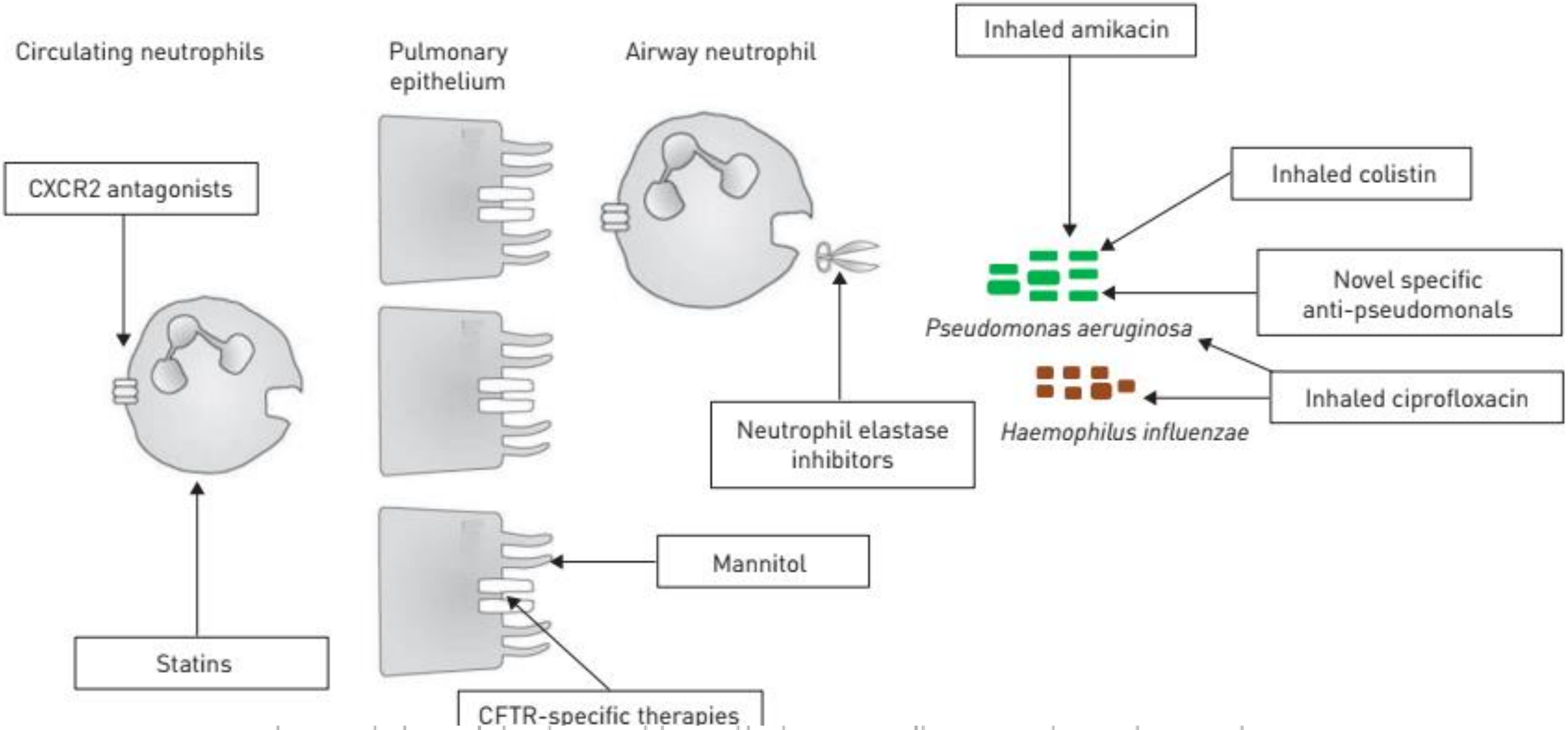
Another emerging endotype is primary ciliary dyskinesia (PCD)
Identification of genotypes causing PCD has allowed for the principle mechanisms of cilia dysfunction to be characterised. Given this, there has been increased attention on gene therapy, focusing on both replacing or modifying the mutated gene sequences.

Phage Therapy:
Phages (or bacteriophages) are viruses that are used specifically to target bacteria. Phage therapy involves using phages to treat bacterial infections. There is currently a US-based trial looking at the use of nebulised phage therapy in the CF with pseudomonas.

