Respiratory infectious burden in a cohort of antibody deficiency patients treated with immunoglobulin replacement therapy: The impact of lung pathology and gastroesophageal reflux disease

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Background: Antibody deficiencies result from reduced immunoglobulin levels and function, increasing susceptibility to, primarily, bacterial infection. Primary antibody deficiencies comprise intrinsic defects in B-cell physiology, often due to inherited errors. Hematological malignancies or B-cell suppressive therapy are major causes of secondary antibody deficiency. Although immunoglobulin replacement therapy (IGRT) reduces infectious burden in antibody deficiency patients, respiratory tract infections remain a significant health burden. We hypothesize that lung pathology and gastroesophageal reflux disease (GORD) increase the risk of pneumonia in antibody deficiency patients, as in the general population.

Objective: For our cohort of patients with primary antibody deficiency and secondary antibody deficiency, we reviewed their respiratory infectious burden and the impact of lung pathologies and GORD.

Methods: The medical records of 231 patients on IGRT at a tertiary referral center, from October 26, 2014, to February 19, 2021, were reviewed to determine microbial isolates from sputum samples and prevalence of common lung pathologies and GORD.

Results: *Haemophilus* and *Pseudomonas* species represent a large infectious burden, being identified in 30.2% and 21.4% of sputum samples demonstrating growth, respectively; filamentous fungal and mycobacterial infections were rare. Diagnosed lung pathology increased the proportion of patients with *Pseudomonas*, *Klebsiella*, *Stenotrophomonas*, and *Candida* species isolated in their sputum, and diagnosed GORD increased the proportion with *Enterobacter* and *Candida* species isolated.

Conclusions: Bacterial respiratory infectious burden remains in primary antibody deficiency and secondary antibody deficiency despite IGRT. Lung pathologies encourage growth of species less susceptible to IGRT, so specialist respiratory medicine input and additional treatments such as inhaled antibiotics are indicated to optimize respiratory outcomes. (J Allergy Clin Immunol Global 2023;2:100133.)

Key words: *Antibody deficiency, immunoglobulin replacement therapy, lung pathology, gastroesophageal reflux disease, microbiology, sputum cultures*

Antibody deficiencies (hypogammaglobulinemia) increase susceptibility to infection via reduced immunoglobulin levels or functioning.[1] Antibody deficiency may be primary (due to intrinsic defects in B-cell physiology; often from inborn errors of immunity disrupting B-cell differentiation[2]), or secondary to malignancies of the B-cell system or immunosuppressants directed at B-cell depletion or reducing abnormal B-cell function.[3]

Antibody deficiency patients are at greater risk of severe and recurrent pulmonary infections,[4] especially infections by encapsulated bacteria and *Haemophilus influenzae*.[5] Antibiotic prophylaxis and prompt antibiotic prescribing in infectious events provide some protection. However, immunoglobulin replacement therapy (IGRT; administering human polyclonal IgG[6] via the subcutaneous or intravenous route) is the standard of care for primary antibody deficiency (PAD), following seminal studies in the 1960s. This reduces infection rates and morbidity in patients with PAD.[7] Studies have demonstrated that IGRT is also effective in reducing infections in secondary antibody deficiency (SAD).[1] However, the impact of IGRT in SAD is less well documented, and thus clinical management guidance for such patients is primarily extrapolated from experience with patients with PAD.[8]

The aim of this study was to investigate the infectious burden in the lower respiratory tract of antibody-deficient patients who are undergoing IGRT. We also investigated the influence of lung pathologies and of gastroesophageal reflux disease (GORD) on sputum microbiology and respiratory infectious burden in these patients. This study also compared the respiratory infectious burden in patients with PAD versus SAD.

METHODS

This study was a service evaluation of the care of antibody deficiency patients within the remit of the Immunology Department at the Cambridge University Hospital, UK, covering the East of

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Received for publication November 29, 2022; revised May 24, 2023; accepted for publication June 6, 2023.

Available online July 1, 2023.

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2772-8293

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https://doi.org/10.1016/j.jacig.2023.100133

Abbreviations used
COPD: Chronic obstructive pulmonary disease
IGRT: Immunoglobulin replacement therapy
GORD: Gastroesophageal reflux disease
PAD: Primary antibody deficiency
PPI: Proton pump inhibitor
SAD: Secondary antibody deficiency

England (approximate population of 5 million), focusing on the microbiology of infections of patients treated with IGRT.

