

The AIR project - Advance care planning Individualised approach and Research project

- *A randomised controlled trial.*

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Background

Chronic obstructive pulmonary disease (COPD) is a common cause of death, and the burden of symptoms may be tremendous in the last period of life. Furthermore, patients with severe COPD often have several co-morbidities. There is an urgent need for palliative intervention targeting patients and informal caregivers. Palliative care is defined as an intervention to improve quality of life for patients and informal caregivers facing life-threatening disease. The Chronic Care Model states that the best way to improve outcomes is by having an informed and active patient and a prepared and proactive health care team. GOLD 2017 and the Danish Respiratory Society recommend Advance Care Planning as a mean to inform and activate patients. The Danish Board of Health recommends use of case managers nurses to follow the COPD patients across the disease trajectory.

Method

We will investigate the effect of a palliative approach in the out-patient management of patients with COPD.

Patients:

- COPD diagnosis based on spirometry
- 2 or more admissions for acute exacerbation of COPD within the last 12 months
- - CAT > 19

Design

Randomised control trial. We will randomise a total of 90 patients 1:1 to either palliative intervention or standard care.

The intervention group will receive follow up in a newly established outpatient clinic for COPD in the palliative ward and the control group will receive standard follow up in the respiratory out-patient clinic.

Outcome

The primary outcome is psychological wellbeing measured by hospital anxiety and depression scale questionnaire HADS at 6 months, secondary outcomes are symptoms registered via patient reported outcomes and frequency of out-patients contacts and hospital admissions at 6 months.

Perspectives

The AIR trial will investigate the effect of a team-based palliative, patient and informal caregiver centred approach on quality of life. If results are positive, the findings will potentially impact both, nationally and internationally, the way we, as a health care system, care for patients with advanced COPD.

Background

Chronic obstructive pulmonary disease (COPD) is a common disease, the fourth leading cause of death worldwide¹. COPD is a disease with substantial co-morbidity, and in the severe stages it could be considered a multi-morbid disease rather than a lung disease². Apart from having a substantial impact on quality of life (QOL) at the individual level, patients with COPD also inflict a high and increasing, economic challenge to society. Patients with COPD spend about three times as much money on medication compared to the average citizen in Denmark³. COPD has a symptom burden equal to or higher than patients with lung cancer⁴, but patients with COPD often live longer and receive far less support in their last years of life than patients with lung cancer⁵.

There is both national and international acceptance of the concept that palliative care should be available to patients with severe symptoms in all stages of disease and not only to the dying^{1,6,7}. The different and unpredictable disease trajectories of COPD compared to that of cancer makes it important to consider which model for palliative care to introduce in COPD^{5,8}.

Where current clinical goals in COPD treatment, defined by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), is to reduce symptom burden and reduce the risk of exacerbations¹, the goal of palliative care defined by The World Health Organization (WHO) is to increase overall QOL for patients and their caregivers⁹.

Palliation

According to the WHO, palliative care is defined as an approach that improves QOL of patients and their caregivers facing the problems associated with life-threatening illness through the prevention and relief of suffering by means of early identification and assessment and treatment of pain and other problems, physical, psychosocial and spiritual⁹. To address this, it is considered crucial that health care professionals have a multidisciplinary, holistic and patient-centred approach, with the aim of achieving a shared understanding of patients' values and goals of care. This shared understanding implies communication of high quality^{10,11}.

For the palliative effort to have success it must meet the total and often complex symptom burden that a life-threatening illness causes. This is best achieved through a multidisciplinary team (MDT), defined as the presence of more than two healthcare providers from different professions in the team¹².