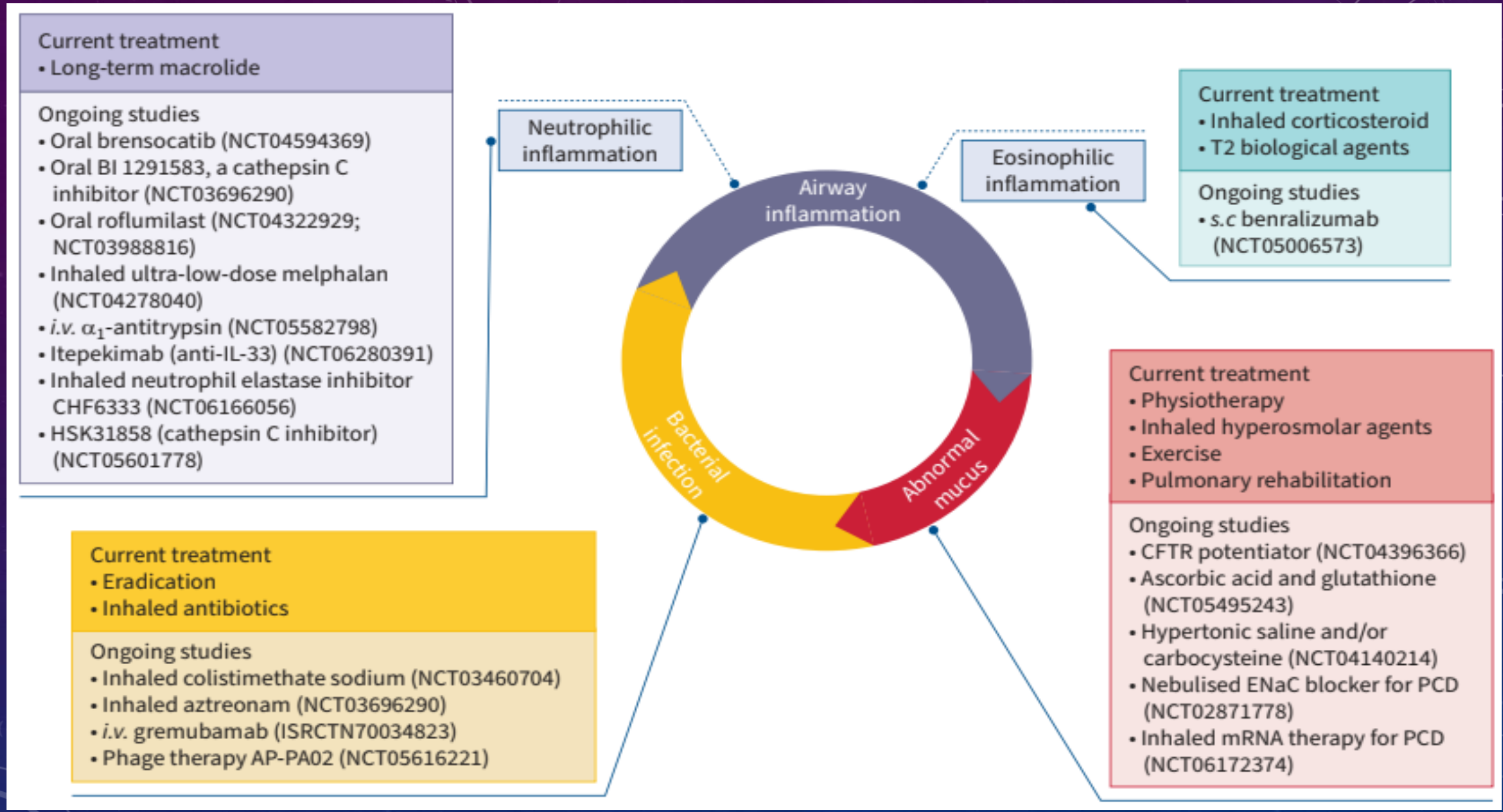
Novel antimicrobials :
Arikayce(a liposomal formulation of the antibiotic amikacin works against pseudomonas as well as NTM lung infections)
lefamullin: is a novel antibiotic aginst pseudo and staph aureus

Alternatives to antibiotics include inhaled immunoglobulin.

inhaled therapies, e.g. alpha-1 antitrypsin augmentation therapy



New therapies in development for bronchiectasis and their possible role. CFTR: cystic fibrosis transmembrane conductance regular.



Summary of management points and ongoing studies in bronchiectasis