Title

Clinical phenotypes in adult patients with bronchiectasis

MATERIALS AND METHODS

Process to define bronchiectasis etiology

Patients in every site underwent the same comprehensive diagnostic work-up as suggested by the 2010 British Thoracic Society (BTS) guidelines including: complete blood count, serum electrophoresis, serum immunoglobulin (Ig) G, IgA, IgM, total IgE, specific IgE and precipitins for *A. fumigatus*, and pulmonary function test with reversibility testing and diffusion capacity test [1]. In case of clinical suspicion of ciliary dyskinesia, such as recurrent sinusitis and/or chronic otitis media, nasal mucociliary clearance was measured by the saccharin test and nasal nitric oxide or referral to a specialist primary ciliary dyskinesia centre. Alpha$_1$-antitripsin was evaluated in the presence of emphysema affecting lower lobes on high-resolution computed tomography (HRCT) scan and/or significant family history. Autoimmunity testing including anti-nucleolar antibodies, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, rheumatoid factor and anti–citrullinated protein antibody, were requested if a rheumatological disease was clinically suspected. Sweat test and cystic fibrosis (CF) transmembrane conductance regulator genetic testing were requested if signs and symptoms suggestive for CF as suggested by BTS guidelines [1].

An evaluation of CT images and testing results was performed, including immunoglobulins, skin prick testing or serum IgE resting to *A. fumigatus* and *Aspergillus* precipitins, and serum electrophoresis, in order to differentiate patients into categories of congenital abnormalities of the bronchial tree, post-obstructive bronchiectasis, primary or secondary immunodeficiency, alpha$_1$-antitrypsin deficiency or allergic bronchopulmonary aspergillosis (ABPA). If all of the above tests

were negative, a history of prior severe respiratory infections was investigated, including previous infection with non-tuberculous mycobacteria. If no history of previous respiratory infections was present, an association between bronchiectasis and other diseases, such as COPD, asthma, inflammatory bowel disease (IBD), gastro-oesophageal reflux disease (GORD) or connective tissue disease (CTD) was investigated. If tests were negative and no association with other diseases was found, a diagnosis of idiopathic bronchiectasis was made.

ABPA was diagnosed in the presence of a serum IgE >1000 IU/ml and *Aspergillus fumigatus* precipitins >10 IU/ml or raised specific IgE to Aspergillus *plus* sputum and/or peripheral blood eosinophilia (>500/mm^3) and central bronchiectasis [2]. A diagnosis of post-infective bronchiectasis was made if the patient reported a history of symptoms due to bronchiectasis with an onset immediately after a severe respiratory infection, such as pneumonia or tuberculosis. Where a patient reported a history of severe respiratory infections, but with at least a five-years period free from respiratory symptoms since that infection, the post-infective diagnosis was not attributed. Bronchiectasis-COPD overlap syndrome was classified in the presence of significant smoking history and airflow obstruction according to GOLD [3]. Bronchiectasis associated with asthma was diagnosed in patients without post-infective bronchiectasis and with normal or negative results of blood investigations according to GINA guidelines [4]. Bronchiectasis associated with IBD was diagnosed if patients had ulcerative colitis or Crohn's disease and no other suggested etiology for bronchiectasis. In the presence of a diagnosis of both bronchiectasis and CTD, including rheumatoid arthritis, Sjögren syndrome and systemic sclerosis, a diagnosis of CTD-associated bronchiectasis was made. Yellow nail syndrome was diagnosed when examination showed yellow discoloration of dystrophic nails together with bronchiectasis and sinusitis, whether or not patients had other features of the syndrome.

Study outcome

Exacerbations. An exacerbation of bronchiectasis was defined as a clinical diagnosis of exacerbation for which antibiotics were prescribed in the presence of at least one (and usually more than one) of the following symptoms: increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnea, increased fatigue/malaise, fever, and haemoptysis [1]. Exacerbations were either documented by the treating physicians or self-reported by the patient during visits in the clinic or during hospitalization. Hospitalizations because of an exacerbation of bronchiectasis have been also double-checked on local electronic system.

Principal Component and cluster analysis

Among the variables reported in Table 1, Spearman correlation selected the following variables: age, Reiff score, daily cough, daily sputum, medical research council (MRC) breathlessness scale, long-term oxygen therapy (LTOT), number of exacerbations in the previous year, the presence of at least one hospitalization in the previous year, FEV_1, chronic infection, chronic infection with *P. aeruginosa*, chronic infection with other pathogens, more than one pathogen causing chronic infection, and Charlson comorbidity index >1, see Table S3. The PCA identified 14 components and 7 were selected because of an eigenvalue >0.70, see Table S4.