Palliative medicine is a team-based symptomatic treatment with both pharmacological and non-pharmacological means and the primary goal is improvement in QOL¹³. In a study of patients with lung cancer it has been shown, that patients receiving early palliative care had less disease modifying treatment at the end of life but longer survival and better QOL compared with patients receiving standard care¹⁴. Furthermore, an improvement in informal caregivers psychological symptoms was seen¹⁵. Both international and national COPD guidelines recommend palliative care incorporated into the treatment strategy for COPD^{1,16}

American Thoracic Society (ATS) and European Respiratory Society (ERS) has in a recommendation for future research highlighted the need for research in COPD and palliation¹⁷. The reason is that although there is a general agreement about the need for a patient- and caregiver focused symptomatic treatment, it is still unclear how this should be organized in practice.

The burden of COPD on the health care system is increasing, and consequently a shift from hospital care to more home care seems inevitable¹⁸. This shift in care organisation rely to a greater extent on informal

caregivers¹⁸, but at present not enough is known about how the informal caregivers will handle this difficult situation. A study of palliative care to patients with cancer has revealed an increase in morbidity among informal caregivers¹⁹, which appears to have impact on healthcare utilization months before the loss of their loved one and for years after²⁰. The recognition of burden for informal caregivers^{18,21,22} and the informal caregivers' involvement is an essential part of the palliative approach⁶, and once the patient dies, the needs of the bereaved relatives should be addressed by a palliative healthcare team as well^{20,23}.

Advance Care Planning

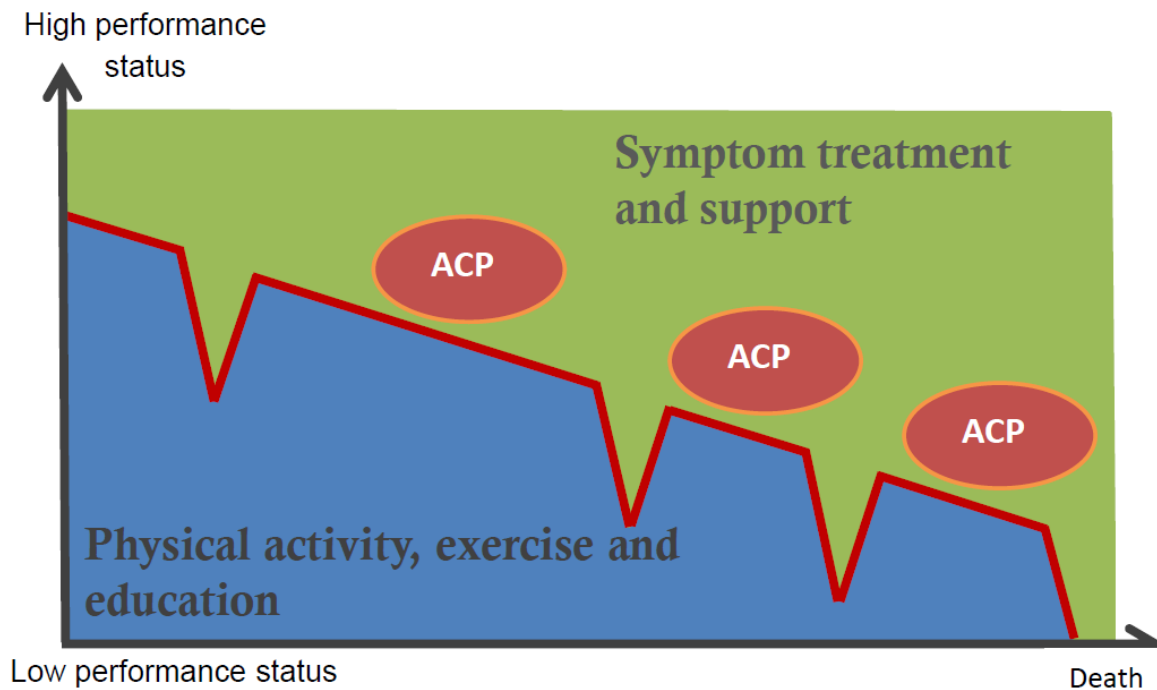
Patients and informal caregivers should be informed about the disease, possible symptoms and prognosis. It is important that this information is delivered in a respectful manner and with an understanding of the patient's needs and capabilities. In addition, it is essential to recognize that such needs can be different between patient and the informal caregiver²⁴. Both Danish and international studies show that the communication and information need develop and change over time^{24,25}.