Data collection

Anonymized data were collected from medical records of patients receiving IGRT under the care of the Immunology Department at the Cambridge University Hospital, UK, from October 26, 2014, to February 19, 2021. The date patients were first known to the medical record system, the date they first received IGRT, and, if applicable, the date they stopped receiving IGRT were recorded.

Infections

All patients with antibody deficiency in this study were recommended and encouraged to submit a sputum sample for microbiological investigation if they developed symptoms of a respiratory infection. For many patients, multiple sputum samples were obtained. To avoid double counting, and to assess the respiratory infectious burden of each patient, the number of so-called sputum sample collection periods was taken as a proxy for the infectious burden for that patient. One "sputum sample collection period" or "infection" was defined as a 2-week period starting from when a sputum sample was collected. This is in line with the length of a typical respiratory tract infection as defined by the UK National Health Service.[9] Any sputum samples collected within 2 weeks of this first sample were classified as part of the same sputum sample collection period.

The criteria used to report a sputum sample as containing clinically significant growth was as follows: for standard bacterial organisms, more than 10^5 colony-forming unit/mL is required; for fungi, growth on specialist media is recorded; in known bronchiectasis, specialist media is used and growth of *Pseudomonas* on this was reported.

Data management and statistics

Data collection and management were carried out using Microsoft Excel. Chi-square tests and Mann-Whitney *U* tests were used as appropriate to explore whether infectious profiles were statistically different in distinct patient groups. Microsoft Excel was used to produce the odds ratios graphs; species were excluded from these graphs if they had zero occurence in 1 of the 2 groups being compared because this prohibits odds ratios being calculated.

Patient population

We studied the health records of 238 patients under the care of the Immunology Department at Addenbrookes Hospital who were receiving IGRT for clinically significant antibody deficiency as per national guidelines. For this study, different products and routes of IGRTs were considered to be equivalent (an assumption supported by Chapel et al[10]). The patients are treated with the current consensus immunoglobulin replacement protocol, commencing with the initial replacement dose of 400 mg/kg bodyweight, every 4 weeks, and aiming to achieve a steady-state replacement IgG level of 8 to 10 g/L. The patients were regularly monitored, and the immunoglobulin dose was increased according to the recommendations of Lucas et al,[11] in patients who continued to have episodes of infection.

All patients were older than 18 years and were grouped into PAD and SAD. PAD was defined as that in any patient who had aspects of PAD that had developed or been diagnosed at any age. SAD was defined as that present in those who only had antibody deficiency that had been acquired (because of a lymphoproliferative disorder or a medication[8]), with no aspect of PAD present in their notes.

Six patients were excluded because of incomplete record keeping relating to the cause of their immunodeficiency. One further patient was excluded because they had never received IGRT. The final number of included patients was 231.

All patients had a formal respiratory clinic review at diagnosis and regularly during follow-up. Patients were classified into those with and without asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), or emphysema. This was done by searching their clinical notes for these clinical diagnoses.

By reviewing their clinical notes, the patient cohort was also stratified into those with a clinical diagnosis of GORD and those without.

TABLE I. Clinical characteristics of the patients included in this study

Characteristics	Patients with PAD	Patients with SAD
No. of patients	147	84
% Female	52	67
Average number of years of data per patient before IGRT	0.80	1.78
Average number of years of data per patient while on IGRT	4.85	3.98
Average number of sputum sample collection periods per patient-year before IGRT	0.71*	0.92
Average number of sputum sample collection periods per patient-year while on IGRT	0.66	0.80
Percentage of patients with asthma, bronchiectasis, or COPD	57.8% (85)	29.8% (25)
Percentage of patients with asthma	26.5% (39)	13.1% (11)
Percentage of patients with bronchiectasis	36.1% (53)	16.7% (14)
Percentage of patients with COPD	15.0% (22)	6.0% (5)
Percentage of patients with GORD	10.9% (16)	6.0% (5)

*One outlier removed because timings of 1 infection in the few days between them being known to the Immunology team and them being started on IGRT artificially inflated their number of infections per year before IGRT.