The most important variables, i.e. those with a factor loading >0.4, were selected for the cluster analysis as detailed in Table S5. These included: age, Reiff score, daily cough, daily sputum, MRC breathlessness scale, LTOT, exacerbations and hospitalization in the previous year, FEV_1, chronic infection with *P. aeruginosa* or other pathogens, and Charlson comorbidity index. Finally, four clusters were detected within the enrolled cohort (Gower dissimilarity value= 20), as depicted in Figure S1. Correlations among variables were assessed in every cluster (see Table S6).

Validation cohort

In order to validate the primary cluster analysis, we recruited an independent population of patients with HRCT confirmed bronchiectasis at Ninewells Hospital, Dundee, UK during 2014. We hypothesized that the clinical clusters identified in the primary study would show differences in neutrophil mediated inflammation. The validation study was conducted as a case control study, with a consecutive cohort of 30 patients recruited in each of the 4 identified phenotype arms (identified by their primary clustering characteristic). The objective of the validation study was to demonstrate differences in inflammatory markers between the groups to validate in biological terms, the differences between the groups. As the study needed to be powered on an individual marker we chose myeloperoxidase as a well-recognised marker of neutrophilic inflammation. Previously published literature showed a difference between patients colonised with *Pseudomonas* vs. those without (13.5 U/ml [4–38.6] vs. 2.6 [0.6–50.8]), $p < 0.0001$ [5]. We therefore used a difference of 10 units with a common standard deviation of 12. This gave the validation study 90% power (with alpha of 5%) with a sample size of 30. Spontaneous sputum samples were obtained and ultracentrifuged at 50,000G for 90mins to obtain supernatant for inflammatory marker measurement as previously described [10]. Clinical evaluation was conducted as described above.

RESULTS

Differences in outcomes between each clusters

Outcomes	Cluster 1 VS. Cluster 2	Cluster 1 VS. Cluster 3	Cluster 1 VS. Cluster 4	Cluster 2 VS. Cluster 3	Cluster 2 VS. Cluster 4	Cluster 3 VS. Cluster 4
Exacerbations during one-year follow-up	<0.0001	<0.0001	<0.0001	0.001	<0.0001	0.002
≥ 1 hospitalization during one-year follow-up	<0.0001	<0.0001	<0.0001	1.00	0.50	0.47
Mortality during one-year follow-up	0.03	0.40	0.92	0.10	0.02	0.40
Mortality during three-year follow-up	0.002	0.002	0.06	0.78	0.16	0.21

REFERENCES

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Table S1. Patients' characteristics of the five study cohorts

Variables		Dundee, UK	Leuven, Belgium	Monza, Italy	Galway, Ireland	Athens, Greece
Total	n.(%)	286 (100)	190 (100)	230 (100)	280 (100)	159 (100)
Demographics and comorbidities						
Age, years	median (IQR)	67 (59-73)	69 (58-79)	70 (60-74)	63 (55-71)	60 (50-73)
Male	n.(%)	119 (42)	93 (49)	93 (40)	92 (33)	58 (37)
Body Mass Index	median (IQR)	25.4 (21.8-28.6)	23.4 (21.0-26.6)	23.7 (20.6-26.4)	26.4 (23.2-30.3)	24.6 (22.7-26.9)
Smokers / Ex-smokers	n.(%)	55 (19)	93 (49)	109 (47)	122 (44)	58 (37)
Charlson Comorbidities Index>1	n.(%)	118 (41)	82 (43)	81 (35)	82 (29)	10 (6.3)
Severity of the disease						
BSI score	median (IQR)	6 (4-11)	7 (4-11)	6 (4-9)	5 (4-9)	9 (5-13)
Radiological Status						
Reiff score	median (IQR)	4 (2-6)	3 (2-6)	5 (4-6)	2 (2-4)	4 (3-6)
Clinical status						
Daily cough	n.(%)	286 (100)	151 (80)	124 (54)	192 (69)	146 (92)
Daily sputum	n.(%)	237 (83)	86 (45)	113 (49)	164 (59)	144 (91)
Prior history of haemoptysis	n.(%)	19 (6.6)	28 (15)	57 (25)	39 (14)	63 (40)
MRC breathlessness scale	median (IQR)	3 (1-4)	2 (1-3)	1 (1-3)	2 (1-3)	5 (5-5)
Long-term oxygen therapy	n.(%)	8 (2.8)	10 (5.3)	33 (14)	9 (3.2)	26 (16)
Exacerbations in the previous year	median (IQR)	2 (1-3)	1 (0-3)	1 (0-3)	3 (2-4)	2 (1-3)
At least one hospitalization	n.(%)	66 (23)	54 (28)	42 (18)	62 (22)	83 (53)

