Targeted AntiBiotics for Chronic pulmonary diseases (TARGET ABC): can targeted antibiotic therapy improve the prognosis of Pseudomonas aeruginosa-infected patients with chronic pulmonary obstructive disease, non-cystic fibrosis bronchiectasis, and asthma? A multicenter, randomized, controlled, open-label trial

Josefin Eklöf1, Imane Achir Alispahic1*, Pradeesh Sivapalan1,2, Torgny Wilcke1, Niels Seersholm1, Karin Armbruster1, Jakob Lyngby Kjærgaard1, Mohamad Isam Saeed1, Thyge Lynghøj Nielsen3, Andrea Browatzki3, Rikke Holmen Overgaard3, Camilla Sund Fenlev3, Zitta Barella Harboe3, Helle Frost Andreassen4, Therese Sophie Lapperre4, Lars Pedersen4, Stine Johnsen4, Charlotte Suppli Ulrik5, Julie Janner5, Mia Moberg5, Maria Heidemann5, Ulla Møller Weinreich6, Roxana Vijdea6, Hans Linde7, Ingrid Tlilstad8, Sofie Lock Johansson8, Flemming Schonning Rosenvinge9, Christian Østergaard10, Khaled Saoud Ali Ghathian10, Lise Gundersen11, Christina Wellendorph Christensen11, Jette Bangsberg11, Torben Tranborg Jensen12, Vibeke Muff Sørensen12, Thilde Ellingsgaard12, Raluca Datcu13, John Eugenio Coia13, Uffe Bodtger2,14 and Jens Ulrik Staehr Jensen1,15

Abstract

Background: Pseudomonas aeruginosa infection is seen in chronic pulmonary disease and is associated with exacerbations and poor long-term prognosis. However, evidence-based guidelines for the management and treatment of P. aeruginosa infection in chronic, non-cystic fibrosis (CF) pulmonary disease are lacking. The aim of this study is to investigate whether targeted antibiotic treatment against P. aeruginosa can reduce exacerbations and mortality in patients with chronic obstructive pulmonary disease (COPD), non-CF bronchiectasis, and asthma.
Methods: This study is an ongoing multicenter, randomized, controlled, open-label trial. A total of 150 patients with COPD, non-CF bronchiectasis or asthma, and *P. aeruginosa*-positive lower respiratory tract samples will be randomly assigned with a 1:1 ratio to either no antibiotic treatment or anti-pseudomonal antibiotic treatment with intravenous beta-lactam and oral ciprofloxacin for 14 days. The primary outcome, analyzed with two co-primary endpoints, is (i) time to prednisolone and/or antibiotic requiring exacerbation or death, in the primary or secondary health sector, within days 20–365 from study allocation and (ii) days alive and without exacerbation within days 20–365 from the study allocation.

Discussion: This trial will determine whether targeted antibiotics can benefit future patients with chronic, non-CF pulmonary disease and *P. aeruginosa* infection in terms of reduced morbidity and mortality, thus optimizing therapeutic approaches in this large group of chronic patients.

Trial registration: ClinicalTrials.gov NCT03262142. Registered on August 25, 2017.

Keywords: Chronic obstructive pulmonary disease, Non-CF bronchiectasis, Asthma, *Pseudomonas aeruginosa*, Antibiotics, Randomized controlled trial

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**Administrative information**

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| Name and contact information for the trial sponsor (5b) | Jens Ulrik Staehr Jensen, MD, PhD, Professor jens.ulrik.jensen@regionh.dk |
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**Introduction**

**Background and rationale**

COPD, non-CF bronchiectasis, and asthma are common chronic pulmonary diseases and important causes of death and disability worldwide [1–3]. These diseases are characterized by shared common symptoms such as productive cough and susceptibility to recurrent exacerbations that are often associated with infections. These exacerbations lead to accelerated loss of lung function, reduced quality of life, and increased morbidity and mortality and have major socio-economic consequences [4–6].