RESULTS

A total of 231 patients receiving IGRT for antibody deficiency were identified under the care of the Immunology Department at

TABLE II. Causes of primary antibody deficiency in our cohort of patients

Cause of PAD	No. of patients
CVID	101
Selective antibody deficiency	12
Possible CVID	6
IgG subclass deficiency	5
X-linked syndromes	5
Good syndrome	4
Panhypogammaglobulinemia with no secondary cause	4
Hyper-IgM syndrome	2
Others*	8

CVID, Common variable immune deficiency.
*Others consists of 1 case each of the following:

- Combined immune deficiency—hemizygous for c.98T>A, p.(Ile33Asn) in CD40LG likely causal variant for X-linked immunodeficiency.
- Autoimmune polyendocrinopathy syndrome type 1 due to a mutation in the autoimmune regulator gene with no detectable $CD19^+$ B cells.
- Primary immunodeficiency, combined T- and B-cell deficiency, mimicking, but not due to CTLA4 deficiency.
- Roifman syndrome.
- Hyper-IgE syndrome.
- PAD, common gamma-chain (γc) mutation associated with significant cell-mediated immunodeficiency and absent natural killer cells.
- Hypogammaglobulinemia with DOCK8 mutation.
- Dysgammaglobulinemia with impaired T-cell receptor Vβ repertoire.

TABLE III. Causes of secondary antibody deficiency in our cohort of patients

Precipitating disease that led to SAD	No. of patients
Immunosuppressive therapy for vasculitis	21
Immunosuppressive therapy for inflammatory arthritis/RA	9
Immunosuppressive therapy for SLE	7
Immunosuppressive therapy for Behçet disease	2
Immunosuppressive therapy for Sjogren syndrome	1
Immunosuppressive therapy for chronic immune thrombocytopenia	1
Immunosuppressive therapy for relapsing polychondritis	1
Immunosuppressive therapy for RA/SLE overlap	1
B-cell lymphoma*	20
CLL*	14
ALL*	2
CML*	1
Large granular lymphocytic leukemia*	1
IgM MGUS*	1
Myeloma*	1
T-cell lymphoma*	1

ALL, Acute lymphocytic leukemia; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myeloid leukaemia; *MGUS*, monoclonal gammopathy of unknown significance; *RA*, rheumatoid arthritis.
*The condition as well as its treatment causes immunodeficiency.

Addenbrookes. The clinical characteristics of the different patient groups are described in Table I.

The SAD group had a preponderance of females relative to the PAD group ($P = .035$ by χ^2 test). This reflects the female preponderance of autoimmune disease,[12] the treatment of which is a common cause of SAD.

The table also shows that lung diseases are more common in our patients with PAD (present in 57.8% vs 29.8% in patients with SAD; $P < .001$ by χ^2 test).

Characteristics of patients with PAD are presented in Table II. The most common PAD was common variable immune deficiency as defined by the European Society for Immunodeficiencies,[13] followed by selective antibody deficiency cases and possible common variable immune deficiency cases.

Characteristics of patients with SAD are presented in Table III. The most common cause was immunosuppressive therapy for an autoimmune condition such as SLE, rheumatoid arthritis, and anti-neutrophil cytoplasmic autoantibody (ANCA)-associated granulomatous vasculitis. It should be noted that the use of rituximab was commonly seen in SAD, with clinical documentation of this on our records for 46 of the 84 patients in this cohort.

Microbiology of respiratory infections

About 39.8% of sputum samples collected showed no clinically significant growth. For cultures that were growth positive, Table IV provides information on the microbial species identified. For the whole cohort, the most common organism grown during an infection period was *H influenzae* (in more than a quarter of infection periods), followed by *Candida* species and *Pseudomonas* species (both in approximately a fifth of infection periods). It should be

TABLE IV. The different microorganisms grown during infection periods

Species group	No. of infection periods observed in	% of infection periods with positive sputum cultures in which the species was observed to grow
Haemophilus influenzae	154	28.89
Other *Haemophilus* species	7	1.31
Candida species	115	21.58
Aspergillus species	3	0.56
Other fungi	1	0.19
Pseudomonas species	114	21.39
Stenotrophomonas maltophilia	36	6.75
Serratia species	33	6.19
Klebsiella species	32	6.00
Staphylococcus aureus	28	5.25
Other *Staphylococcus* species	1	0.19
Enterobacter species	26	4.88
Streptococcus pneumoniae	25	4.69
Other *Streptococcus* species	7	1.31
Moraxella species	19	3.56
Escherichia coli	17	3.19
Citrobacter species	14	2.63
Mixed upper respiratory tract flora	12	2.25
Acinetobacter species	3	0.56
Coliform bacilli	3	0.56
Mycobacterium species	3	0.56
Proteus species	3	0.56
Morganella morganii	3	0.56
Hafnia alvei	2	0.38
Mixed gram-negative flora	2	0.38
Enterococcus species	1	0.19
Pasteurella canis	1	0.19
Raoultella ornithinolytica	1	0.19