	in the previous year						

Functional Status						
FEV$_1$, % predicted	median (IQR)	72 (50-92)	70 (50-88)	82 (57-101)	79 (63-98)	74 (55-88)
Microbiology						
Chronic infection with *P. aeruginosa*	n.(%)	44 (15)	16 (8.4)	23 (10)	39 (14)	58 (36)
Chronic infection with other pathogens	n.(%)	128 (45)	19 (10)	24 (10)	78 (28)	26 (16)
Laboratory findings						
C-reactive protein, mg/L	median (IQR)	6.0 (4.0-8.0)	3.1 (1.0-8.0)	3.5 (1.5-9.7)	3.9 (1.5-7.0)	22.0 (12.0-46.0)
Long-term antibiotic treatment						
Long-term macrolide	n.(%)	98 (34)	81 (43)	12 (5.2)	126 (45)	41 (26)
Long-term inhaled antibiotic treatment	n.(%)	16 (5.6)	0 (0.0)	2 (0.9)	24 (8.6)	48 (30)

n: number; IQR: interquartile range 25-75; BSI: Bronchiectasis Severity Index; MRC: medical research council; LTOT: long-term oxygen therapy. SGRQ: St. George's Respiratory Questionnaire; FEV$_1$: forced expiratory volume in the first second; NA: not available

Table S2. Distribution of the four clusters among the five study centers.

Cluster		Dundee, UK	Leuven, Belgium	Monza, Italy	Galway, Ireland	Athens, Greece	p
Total	n.(%)	286 (100)	190 (100)	230 (100)	280 (100)	146 (100)	
"Pseudomonas"		44 (15)	16 (8)	23 (10)	39 (14)	57 (39)	<0.001
"Other chronic infection"		128 (45)	19 (10)	24 (10)	78 (28)	24 (16)	<0.001
"Daily sputum"		90 (32)	66 (35)	87 (38)	74 (26)	56 (38)	0.035
"Dry bronchiectasis"		24 (8)	89 (47)	96 (42)	89 (32)	9 (7)	<0.001

Table S3. Spearman correlation between the demographic, epidemiological, and clinical variables.

	Age	Sex	BMI	Smokers/ ex smokers	Reiff_score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV$_1$	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
Age	1																		
Sex	0.1019	1																	
Body mass index	0.0087	0.1182	1																
Smokers/ ex smokers	0.1428	0.2064	0.0009	1															
Reiff_score	0.1789	0.0787	-0.1806	-0.0011	1														
Daily cough	0.0064	0.0420	0.0037	-0.0666	0.0545	1													
Daily sputum	0.0671	0.0655	0.0555	-0.0460	0.1230	0.3820	1												
Prior history of haemoptysis	0.0443	-0.0042	-0.0228	0.0005	0.0876	-0.0157	0.0995	1											
MRC	0.1882	0.1001	0.0066	0.0851	0.2947	0.1651	0.2147	0.0332	1										
LTOT	0.0523	0.1127	-0.0416	0.1354	0.1958	0.0301	0.0991	0.0113	0.4399	1									
Exacerbations in the previous year	-0.1057	-0.0378	0.1189	0.0390	0.0240	0.0779	0.1801	0.0297	0.2183	0.1777	1								
At least one hospitalization in the previous year	0.0400	0.0557	-0.0294	0.0318	0.1779	0.1334	0.2090	0.0762	0.3465	0.2218	0.4420	1							
FEV$_1$	-0.1424	-0.1796	0.0299	-0.1115	-0.3086	-0.1337	-0.1632	-0.0737	-0.5271	-0.2940	-0.1680	-0.2409	1						
Chronic infection	-0.0168	0.0571	-0.0236	-0.0971	0.1892	0.2463	0.2916	-0.0098	0.2220	0.1084	0.1498	0.2051	-0.1903	1					
Chronic infection with *P. aeruginosa*	0.0274	0.0595	-0.0293	-0.0758	0.2245	0.1517	0.2292	0.0565	0.2550	0.2227	0.2123	0.3554	-0.1828	0.4970	1				
Chronic infection with other pathogens	-0.0407	0.0163	-0.0030	-0.0480	0.0323	0.1543	0.1431	-0.0561	0.0445	-0.0566	-0.0020	-0.0544	-0.0668	0.7211	-0.2428	1			
More than one pathogen causing chronic infection	-0.0356	0.0927	0.0378	-0.0289	0.1047	0.1202	0.2292	0.0194	0.1585	0.0228	0.1400	0.1806	-0.1401	0.4970	0.2496	0.3563	1		
Charlson Comorbidities Index>1	0.2547	0.1592	0.0159	0.1702	0.0376	0.0240	0.0331	0.0169	0.2326	0.0883	-0.0070	0.0730	-0.1325	0.0229	-0.0194	0.0411	0.0144	1	
C-reactive protein	0.0720	0.0541	0.0339	-0.0045	0.1870	0.1926	0.1739	0.0566	0.2224	0.1559	0.0883	0.1730	-0.2522	0.2272	0.1927	0.1001	0.1597	0.1024	1