Compared to COPD and asthma, which both are diagnosed on the basis of airflow obstruction and therefore are physiological diagnoses, bronchiectasis is a structural diagnosis with the presence of permanent airway dilatation on radiological imaging [4, 6, 7]. However, the co-existence of bronchiectasis and asthma or COPD is common [8].

*Pseudomonas aeruginosa* [9] has been reported to be present in the lower airways in up to 20% of patients with COPD [10–12] and is frequently detected in patients with non-CF bronchiectasis [13]. The bacterium has also been observed in patients with asthma [14]. Nevertheless, the influence of *P. aeruginosa* on the progression of these diseases is far from fully elucidated. The bacterium is seen primarily in advanced diseases with severely impaired lung function [13–15] and is associated with increased frequency of exacerbation, prolonged hospitalization, and poor long-term prognosis with increased mortality rates compared to *P. aeruginosa*-negative patients [16].

However, since an impairment of lung function itself is a strong predictor of morbidity and mortality, it is not certain whether infection with *P. aeruginosa* is secondary to lung function impairment or whether the presence of *P. aeruginosa* itself leads to pulmonary tissue inflammation and remodeling, impaired lung function, and overall poor prognosis.

Thus, the role of *P. aeruginosa* on the progression of COPD, non-CF bronchiectasis, and asthma is poorly characterized. To date, evidence-based guidelines for the management and treatment of *P. aeruginosa* infection are lacking, and the management of *P. aeruginosa*
is often based on expert consensus and studies of other chronic lung diseases, including CF. In CF, *P. aeruginosa* is a leading cause of morbidity and early death with evidence of improved clinical outcomes through aggressive and targeted antibiotic treatment [17]. In Denmark, the first treatment choice for clinically treatment-requiring *P. aeruginosa* infection is usually 10–14 days of antibiotic combination therapy with intravenous piperacillin/tazobactam and oral ciprofloxacin [18].

The SPIRIT reporting guidelines have been used for the present protocol [18].

**Objectives**

With this randomized controlled trial, we aim to increase the understanding of the clinical significance and consequences of *P. aeruginosa* infection in patients with chronic, non-CF pulmonary disease.

The main purpose is to investigate if targeted, antibiotic treatment of *P. aeruginosa* improves the disease prognosis in patients with exacerbation of COPD, non-CF bronchiectasis or asthma, and *P. aeruginosa*-positive sputum/bronchoalveolar lavage (BAL) sample.

Our hypothesis is that antipseudomonal antibiotics given for 14 days increase the number of days alive and out of hospital for 1 year.

**Trial design**

The study is a multicenter, randomized, controlled, open-label trial in patients with COPD, non-CF bronchiectasis, or asthma with current *P. aeruginosa*-positive lower respiratory tract sample. Study participants are followed for 1 year.

**Methods: participants, interventions, and outcomes**

**Study setting**

Participants are recruited by investigators who are employed at the participating pulmonary departments in Denmark. In total, 150 patients are expected to be included in the study (Fig. 1). The sample size is calculated based on a superiority framework with a two-sided 5% significance level 80% power and the following estimates and indicative figures. They are enrolled in seven different sites: Sydvestjysk Hospital, Aarhus University Hospital, Bispebjerg Hospital, Herlev and Gentofte Hospital, Hvidovre Hospital, Nordsjællansk Hospital, and Odense University Hospital.

**Eligibility criteria**

Patients with COPD, non-CF bronchiectasis or asthma, and current *P. aeruginosa*-positive lower respiratory tract samples (i.e., sputum, tracheal secretion, bronchial secretion, and bronchial alveolar lavage) from the participating study centers are considered for study enrollment. Patients are invited to participate in the trial if they fulfill the following inclusion and exclusion criteria.