In order to achieve best possible QOL, despite life-threatening illness, it is important that the treatment is directed towards the symptoms and problems experienced by patients and the informal caregivers. In studies it has been shown that even treatable symptoms are missed, if a systematic and patient centred approach is not used^{26,27}.

Advance care planning (ACP) is a communication process of discussing and recording patients' preferences for future care, aiming to guide healthcare decisions at the end of life. The ACP is an opportunity to discuss a realistic assessment of disease stage, treatment options and prognosis, which is of major importance for patients and their caregivers¹⁰. ACP is increasingly recommended for patients with COPD^{1,7,28}, but in Denmark it is not yet a standard part of out-patient follow-up.

The Danish Respiratory Society has made a Danish manual for ACP conversations and defined ACP as: *“A communication process between healthcare team, patient and informal caregiver focusing on life with disease and symptoms. In this process, issues such as the treatment level and end of life care can be discussed, but the ACP is not limited to these topics”*²⁹. The manual is structured as an inspirational guide and framework for an ACP conversation.

Personalized management



Support includes psychological, social and existential support that may continue into care for informal care giver after the patients death.
Routine and early Advance Care Planning (ACP) gives the ability to adjust treatment goals depending of patient values and disease trajectory.

Figure 1 The Progression development from the focus on physical activity, which is gradually replaced by a more supportive care approach. The figure is from The Danish Respiratory Society's report, and it describes the overall understanding of a palliative approach and the change of such during the disease trajectory – translated from Danish⁷.

CASE MANAGER

To secure and maintain a continuous contact between healthcare professionals and patients, the Danish Board of Health recommends a case-manager based concept thus: *"The purpose of case management is to ensure intensified, personal restated support for patients with severe and complex needs. This includes both acute and stable phases of the disease"*³⁰. Such case manager driven systems are develop across Denmark³¹ but little is known about consequences and effect.

To support the patient in health-promoting behaviours changes and early onset of treatment of exacerbation it is important to have a close contact between the patient and case-manager. Phone contact is a good screening contact, and a Canadian study showed that, on average, a case-manager has 12 phone contacts per year per patient and about 2 home visits³². The goal of such a system is not to reduce the number of contacts to the health care system but to reduce acute admissions and irreversible deterioration of the health condition. The model requires highly trained case-managers, easy accessibility and frequent contact³³. In the Canadian system, the case-manager nurses each cared for 70 -100 patients³². Studies

suggest that a structure with supported self-management and case-manger can reduce utilization of health care services and improve health status^{12,34,35}. The goal of the case-manager and the MDT is to establish a “therapeutic alliance” with the patient and informal caregivers and through shared decision making and close follow-ups increase patient quality of life and medical adherence³⁶.

The objective of AIR is:

To test a palliative out-patient care structure for highly symptomatic patients with advanced COPD based on ACP, MDT and a case-manager driven system with individualised support to patients and informal caregivers versus usual care.

Hypothesis

The palliative approach will, within 6 months, reduce emotional distress, as measured by the Hospital Anxiety and Depression Scale (HADS) questionnaire in patients with severe COPD and a large symptom-burden compared to usual care.

Methods

This investigator-initiated study is a randomized controlled trial study (RCT) with two study arms. We will perform online randomization 1:1. We plan to recruit 90 patients into the trial (see below). The primary endpoint – significant changes/reduction in HADS – will be assessed after 6 months. Secondary endpoints include following of symptom- and disease development over 6 months to see whether a possible reduction in psychological distress translates into a decrease in healthcare contacts.