MRC: medical research council; LTOT: long-term oxygen therapy; FEV$_1$: forced expiratory volume in the first second.

Table S4. Principal components detected in the recruited cohort of patients.

Component	Eigenvalue	Difference	Proportion	Cumulative
Component 1	3.36719	1.41608	0.2405	0.2405
Component 2	1.95111	.531262	0.1394	0.3799
Component 3	1.41985	.286922	0.1014	0.4813
Component 4	1.13293	.0800947	0.0809	0.5622
Component 5	1.05283	.0948883	0.0752	0.6374
Component 6	.957942	.176139	0.0684	0.7058
Component 7	.781803	.0844368	0.0558	0.7617
Component 8	.697366	.0370576	0.0498	0.8115
Component 9	.660309	.0644335	0.0472	0.8587
Component 10	.595875	.0384295	0.0426	0.9012
Component 11	.557446	.0675654	0.0398	0.9410
Component 12	.48988	.154401	0.0350	0.9760
Component 13	.335479	.335479	0.0240	1
Component 14	0	.	0.0000	1

Table S5. Factor loadings of the variables in relation with the principal components.

Variable	Comp1	Comp2	Comp3	Comp4	Comp5	Comp6	Comp7	Comp8	Comp9	Comp10	Comp11	Comp12	Comp13
Age	0.0801	-0.2111	0.4834	0.2918	0.2115	0.2494	-0.0935	0.6772	0.0825	-0.1367	0.0684	0.1401	-0.0784
Reiff score	0.2500	-0.1581	0.1055	-0.1205	0.4029	-0.2149	-0.6720	-0.2396	0.1847	0.3265	0.0658	0.1541	-0.0246
Daily cough	0.2088	0.1764	-0.0576	0.6118	-0.0871	-0.3391	0.0033	-0.2208	0.1089	-0.3550	0.4340	0.2098	-0.0774
Daily sputum	0.2733	0.1565	-0.0897	0.5392	-0.0374	-0.1474	0.0438	0.1449	-0.1949	0.5449	-0.4055	-0.2378	0.0073
MRC breathlessness scale	0.3864	-0.2830	0.1608	-0.1004	-0.1583	-0.1401	0.1639	0.0059	-0.0752	-0.0030	0.1043	0.0168	0.8039
Long-term oxygen therapy	0.2714	-0.3172	0.0291	-0.2297	-0.1688	-0.2904	0.4727	0.1015	0.2790	0.3126	0.1407	0.1608	-0.4519
Exacerbations in the previous year	0.2328	-0.0340	-0.4349	-0.0065	-0.4253	0.3100	-0.2656	0.1479	0.0772	-0.0313	-0.2314	0.5705	0.0109
At least one hospitalization in the previous year	0.3257	-0.1484	-0.2901	-0.0047	-0.1584	0.3429	-0.1996	0.0785	0.1552	-0.0286	0.3809	-0.6466	-0.1042
FEV$_1$	-0.3195	0.2255	-0.1544	0.1450	0.1396	0.2486	0.1748	0.0497	0.5152	0.4488	0.3111	0.1402	0.3234
Chronic infection	0.3604	0.4401	0.0971	-0.1770	0.1494	0.0492	0.1095	0.0131	0.2930	-0.1762	-0.2072	-0.0501	0.0105
Chronic infection with *P. aeruginosa*	0.3164	-0.0473	-0.2839	0.0188	0.5833	0.1842	0.3135	-0.1079	0.1024	-0.2305	-0.2260	0.0421	0.0113
Chronic infection with other pathogens	0.1543	0.5302	0.3325	-0.2131	-0.2923	-0.0901	-0.1245	0.0997	0.2474	-0.0157	-0.0540	-0.0893	0.0028
More than one colonization	0.2537	0.3500	0.0259	-0.1830	0.1479	0.2418	0.0945	0.0351	-0.6081	0.2346	0.4502	0.2283	-0.0942
Charlson Comorbidities Index>1	0.0957	-0.1430	0.4677	0.2019	-0.1874	0.5220	0.1089	-0.5919	0.0549	0.1062	-0.1114	0.0474	-0.1095