noted that the sum of the percentage's column totals more than 100% because multiple organisms were grown during some infection periods.

No statistically significant differences were found in the microbiology of infections for patients with PAD versus patients with SAD (see Figs E1 and E2 in this article's Online Repository at www.jaci-global.org).

The impact of lung pathology on bacterial isolates from patient sputum samples after commencing IGRT

Of the 231 patients in this study, 110 had a diagnosis of asthma, bronchiectasis, or COPD/emphysema: 50 diagnosed with asthma, 67 with bronchiectasis, and 27 with COPD/emphysema. It should be noted that some patients had multiple lung pathology diagnoses. We analyzed how these lung pathologies altered the microorganisms grown by patients in their sputum samples and this is shown in Fig 1.

We also analyzed how lung pathology impacted infection periods per patient year. The presence of 1 of asthma, bronchiectasis, or COPD increased the average number of infection periods per patient-year from 0.46 to 0.98 ($P < .001$) and increased how many times per patient-year *Candida*-containing sputum was seen, increasing it from 0.016 per patient-year to 0.156 times per patient-year ($P = .003$). A further breakdown of the above results by type of lung disease is provided by Tables E1 and E2 (in the Online Repository available at www.jaci-global.org).

The impact of gastroesophageal reflux on sputum microbiological isolates in antibody-deficient patients on IGRT

Previous studies have shown that GORD increases the long-term risk of pneumonia,[14,15] and esophageal diseases encourage the growth of gram-negative species in the esophagus.[16] We aimed to analyze whether preexisting GORD was associated with a different sputum microbiology once patients are on IGRT. Of the 231 patients included in the study, 21 had a diagnosis of GORD. We analyzed how GORD altered the microorganisms grown by patients in their sputum samples and this is shown in Fig 2.

It should also be noted that the presence of GORD has been previously shown to be correlated with the presence of asthma,[17] bronchiectasis, and COPD.[18] This relationship was observed in our study too: a higher percentage of patients with GORD have 1 of asthma, bronchiectasis, or COPD compared with patients without GORD (71.4% vs 47.5%; $P = .036$).

The impact of immunoglobulin replacement on infection burden and profile

All 231 patients included in the study were initiated on IGRT by the Immunology Department at Addenbrookes. We aimed to investigate whether the use of IGRT altered the microbiology of respiratory infections. This study has on average 1.15 patient-years of data per patient before on IGRT but an almost 4-fold greater 4.54 patient-years of data per patient while on IGRT. In view of this, as in the analyses above, we focused on changes in how commonly species appeared in sputum samples and on changes in infections per patient year.

We specifically wanted to measure whether IGRT reduced the infectious burden of microbial species against which antibodies are an important host defense mechanism. This group comprised *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenza*.[19,20] We then compared these against a group of species for which antibodies are less important as a host defense mechanism. This group comprised *Pseudomonas* species,[21] *Klebsiella* species,[22,23] and *Stenotrophomonas* species.[24,25] All the species in this group are less susceptible to antibody defenses and known to readily produce biofilms that help protect them against host immunity and immunoglobulins.[26,27] Other species such as *Nontypeable H influenzae*[28] also produce biofilms but have not demonstrated resistance to antibody defenses as members of this group have. Therefore, other mechanisms of antibody resistance beyond biofilm formation, such as resistance to opsonization, which has been reported for *Pseudomonas aeruginosa*, are likely also involved.[29]

For both patients with PAD and patients with SAD, we did not observe a statistically significant difference in the number of infections per patient-year before versus after IGRT for the 2 categories of bacteria, as described above. A table presenting these results is found in Table E4 (in the Online Repository available at www.jaci-global.org). It should be noted that sputum surveillance was incomplete before patients were referred to our service with suspected or diagnosed antibody deficiency for consideration of IGRT. Ascertainment bias from increased surveillance on IGRT makes comparison unreliable for determining the impact of IGRT on infection rates in antibody deficiency patients.