The following are the inclusion criteria:

1. *P. aeruginosa*-positive lower respiratory tract sample
2. COPD, non-CF bronchiectasis, or asthma verified by a respiratory specialist based on clinical assessment and additional tests:
   - (a) COPD: spirometry
   - (b) Asthma: reversibility
   - (c) Non-CF bronchiectasis: high-resolution computed tomography scan
3. Minimum of two previous exacerbations, or one previous hospitalization-requiring or emergency room-demanding exacerbation, with the treatment of systemic prednisolone and/or antibiotics within the last 12 months
4. Written informed consent

The following are the exclusion criteria:

1. Immunomodulating treatment (except ≤ 10 mg prednisolone/day)
2. Men < 40 years
3. Women ≤ 55 years
4. Non-menopausal women > 55 years (i.e., menstruation within the last 12 months)
5. Life expectancy < 90 days
6. Severe mental illness or severe linguistic problem
7. Known drug allergy to (i) fluoroquinolone and (ii) both penicillin/piperacillin, cephalosporin, and carbapenems
8. ≥ 2 previous eradication attempts of *P. aeruginosa* within the last 12 months or 1 completed within the last 14 days
9. Patients who clinically require hospitalization and anti-pseudomonal antibiotic treatment. This exclusion criterion must be discussed with the coordinating investigator before the final decision on exclusion is made (Fig. 2).

**Project management**

The study is managed by the coordinating investigator (Josefin Eklöf). The daily project management is carried out by sub-investigators, consisting of health professionals from the departments involved in the trial. A filled patient informed consent form is required from all participants in the study and must be signed by both the study participant and the informing investigator. A
Fig. 1 Flow diagram for the Targeted AntiBiotics for COPD trial: primary outcome overview

Patients allocated to the intervention group:
Intravenous beta-lactam and oral ciprofloxacin for 14 days

Exclusion criteria:
- Immunomodulating treatment
- Men < 40 years
- Women ≤ 55 years
- Non-menopausal women > 55 years
- Life expectancy < 90 days
- Severe mental illness or severe linguistic problem
- Known drug allergy to i) fluoroquinolone and ii) both penicillin/piperacillin, cephalosporin, and carbapenems
- ≥ 2 previous eradication attempts of *P. aeruginosa* within the last 12 months, or 1 completed within the last 14 days
- Patients who clinically require hospitalization and anti-pseudomonal antibiotic treatment. This exclusion criterion must be discussed with the coordinating investigator before a final decision on exclusion is made.
- Declined to participate

Randomization 1:1 (open-label design)

Patients allocated to the intervention group: intravenous beta-lactam and oral ciprofloxacin for 14 days

Patients allocated to control group:
No antibiotic intervention

Outcome measurements after 365 days

Primary outcome
- Time to prednisolone and/or antibiotic requiring exacerbation or death, in primary or secondary health care sector from day 20 to day 365 from randomization
- Days alive and without exacerbation from day 20 to day 365 from randomization

Analysed
separate consent form is obtained from the participants to store the whole blood and serum in a biobank.

**Intervention**
Patients will be randomly assigned 1:1 to either of the following:

1. Control group: no antibiotic treatment
2. Intervention group: antibiotic treatment

The first choice of antibiotic treatment is dual therapy with intravenous piperacillin/tazobactam 4/0.5 g, 4 times daily, and oral ciprofloxacin 500 mg, 2 times daily for 14 days. In case of penicillin allergy or antibiotic resistance, intravenous piperacillin/tazobactam is replaced by intravenous ceftazidime or meropenem. In case of fluoroquinolone allergy or antibiotic resistance, intravenous beta-lactam is given as monotherapy.

**Criteria for discontinuing or modifying allocated interventions**
Sub-investigators may interrupt the intervention at any time if there is a medical justification, safety risk, or a requirement from the authorities. If the investigator deems it necessary, he or she may exclude the participant from the trial. However, in general, no subject should be removed from the study for a protocol violation prior to confirmation by the coordinating investigator. In addition, a study participant can at any time withdraw from the study without the needed explanation.

**Strategies to improve adherence to interventions**
The participants are well-informed at randomization about the importance of following our guidance. The patients, who received treatment, are hospitalized in order to give them intravenous antibiotics. This ensures that the patients take their medicine at the right time.