MRC: medical research council; LTOT: long-term oxygen therapy; FEV$_1$: forced expiratory volume in the first second.

Table S6. Correlations among variables as assessed in every cluster.

		Age	Sex	BMI	Smokers/ex smokers	Reiff_score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV$_1$	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More_than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
																			Cluster 1 "Pseudomonas"	
Age	ρ	1																		
	p-value																			
Sex	ρ	0.0173	1																	
	p-value	0.8477																		
BMI	ρ	-0.0517	0.1566	1																
	p-value	0.5655	0.0800																	
Smokers/ ex smokers	ρ	0.2610	0.1811	0.0283	1															
	p-value	0.0032	0.0425	0.7535																
Reiff_ score	ρ	0.1300	0.1153	-0.1150	-0.0570	1														
	p-value	0.1469	0.1985	0.1996	0.5260															
Daily cough	ρ	0.1388	-0.0166	0.1119	0.0926	-0.0054	1													
	p-value	0.1212	0.8539	0.2124	0.3022	0.9522														
Daily sputum	ρ	-0.0976	0.0046	0.1370	-0.0743	0.0083	0.0187	1												
	p-value	0.2769	0.9595	0.1261	0.4086	0.9266	0.8355													
Prior history of haemoptysis	ρ	-0.1637	-0.0907	0.0511	0.0959	0.0098	-0.1224	0.0316	1											
	p-value	0.0669	0.3127	0.5697	0.2856	0.9136	0.1723	0.7251												
MRC	ρ	0.2156	0.1521	0.0207	0.2148	**0.4265**	0.1012	0.0613	-0.0705	1										
	p-value	0.0153	0.0890	0.8178	0.0157	**0.0000**	0.2596	0.4953	0.4327											
LTOT	ρ	0.0665	0.1301	-0.0319	**0.3119**	0.1637	-0.0227	-0.0136	0.0422	**0.6190**	1									
	p-value	0.4593	0.1464	0.7228	**0.0004**	0.0670	0.8011	0.8796	0.6388	**0.0000**										
Exacerbations in the previous year	ρ	-0.1739	-0.0013	0.1701	0.0212	0.0109	-0.0114	0.2152	0.0074	0.1664	0.1856	1								
	p-value	0.0514	0.9881	0.0568	0.8138	0.9033	0.8991	0.0155	0.9347	0.0626	0.0375									
At least one hospitalization in the previous year	ρ	-0.1637	-0.0344	0.0016	-0.1081	0.0976	-0.0742	0.1576	0.0553	0.2302	0.1389	**0.3910**	1							
	p-value	0.0670	0.7018	0.9861	0.2282	0.2771	0.4091	0.0780	0.5387	0.0095	0.1210	**0.0000**								
FEV$_1$	ρ	-0.0002	-0.2581	-0.0690	-0.1916	**-0.4543**	0.0300	-0.0190	-0.2440	**-0.4698**	**-0.3394**	-0.1267	-0.0768	1						
	p-value	0.9983	0.0035	0.4427	0.0317	**0.0000**	0.7389	0.8326	0.0059	**0.0000**	**0.0001**	0.1574	0.3928							
Chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.						
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.						
Chronic infection with *P. aeruginosa*	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.						
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.						
Chronic infection with other pathogens	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.						
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.						
More_than one pathogen causing chronic infection	ρ	-0.0916	0.1636	0.2136	0.0786	-0.1185	-0.0097	0.1439	0.0181	-0.0186	-0.1874	0.1666	0.1869	-0.0271	.	.	.	1		
	p-value	0.3078	0.0672	0.0163	0.3819	0.1864	0.9141	0.1079	0.8408	0.8359	0.0356	0.0623	0.0362	0.7632	.	.	.			
Charlson Comorbidities Index>1	ρ	0.1561	0.1967	-0.1024	0.2488	0.0724	0.0501	-0.0310	-0.0934	0.1446	0.0728	-0.0784	-0.0439	-0.0196	.	.	.	0.0574	1	
	p-value	0.0809	0.0272	0.2539	0.0050	0.4208	0.5773	0.7303	0.2984	0.1063	0.4176	0.3827	0.6257	0.8279	.	.	.	0.5233		
C-reactive protein	ρ	-0.0437	0.0011	-0.1064	0.0582	0.1647	0.1481	-0.0391	0.0103	**0.3710**	**0.4532**	0.1349	0.0031	-0.2245	.	.	.	-0.0579	0.0520	1