Once patients with SAD were on IGRT, fungal species (most often *Candida*) were less frequently isolated during infection periods (17.4% to 8.1% of infection periods, $P = .028$) (see Table E5 in this article's Online Repository available at www.jaci-global.org). This finding is discussed later.

DISCUSSION

The study provides information on the burden of bacterial infection in the lower respiratory tract of patients with PAD and patients with SAD, the impact of IGRT on the above, the influence of preexisting lung disease on the bacteriological isolates, and the impact of gastroesophageal reflux on the bacteriological profile of the respiratory tract in these patients.

Overall infectious burden for antibody deficiency patients

Our results demonstrated that gram-negative organisms such as *H influenzae*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Serratia* species, and *Klebsiella* species comprise a significant burden in antibody-deficient patients. Moreover, the gram-positive organisms of *Staphylococcus aureus* and *S pneumoniae* were seen regularly in the sputum cultures of our patients. This is similar to what Demirdag and Gupta[30] showed as common bacterial causes of pneumonia in patients with common variable immune deficiency.

Of note, 21.6% of the isolates were *Candida* species. Overwhelmingly, these were considered to represent oropharyngeal colonization, rather than being etiological agents for lower respiratory infection. Well-recognized factors that contribute to oropharyngeal colonization by *Candida* species are the use of antibiotic therapy and inhaled corticosteroids.[31]