**Outcomes**
The primary outcomes, analyzed with two co-primary endpoints, are as follows:

- Time to prednisolone and/or antibiotic requiring exacerbation or death, in primary or secondary health care sectors from day 20 to day 365 from randomization
- Days alive and without exacerbation from day 20 to day 365 from randomization

The secondary endpoints are as follows:

- Death within 365 days from randomization
- Number of re-admissions with pulmonary exacerbation within 365 days from randomization
- Number of days with non-invasive ventilation or invasive ventilation within 90 days from randomization
- Microbiological cure*
- Clinical cure day 14**
- Change in COPD Assessment Test (CAT) from randomization to day 90
- Change in body mass index (BMI) from randomization to day 90
- Change in forced expiratory volume in the first second (FEV₁) from randomization to day 90
- Decrease of ≥ 200 ml in FEV₁ from randomization to day 365

*Microbiological cure: P. aeruginosa-negative sputum culture until day 90. No microbiological cure: positive sputum culture with clonally same P. aeruginosa strain ≤ day 90. Re-infection: positive sputum sample with non-clonally same P. aeruginosa strain ≤ day 90.

**Clinical cure: improvement of clinical signs and symptoms related to P. aeruginosa before or on day 14. Clinical failure: persistent or worsening of clinical signs and symptoms related to P. aeruginosa before or on day 14.

Sample size
Data will be analyzed using intention-to-treat (ITT) principles, including all the data available, regardless of whether the intervention was completed or not. The aim of the ITT analysis is also to provide unbiased comparisons among the two study groups and to avoid the effects of potential study dropouts and protocol deviations.

Patients in the control group will be compared to patients in the intervention group. We will use Fisher’s exact test and chi-squared test for dichotomous outcomes and T-test for continuous outcomes. The timed dichotomous outcomes will be visualized through Kaplan-Meier plots. Furthermore, adjusted analyses will be performed with a multivariable Cox proportional hazards model, adjusting for baseline variables and calculating hazard ratios. Data will be processed and analyzed in SAS and graphs are generated in Microsoft Excel and other graph programs.

Assignments of interventions: allocation
Sequence generation
Pre-stratified block randomization with blocks of varying and blinded size is applied to ensure equal distribution of patients in the study groups based on site (pulmonary department) and age (above or below 70 years of age). The allocation sequence is generated by Pradeesh Sivapalan, with instructions from the scientific sponsor of the trial. The final randomization is conducted using a secure web application (REDCap;
where inclusion and exclusion criteria are required to be filled out correctly in order to randomize a study participant. Each investigator had access to allocation and randomization through REDCap.

**Assignment of interventions: blinding**

Our study is not blinded. It is an open-label trial. Home treatment with antibiotics was not feasible due to local restrictions at the participating study sites. Thus, attempting blinding would demand hospital admission of control patients to receive placebo infusions. Sites expressed that they would not participate with such a design, so the Steering Committee found it non-feasible. Moreover, we anticipated that a blinded placebo intervention would be a major barrier to recruiting patients.

**Data collection and management**

**Plans for assessment and collection of outcomes**

Data is collected in case report forms, specific to each participant, where demographic data, current and past illnesses, health status, hospitalizations, clinical parameters, study results, and prescribed medication are recorded. Follow-up visits are scheduled after 14, 30, 60, 90, and 365 days. The study overview is summarized in Table 1. Antibiotic therapy is administered according to standard practice, including routine adjustment based on co-medication, kidney function, age, etc. The administration of antibiotics is registered using the standard electronic medicine module in the department. High-resolution computed tomography is performed at the start of the study to identify the underlying presence of emphysema and bronchiectasis.

**Plans to promote participant retention and complete follow-up**

At the inclusion date, every patient is well-informed about the number of visits, so the patient knows exactly what she/he is going into. The patient and investigator agree on the next visit date at every follow-up visit.

**Confidentiality**

The collection of data and storage is in compliance with the Good Clinical Practice (GCP) guidelines and is regularly monitored by local GCP units. Data is stored in a double-locked locker, which only sub-, coordinating, and principal investigators have access to.