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		Age	Sex	BMI	Smokers/ex smokers	Reiff_score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV₁	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More_than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
	p-value	0.6272	0.9903	0.2356	0.5173	0.0653	0.0978	0.6637	0.9090	**0.0000**	**0.0000**	0.1320	0.9722	0.0115	.	.	.	0.5199	0.5629	

Cluster 2 "Other chronic infection"

		Age	Sex	BMI	Smokers/ex smokers	Reiff_score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV₁	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More_than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
Age	ρ	1																		
	p-value																			
Sex	ρ	0.1493	1																	
	p-value	0.0238																		
BMI	ρ	-0.0269	0.1549	1																
	p-value	0.6855	0.0190																	
Smokers/ ex smokers	ρ	0.0556	0.1765	-0.0028	1															
	p-value	0.4023	0.0074	0.9664																
Reiff_ score	ρ	0.1437	0.1053	-0.2456	0.0555	1														
	p-value	0.0297	0.1121	0.0002	0.4031															
Daily cough	ρ	0.1545	0.0075	0.0028	-0.0176	0.0930	1													
	p-value	0.0193	0.9106	0.9669	0.7911	0.1608														
Daily sputum	ρ	0.2181	0.0653	0.0738	-0.0457	0.0359	0.2740	1												
	p-value	0.0009	0.3250	0.2661	0.4915	0.5885	0.0000													
Prior history of haemoptysis	ρ	0.1619	0.0495	0.0049	-0.0713	0.1096	-0.1020	0.0782	1											
	p-value	0.0142	0.4563	0.9415	0.2825	0.0981	0.1239	0.2388												
MRC	ρ	0.2236	0.0871	0.0225	0.0457	0.1769	0.1670	0.1310	0.0384	1										
	p-value	0.0007	0.1892	0.7353	0.4914	0.0073	0.0114	0.0477	0.5633											
LTOT	ρ	0.0895	0.1447	-0.0941	0.0563	0.1515	0.0786	-0.0077	0.0523	0.3622	1									
	p-value	0.1772	0.0286	0.1560	0.3969	0.0218	0.2359	0.9072	0.4306	0.0000										
Exacerbations in the previous year	ρ	-0.0433	0.0215	0.0616	0.0938	-0.1154	-0.0107	0.0375	0.0555	0.0913	0.1432	1								
	p-value	0.5146	0.7461	0.3536	0.1573	0.0815	0.8726	0.5728	0.4035	0.1685	0.0303									
At least one hospitalization in the previous year	ρ	0.1185	0.1356	-0.0714	0.1507	0.1870	0.0707	0.1458	0.2089	**0.3397**	0.0913	**0.3234**	1							
	p-value	0.0734	0.0404	0.2820	0.0225	0.0045	0.2870	0.0273	0.0015	**0.0000**	0.1687	**0.0000**								
FEV₁	ρ	-0.1457	-0.1132	0.0288	0.0030	-0.1810	-0.0421	-0.0280	-0.0397	**-0.5561**	-0.2704	-0.0683	-0.2355	1						
	p-value	0.0274	0.0875	0.6650	0.9639	0.0060	0.5266	0.6731	0.5498	**0.0000**	0.0000	0.3035	0.0003							
Chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
Chronic infection with *P. aeruginosa*	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
Chronic infection with other pathogens	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
More_than one pathogen causing chronic infection	ρ	-0.0214	0.0882	0.0204	0.0148	0.0811	-0.0046	0.2061	0.0632	0.1383	0.0901	0.0777	0.1078	-0.1192	.	.	.	1		
	p-value	0.7471	0.1835	0.7590	0.8240	0.2215	0.9448	0.0017	0.3412	0.0365	0.1743	0.2413	0.1037	0.0718	.	.	.			
Charlson Comorbidities Index>1	ρ	0.2168	0.2113	0.0396	0.1209	-0.0023	0.1126	0.1315	0.0305	0.2785	0.0262	0.0376	0.1274	-0.1808	.	.	.	-0.0222	1	
	p-value	0.0010	0.0013	0.5508	0.0678	0.9722	0.0892	0.0468	0.6463	0.0000	0.6928	0.5710	0.0542	0.0061	.	.	.	0.7386		
C-reactive protein	ρ	0.0456	0.0222	0.0580	-0.0468	0.1169	0.0716	0.0921	0.0229	0.2555	0.1006	0.0318	0.2172	-0.2963	.	.	.	0.1568	0.0691	1
	p-value	0.4925	0.7381	0.3819	0.4808	0.0774	0.2809	0.1647	0.7300	0.0001	0.1289	0.6319	0.0009	0.0000	.	.	.	0.0176	0.2979	