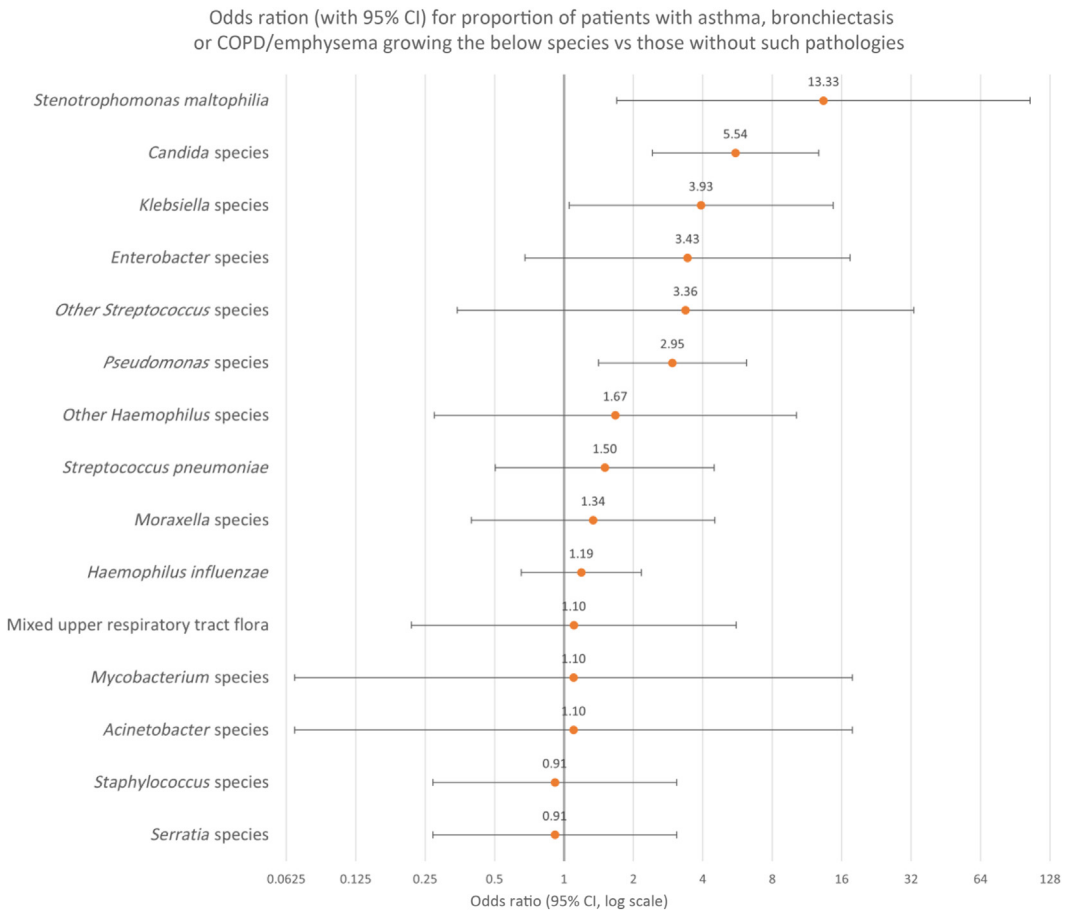

FIG 1. As anticipated, Fig 1 shows that the presence of lung pathology has a significant impact on microbial isolates from patients' sputum samples. In particular, those with lung pathology were more likely to grow *Candida* species, *Stenotrophomonas maltophilia*, and *Pseudomonas* and *Klebsiella* species in their sputa. The proportion of patients growing these bacteria rose from 6.6% to 28.2%, from 0.8% to 10.0%, from 9.9% to 24.5%, and from 2.5% to 9.1%, respectively ($P < .001$, .003, .003, and .029). Meanwhile the proportion of patients growing *Mycobacterium* species and the commonly observed *Haemophilus* species was relatively unaffected.

Impact of IGRT on microbiology profile

A substantial body of publications already shows that IGRT reduces the incidence of infections in antibody-deficient patients.[32] However, because of ascertainment bias with increased surveillance of patients once they are known to be antibody deficient and receiving IGRT, we were unable to demonstrate this in this study. In our experience, patients with immunodeficiency, even when referred by respiratory physicians to Immunology, have a paucity of sputum microbiological investigations coinciding with respiratory infection episodes. Moreover, this study has 4-fold as many patient-years of data for once patients are on IGRT compared with before they have received IGRT. To discern a difference in the rate of infection due to starting IGRT, it will be necessary to undertake studies of a prospective design where sputum microbiology testing is encouraged prior to patients meeting the clinical criteria for starting IGRT.

Interestingly, we were able to show that IGRT causes a statistically significant reduction in how likely fungi (mostly *Candida* species) are to be isolated during infection periods in patients with SAD. A possible explanation could be that IGRT was helping to also treat patient's concurrent asthma[33] and COPD,[34] thus reducing the need for such patients to use inhaled corticosteroids, which increase the likelihood of colonization by fungi.[35] Furthermore, studies have shown that IGRT changes the physical composition of respiratory secretions and encourages flow of secretions out of the lungs,[36] making the respiratory tract less hospitable for fungal growth. Moreover, if IGRT reduces the severity of patient's asthma and COPD it could also reduce the incidence of exacerbations requiring antibiotics, again making fungal colonization less likely. We do not have data to corroborate this possibility.

Overall, this study clearly demonstrates that significant burden of bacterial lower respiratory tract infection persists in patients with PAD and patients with SAD despite IGRT. The infectious burden of antibody-deficient patients is significantly influenced by preexisting lung disease and GORD as explained below. In addition, in a notable number of cases, the infectious burden of patients was very individual. One patient with GORD and asthma grew *Enterobacter* species (an organism found in only 4.9% of sputum results) 14 times after being on IGRT. This highlights that to improve patient care a holistic multidisciplinary approach will be required, with individual patient risk factors being addressed. Targeted prophylactic and therapeutic courses of antibiotic therapy will also play a part in managing patients with recurrent infections despite appropriate and adequate IGRT.