**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use**

A research biobank is set up with whole blood from the time of randomization and serum, EDTA plasma, and citrate plasma from the time of randomization and day

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**Table 1  SPIRIT figure illustrating the TARGET ABC study overview**

| Study period | Enrollment | Intervention | Follow-up |
|--------------|------------|--------------|-----------|
| Visit number | 1          | 0–14         | 14        |
| Study day    | 0          | 30           | 365       |

**Enrollment**

- Eligibility screening
- Informed consent
- Randomization

**Study arm**

- Intervention group: antibiotic treatment, in-hospital
- Control group: no antibiotic treatment, not hospitalized

**Data collection and examinations**

- Demographics
- Sputum sample
- Body mass index (BMI)
- Medical Research Council Dyspnea Scale (MRC)
- COPD Assessment Test (CAT)
- Spirometry
- Vital parameters
- High-resolution computed tomography (HRCT)
- Blood samples

| Data collection and examinations | X | X | X | X | X | X | X | X |
|----------------------------------|---|---|---|---|---|---|---|---|
| Demographics                     | X |   |   |   |   |   |   |   |
| Sputum sample                    | X |   |   |   |   |   |   |   |
| Body mass index (BMI)            | X |   |   |   |   |   |   |   |
| Medical Research Council Dyspnea Scale (MRC) | X |   |   |   |   |   |   |   |
| COPD Assessment Test (CAT)       | X |   |   |   |   |   |   |   |
| Spirometry                       | X |   |   |   |   |   |   |   |
| Vital parameters                 | X |   |   |   |   |   |   |   |
| High-resolution computed tomography (HRCT) | X |   |   |   |   |   |   |   |
| Blood samples                    | X |   |   |   |   |   |   |   |
14 for future unspecified research. Sputum samples are longitudinally collected from the time of randomization and days 14, 30, 60, 90, and 365 for future microbiome and genetic analyses.

Statistical methods
Statistical methods for primary and secondary outcomes
A detailed statistical analysis plan is made and is attached.

Oversight and monitoring
Composition of the coordinating center and trial steering committee
The coordinating center is Gentofte Hospital, where the principal investigator is located. The seven sites are weekly in contact with the coordinating investigator through online meetings. The trial steering committee is driven by professors and senior consultants from different sites. The trial steering committee is invited to a meeting twice a year. It is the coordinating site that decides if more meetings are needed.

Composition of the data monitoring committee, its role, and reporting structure
The data monitoring committee, which is also known as the GCP units, closely monitors every site (several times per year and per site). Their role is to check every included patient at every site and to see if the protocol has been followed, and the registrations are correctly made. After a GCP unit has checked the site, a report is then made and sent to the sponsor, the coordinating investigator, and the sub-investigators responsible for the site.

Adverse event reporting and harms
The occurrence of adverse events and adverse effects will be registered and reported to the Danish Medicines Agency at the end of the trial. Moreover, any serious adverse events and adverse effects are reported annually in a safety report to the Danish Medicines Agency.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)
If any changes are made, every site will be informed promptly by mail and through Trial Setting Committee meetings.

Dissemination plans
The data from the TARGET ABC trial will be available once the study is completed. All results will be published in scientific contexts, including international journals, regardless of whether they are positive, negative, or inconclusive, and with authorship according to the Vancouver recommendations.

Discussion
P. aeruginosa represents a potentially significant cause of exacerbation and mortality in patients with COPD, non-CF bronchiectasis, and asthma. However, the influence of P. aeruginosa on the progression of these chronic pulmonary diseases is poorly characterized, and to date, evidence-based guidelines for the management and treatment of P. aeruginosa infection are lacking. With this trial, we aim to increase the understanding of the clinical significance and consequences of P. aeruginosa infection in patients with non-CF chronic pulmonary disease.