Cluster 3 "Daily sputum"																			
		Age	Sex	BMI	Smokers/ ex smokers	Reiff_ score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV₁	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More_than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
Age	ρ	1																		
	p-value																			
Sex	ρ	0.0029	1																	
	p-value	0.9621																		
BMI	ρ	-0.0021	0.0431	1																
	p-value	0.9717	0.4776																	
Smokers/ ex smokers	ρ	0.0552	0.1984	0.0357	1															
	p-value	0.3628	0.0010	0.5566																
Reiff_ score	ρ	0.0832	0.0213	-0.1482	0.0229	1														
	p-value	0.1699	0.7262	0.0141	0.7059															
Daily cough	ρ	-0.0957	0.0049	-0.0064	-0.0980	-0.0362	1													
	p-value	0.1139	0.9353	0.9159	0.1054	0.5512														
Daily sputum	ρ	-0.0478	0.0822	0.0874	-0.0498	-0.0181	0.1989	1												
	p-value	0.4303	0.1749	0.1489	0.4118	0.7661	0.0009													
Prior history of haemoptysis	ρ	0.0325	-0.0102	-0.0185	0.0194	0.0782	0.0032	0.0765	1											
	p-value	0.5921	0.8668	0.7603	0.7489	0.1970	0.9585	0.2068												
MRC	ρ	0.1402	0.0138	0.0041	0.1291	0.2132	-0.0030	-0.2632	-0.0155	1										
	p-value	0.0202	0.8197	0.9457	0.0327	0.0004	0.9604	0.0000	0.7986											
LTOT	ρ	0.0139	0.0982	-0.0375	0.2041	0.2125	-0.1889	**-0.5001**	-0.0885	**0.4970**	1									
	p-value	0.8183	0.1048	0.5368	0.0007	0.0004	0.0017	**0.0000**	0.1440	**0.0000**										
Exacerbations in the previous year	ρ	-0.0700	-0.0726	0.1469	0.1655	0.0710	-0.0344	0.0466	0.0492	0.2651	0.1309	1								
	p-value	0.2479	0.2313	0.0149	0.0060	0.2415	0.5708	0.4427	0.4171	0.0000	0.0302									
At least one hospitalization in the previous year	ρ	0.0371	0.0103	0.0192	0.0861	0.0870	0.0642	-0.0261	0.0012	**0.3180**	0.2200	**0.4536**	1							
	p-value	0.5413	0.8652	0.7518	0.1550	0.1509	0.2899	0.6668	0.9847	**0.0000**	0.0002	**0.0000**								
FEV₁	ρ	-0.1005	-0.0981	0.0769	-0.2089	-0.2590	-0.0332	0.1436	-0.0598	**-0.5372**	**-0.3220**	-0.2099	-0.2481	1						
	p-value	0.0969	0.1050	0.2047	0.0005	0.0000	0.5848	0.0174	0.3240	**0.0000**	**0.0000**	0.0005	0.0000							
Chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.						
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.						
Chronic infection with *P. aeruginosa*	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
Chronic infection with other pathogens	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
More_than one pathogen causing chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
Charlson Comorbidities Index>1	ρ	0.2340	0.0831	0.0775	0.1455	-0.0139	-0.0198	-0.0708	0.0184	0.2224	0.1972	0.0716	0.1161	-0.1651	.	.	.	.	1	
	p-value	0.0001	0.1699	0.2011	0.0160	0.8188	0.7447	0.2426	0.7620	0.0002	0.0010	0.2373	0.0549	0.0061						
C-reactive protein	ρ	0.0455	-0.0926	0.0628	-0.1636	0.1252	0.1542	0.0234	0.0886	0.0233	-0.0137	0.0123	0.0801	-0.1479	.	.	.	.	0.1319	1
	p-value	0.4536	0.1264	0.3006	0.0066	0.0383	0.0106	0.6996	0.1436	0.7013	0.8213	0.8396	0.1861	0.0143	.	.	.	.	0.0291	