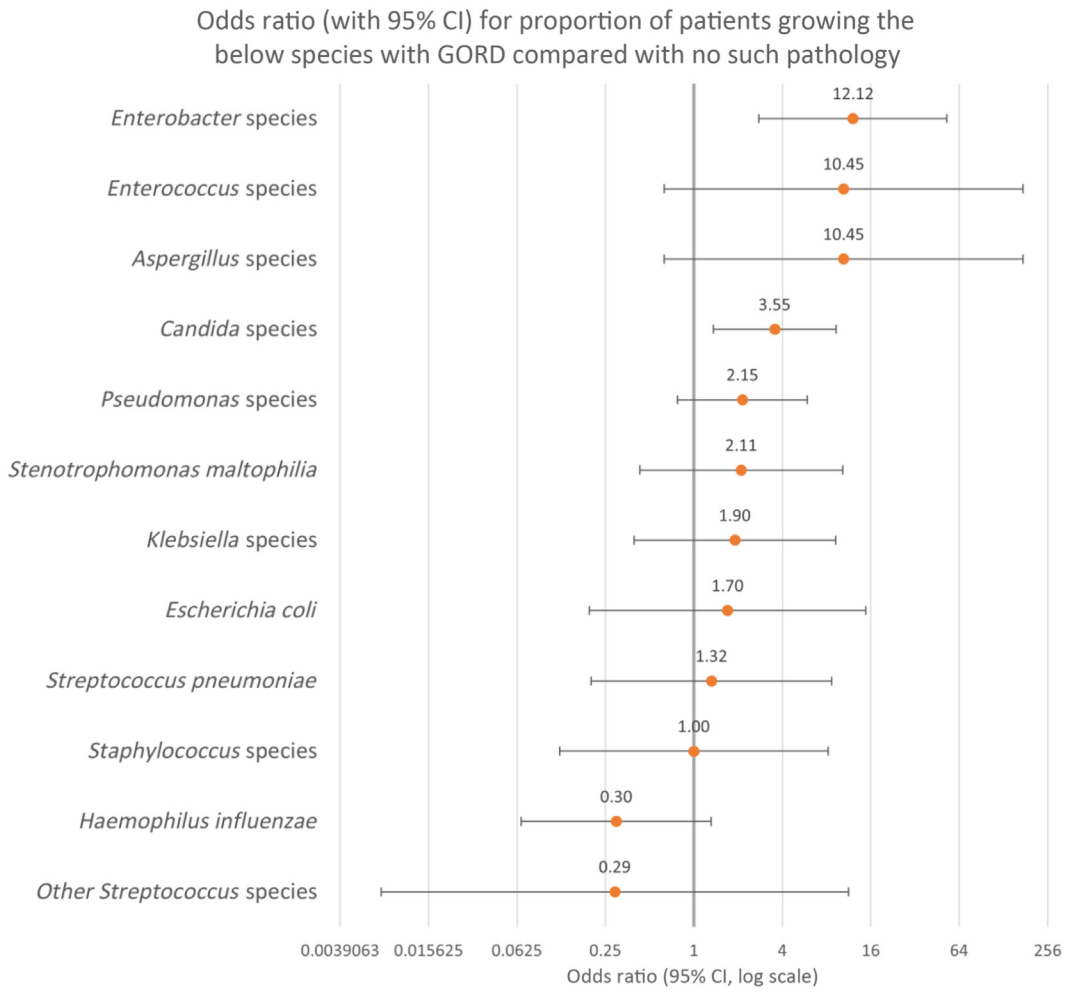

FIG 2. Fig 2 shows that when GORD is present, the infectious profile is altered, with the proportion of patients growing *Candida* species in their sputum samples increasing from 14.8% to 38.1% ($P < .01$; odds ratio = 3.55) and the proportion of those growing *Enterobacter* species increasing from 1.9% to 19.0% ($P < .001$; odds ratio = 12.12). Other species such as *Pseudomonas* species and *Klebsiella* species were also seen more frequently in patients with GORD; however, these changes were not statistically significant. A further breakdown of the above results is provided by Table E3 (in the Online Repository available at www.jaci-global.org).

Impact of lung pathology on microbiology profile

Fig 1 demonstrates that *Stenotrophomonas maltophilia* and *Pseudomonas*, *Klebsiella*, and *Candida species* were grown in the sputa of significantly more patients with asthma, bronchiectasis, or COPD. The environment created in these common lung pathologies could be serving as a niche that favors the growth of these organisms. The increased proportion of patients growing *Pseudomonas* species should be considered, bearing in mind that patients with bronchiectasis are specifically tested for this organism on specialist media as explained in the Methods section, making this more likely to be found in their sputum.

Increased growth of *Candida* in the sputum of patients with lung pathology is likely due to their use of inhaled corticosteroids.[35] Another explanation could be that such patients use antibiotics more often, to help control exacerbations of their lung disease, which encourages the appearance of *Candida* species in their sputum.[31]

With regard to the other species seen more often in patients with preexisting lung disease: immunoglobulin is not contributory to the prevention of such respiratory infections by *Pseudomonas*,[21] *Klebsiella*,[22] or *Stenotrophomonas* species.[24,25] Thus, IGRT is of minimal therapeutic benefit in clearing infection by these and other measures; for example, inhaled antibiotics, as used in patients with cystic fibrosis and patients with bronchiectasis,[37] are likely required. This highlights the need for regular input from respiratory physicians.