Using a multicenter, randomized, controlled design, we will allocate 150 patients with COPD, non-CF bronchiectasis, or asthma and a current P. aeruginosa-positive sputum/BAL sample evenly to either no antibiotic treatment or 14 days of dual anti-pseudomonal antibiotic therapy. Thus, we seek to create evidence at level 1B to determine whether targeted antibiotic treatment against P. aeruginosa can improve the prognostic outcome in this large group of patients with chronic pulmonary disease.

The trial is carried out according to the Declaration of Helsinki and in accordance with the Good Clinical Practice guidelines. The study methods and statistical analyses have been carefully considered, and it is our strongest belief that the trial will contribute essential knowledge that will help clinicians to guide future patients towards evidence-based and improved treatment strategies, ultimately improving the disease prognosis.

Trial status
Patient recruitment commenced in October 2017 and is ongoing.

Abbreviations
BAL: Bronchoalveolar lavage; BMI: Body mass index; CAT: COPD assessment test; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; FEV1: Forced expiratory volume in the first second; GCP: Good Clinical Practice; HRCT: High-resolution computed tomography; MRC: Medical Research Council; PAi: Pseudomonas aeruginosa incidence.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13063-022-06720-z.

Additional file 1.
Additional file 2.
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Authors’ contributions

JE and IAA formulated the study design and drafted the first version of the protocol in collaboration with JUSJ. The protocol has been critically revised and approved by the Trial Steering Committee of COPTRIN. JE and IAA applied for approvals from the Danish National Committee on Health Research Ethics, Danish Medicines Agency, and the Danish Data Protection Agency and registered the trial at ClinicalTrials.org. JE and JUSJ applied for financial grants. The authors read and approved the final manuscript.

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Availability of data and materials

The data from the TARGET ABC study will be available once the study is completed. Applications for data require a formal application and will be decided on by the board of the TARGET ABC study group.

Declarations

Ethics approval and consent to participate

The study will be carried out to include the protection of human participants according to the Helsinki Declaration and in accordance with the Good Clinical Practice guidelines. A completed patient informed consent form is required from all participants in the study and must be signed by both the study participant and the informing investigator. A separate consent form is given to the participants to store the whole blood and serum. The study has been approved by the Danish National Committee on Health Research Ethics (H-15019949) and the Danish Medicines Agency (EudraCT. 2015-003399-58).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests. Pradeesh Sivapalan reports personal fees from Boehringer Ingelheim, outside the submitted work.

Author details

1. Department of Internal Medicine, Section of Respiratory Medicine, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark.
2. Department of Internal Medicine, Zealand Hospital, University of Copenhagen, Roskilde, Denmark.
3. Department of Respiratory and Infectious Diseases, Frederikssund and Hillerod Hospital, University of Copenhagen, Copenhagen, Denmark.
4. Department of Respiratory Medicine, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark.
5. Department of Respiratory Medicine, Aalborg University Hospital, University of Aalborg, Aalborg, Denmark.
6. Department of Clinical Microbiology, Aalborg University Hospital, University of Aalborg, Aalborg, Denmark.
7. Department of Respiratory Medicine, Odense University Hospital, University of Southern Denmark, Odense, Denmark.
8. Department of Clinical Microbiology, Odense University Hospital, University of Southern Denmark, Odense, Denmark.
9. Department of Clinical Microbiology, Aalborg University Hospital, University of Copenhagen, Copenhagen, Denmark.
10. Department of Clinical Microbiology, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark.
11. Department of Internal Medicine, Section of Respiratory Medicine, Hospital of South West Jutland, Esbjerg, Denmark.
12. Department of Clinical Microbiology, Hospital of South West Jutland, Esbjerg, Denmark.
13. Department of Respiratory Medicine, Naestved Hospital, University of Southern Denmark, Naestved, Denmark.
14. Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
15. PERSIMUNE: Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