Cluster 4 "Dry bronchiectasis"

		Age	Sex	BMI	Smokers/ ex smokers	Reiff_ score	Daily cough	Daily sputum	Prior history of haemoptysis	MRC	LTOT	Exacerbations in the previous year	At least one hospitalization in the previous year	FEV$_1$	Chronic infection	Chronic infection with *P. aeruginosa*	Chronic infection with other pathogens	More_than one pathogen causing chronic infection	Charlson Comorbidities Index>1	C-reactive protein
Age	ρ	1																		
	p-value																			
Sex	ρ	0.2000	1																	
	p-value	0.0015																		
BMI	ρ	0.0557	0.1460	1																
	p-value	0.3801	0.0209																	
Smokers/ ex smokers	ρ	0.2541	0.2837	-0.0541	1															
	p-value	0.0000	0.0000	0.3946																
Reiff_ score	ρ	**0.3175**	0.0576	-0.1764	0.0300	1														
	p-value	**0.0000**	0.3641	0.0052	0.6366															
Daily cough	ρ	-0.0488	0.0503	-0.0264	-0.0629	-0.0666	1													
	p-value	0.4428	0.4281	0.6776	0.3222	0.2942														
Daily sputum	ρ	.	.	.	.	.	.													
	p-value																			
Prior history of haemoptysis	ρ	0.0620	-0.0070	-0.1108	-0.0162	0.0556	-0.0454	.	1											
	p-value	0.3287	0.9122	0.0802	0.7987	0.3813	0.4753	.												
MRC	ρ	0.1750	0.1213	0.0126	0.1174	0.2216	0.0485	.	0.1007	1										
	p-value	0.0055	0.0554	0.8428	0.0638	0.0004	0.4457	.	0.1123											
LTOT	ρ	.	.	.	.	.	.	.	.	.										
	p-value	.	.	.	.	.	.	.	.	.										
Exacerbations in the previous year	ρ	-0.2068	-0.1623	0.1336	-0.0850	-0.1229	0.0479	.	-0.0977	0.0472	.	1								
	p-value	0.0010	0.0102	0.0347	0.1803	0.0523	0.4511	.	0.1233	0.4572	.									
At least one hospitalization in the previous year	ρ	0.0651	0.0008	-0.0515	0.0665	0.0458	0.0817	.	-0.0379	0.1257	.	**0.3691**	1							
	p-value	0.3056	0.9894	0.4176	0.2951	0.4709	0.1979	.	0.5509	0.0472	.	**0.0000**								
FEV$_1$	ρ	-0.2266	-0.2611	0.0003	-0.1578	-0.2214	-0.0796	.	0.0275	**-0.3478**	.	-0.0117	-0.0905	1						
	p-value	0.0003	0.0000	0.9963	0.0125	0.0004	0.2096	.	0.6651	**0.0000**	.	0.8537	0.1536							
Chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.					
Chronic infection with *P. aeruginosa*	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.				
Chronic infection with other pathogens	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.			
More_than one pathogen causing chronic infection	ρ	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
	p-value	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
Charlson Comorbidities Index>1	ρ	**0.3642**	0.1759	-0.0141	0.2137	0.1327	-0.0157	.	0.0812	0.2709	.	-0.1014	0.0867	-0.0914	.	.	.	.	1	
	p-value	**0.0000**	0.0053	0.8247	0.0007	0.0359	0.8044	.	0.2007	0.0000	.	0.1099	0.1718	0.1495	.	.	.	.		
C-reactive protein	ρ	0.1515	0.1949	0.0709	0.2202	0.1435	0.0920	.	0.0579	0.1282	.	0.0273	0.0746	-0.1763	.	.	.	.	0.1009	1
	p-value	0.0165	0.0020	0.2641	0.0005	0.0233	0.1471	.	0.3623	0.0429	.	0.6679	0.2402	0.0052	.	.	.	.	0.1114	

ONLINE FIGURE LEGEND

Figure S1. Dendrogram describing the cluster tree.