Other notable findings were that *H influenzae* was commonest in those with bronchiectasis, and that preexisting lung disease, namely asthma, bronchiectasis, COPD, and emphysema, were more common in patients with PAD than in patients with SAD. The reason for this finding is uncertain.

Impact of GORD on microbiology profile

In our study *Klebsiella*, *Escherichia coli*, and *Enterobacter* species, which may have originated from the oropharynx and gastrointestinal tract,[38] were seen in patients' sputa. Thus, for antibody-deficient patients, gastroesophageal reflux may

contribute to lower respiratory morbidity. Indeed, GORD has been shown to increase the long-term risk of pneumonia[14,15] and esophageal diseases have been shown to alter the esophageal microbiome in favor of gram-negative species.[16]

Our data support this; in Fig 2, more patients with GORD grew species in their sputa that are typically found in the esophagus of patients with reflux disease, such as *Enterobacter* species.[39] In addition, *E coli*, which usually colonizes the gastrointestinal tract,[40] is more common in their sputa. This suggests that GORD causes overt or microaspiration of gastrointestinal contents and subsequent seeding of the respiratory tract with these organisms.[15] Therefore, increased attention should be paid to the presence of gastroesophageal reflux in antibody deficiency patients. Measures to reduce volume of reflux, such as raising the head of the bed and avoiding meals for several hours preceding sleep, could provide benefits. In addition, approaches to manage gram-negative infections secondary to GORD would be helpful, as is already available in conditions such as bronchiectasis.[41]

The mainstay of GORD treatment is proton pump inhibitors (PPIs).[42] Some articles indicate that PPIs encourage colonization of the oropharynx, stomach, and duodenum[43,44] by gut flora. Further studies are needed to evaluate the risk-benefit balance of PPIs in antibody-deficient patients who are more at risk from inoculation of the respiratory tract by gut flora. Such studies should focus on whether PPIs alter the microbiome of the upper gastrointestinal tract and oropharynx in favor of, or against, pathogenic organisms.

Finally, our results demonstrated that *Candida* species are also more often found in the sputum of those with GORD. This could be explained by our patients with GORD having 1 of asthma, bronchiectasis, and COPD significantly more often than patients without GORD. These lung pathologies all increase the likelihood of *Candida* species appearing in sputum results as discussed above, so are likely confounding factors in this result.

The utility of sputum samples as a diagnostic tool

A large proportion (11.7%) of all sputum samples grew *Candida* species. This organism could have been colonizing the mucous membranes of the oral cavity[45] rather than the upper respiratory tract. Previous articles demonstrate that, in mycobacterial-specific cultures, antiseptic mouthwash use shows promise in reducing contamination.[46] However, this approach needs further data corroboration and evaluation for routine sputum culture.

Moreover, 39.8% of sputum samples showed no growth. Thus, conventional sputum culture may lack sensitivity to detect pathogens, or some exacerbations are not driven by bacterial/fungal infection. Alternative diagnostic tests, such as bronchioalveolar lavage, have not been shown to be significantly better than sputum cultures despite being more invasive and expensive to perform.[47] The potential value of emerging methods such as molecular microbiology techniques for sputum microbial identification needs evaluation.

Conclusions

This study demonstrates that *Haemophilus* and *Pseudomonas* species represent a large infectious burden for antibody deficiency patients. IGRT alone may be inadequate for completely reducing the burden of lower respiratory tract infections in antibody deficiency patients. Other treatments, such as inhaled antibiotics, will remain important.

Preexisting lung diseases and GORD cause statistically significant impacts on the microbiology of infections in these patients. Moreover, we show that lung diseases increase the number of infections patients suffer per year. Considering this, for optimal care, a multidisciplinary approach will be needed with focus on reducing these specific comorbidities.

DISCLOSURE STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Many thanks to the Immunology Department of Cambridge University Hospitals NHS Foundation Trust for allowing the collection of the data used in this article, and for generously covering the publication charges.

Clinical implications: We suggest that lung pathology and GORD significantly impact respiratory infectious burden in antibody-deficient patients. In this patient group, in addition to IGRT, respiratory specialist input is important for optimal care delivery.

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