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References

1. Sonano JR, Abajobir AA, Abate KH, Abers SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691–706.
2. Henké E, Chan B, Curtis JR, Aksamit TR, Daley CL, Winthrop KL. Characteristics and health-care utilization history of patients with bronchiectasis in US Medicare enrollees with prescription drug plans, 2006 to 2014. Chest. 2018;154(8):1311–20.
3. Jacobs DM, Ochs-Balcom HM, Noyes K, Zhao J, Leung WY, Pu CY, et al. Impact of Pseudomonas aeruginosa isolation on mortality and outcomes in an outpatient chronic obstructive pulmonary disease cohort. Open Forum Infect Dis. 2020.
4. GOLD. Global initiative for Chronic Obstructive Lung Disease 2020 Report: pocket guide to COPD diagnosis, management, and prevention, a guide for health care professionals. GOLD 2020. 2020. https://goldcopd.org/wpcontent/uploads/2020/03/GOLD-2020-POCKET-GUIDE-ver1.0_FINAL-WM.pdf.
5. Asthma G initiative for. Global Strategy Asthma 2019. Glob Stratger Asthma Manag Prev. 2019. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7065541/.
6. Global Initiative for Asthma: 2019 GINA Report. Global strategy for asthma management and prevention. https://ginasthma.org/wpcontent/uploads/2019/06/GINA-2019-main-report-June-2019-vrms.pdf.
7. Polverino E, Gromimene PC, McDonnell MJ, Alberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017. https://erj.ersjournals.com/content/50/3/1700629.
8. Quint JK, Millett ERC, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J. 2016;47(1):186–93. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4982534/pdf/emss-69429.pdf.
9. Tuon FF, Dansar LR, Suss PH, Tasca Ribeiro VS. Pathogenesis of the Pseudomonas aeruginosa biofilm: a review. Pathogens. 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8950567/.
10. Garcia-Vidal C, Almagro P, Romani V, Rodriguez-Caballera M, Cuchi E, Canales L, et al. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J. 2009. https://erj.ersjournals.com/content/34/5/1072.long.
11. Groenewegen KH, Wouters EFM. Bacterial infections in patients requiring admission for an acute exacerbation of COPD; a 1-year prospective study. Respir Med. 2003. https://www.sciencedirect.com/science/article/pii/S095461110300026X?via%3Dihub.
12. Patel IS, Seemungal TAR, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax. 2002. https://thorax.bmj.com/content/57/9/759.long.
13. Borekci S, Halis AN, Aygun G MB. Bacterial colonization and associated factors in patients with bronchiectasis. Ann Thorac Med. 2016;11(1):55–9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC478616/.
14. Holm JPY, Hilberg O, Noerkov-Lautsen N, Bendstrup E. Pseudomonas aeruginosa in patients without cystic fibrosis is strongly associated with chronic obstructive lung disease. Dan Med J. 2013. https://ugekskrift.dk/dm/pseudomonas-aeruginosa-patients-without-cystic-fibrosis-strongly-associatedwithchronic-obstructive-lung.
15. Miravitles M. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Chest J. 1999;116(1):40–6. https://www.sciencedirect.com/science/article/pii/S0012369215381496?via%3Dihub, https://reader.sciencedirect.com/reader/sd/pii/S0012369215381496?token=92904FAED6D5ADD9EDE8202950576
16. Sangtam N, Haorongbam S, Silpa K, Singh YP. Bronchiectasis in patients with chronic obstructive pulmonary disease in a tertiary care center in North-East India. Int J Adv Med. 2020. https://www.ijmedicine.com/index.php/ijam/article/view/2218.

17. Folkesson A, Jelsbak L, Yang L, Johansen HK, Ciofu O, Hoiby N, et al. Adaptation of Pseudomonas aeruginosa to the cystic fibrosis airway: an evolutionary perspective. Nat Rev Microbiol. 2012;10(12):841–51. https://www.nature.com/articles/nrmicro2907.

18. Guidelines for antibiotic treatment of acute pulmonary infection with Pseudomonas aeruginosa in COPD. Denmark: Capital Region; https://lungemedicine.dk/wp-content/uploads/2022/01/DLS_DSI_Pneumonia_2021_110122_CFF.pdf.

19. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index an international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576–85. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3977711/.

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