After 45 patients have completed an interim analysis will be performed by a Data and Safety Monitoring Board. This is to investigate whether the number of patients lost to project, either dead or drop out, will influence total number of patients needed in the project. Likewise, missing values in the form of uneven number of deaths in the two groups may result in a need for an increased total number of participants.

Patients who meet the inclusion criteria, see below, will be asked to participate and if willing, they will be contacted by the study personal.

The randomisation will be performed by study personnel not involved in screening for eligible participants. When the patient is seen in one of the outpatient clinics or at discharge from a pulmonary ward and found to fulfil the inclusion criteria, they will give oral consent and be invited to a baseline screening and randomisation. At this second appointment the patient will give written consent and undergo randomisation. The intervention is based in a newly established non-malign palliative outpatient clinic in the palliative unit at Herlev University Hospital. The control group will receive usual care in Herlev/Gentofte Respiratory department outpatient clinics, including offering of pulmonary rehabilitation. If randomised to intervention, any participation in standardised rehabilitation in the AIR group will be performed by the respiratory department as described in national guidelines.

Questionnaires:

1. **Hospital Anxiety and Depression Scale** (primary outcome). This 14 items questionnaire is used in both COPD³⁷⁻³⁹ and palliative research¹⁵ as a tool of measuring emotionally distress. It is divided into two subscales; anxiety and depression. In the AIR study we will use HADS total. The minimal clinically important difference is validated for COPD research⁴⁰. It is not a diagnostic tool but an instrument to assess the severity of symptoms of mood disorders. The HADS include two domains, one for anxiety and one for depression, each containing 7 questions.
2. **EORTC QLQ-C15-PAL**. A 15-item symptom screening schedule made by the European Organisation for Research and Treatment of Cancer (EORTC). This questionnaire is validated to identify and grade the most common symptoms in patients assigned to highly specialized, oncological palliative treatment. The questionnaire assesses physical symptoms such as pain, shortness of breath, nausea, constipation etc. Furthermore, psychological issues like anxiety, depression and QO- and self-reported physical activity are also determined. This questionnaire measures general end of life symptoms.
3. **COPD Assessment Test (CAT)**: Questionnaire, which measures the specific symptom burden of COPD asking 8 common COPD symptoms. The 8 items can be answered with a number between 0 and 5, where 0 is best. A CAT score of ≥ 10 is considered medium symptom burden and above 20 is high symptom burden⁴¹.
4. **Life-Space Assessment (LSA)** is a questionnaire with the intension to give an impression of the patient's activity level⁴². The questionnaire assesses to which extent the patient leaves home and the degree to which the patient feels independent. The questionnaire covers up to 5 different areas such as "have you been in other rooms than your bedroom? Have you been outside your home? Been in the neighborhood? Been around your city? Have you been outside your town? LSA is an American test, which in 2016 was translated and validated into Danish by physiotherapist researchers from Hvidovre Hospital. A change in LSA is significantly associated with increased risk of 6 month mortality⁴³.

Outcomes

Primary outcome at 6 months

- Change in HADS [Mann-Whitney or T-test depending on normality assessment]/ decrease of at least 1,5 points in HADS [Chi-square for equal proportions].

Secondary outcomes at 6 months

• *In case of death before 6 month follow up last recorded HADS score. If only baseline data is recorded If only baseline data is found, set development in HADS to + 1.5 for use in statistical analysis.*

- Change in EORTC QLQ-C15-PAL score
- Change in CAT score
- Change in LSA

- Adherence measured by inhaled medicine bought at the pharmacy
- Proportion of patients who complete pulmonary rehabilitation
- Use of health care services in the study period of 2,5 years or death
 - Visits to the out-patient clinic in the study period
 - Other contacts e.g .telephone or letter/e-mail
 - Hospitalization frequency
 - Readmission measured as hospitalization within 30 days since last hospitalization
 - Hospitalization length of stay
 - Number of contacts with general practitioner
- All-cause mortality and respiratory associated death

All patients will be assessed with questionnaires at inclusion (baseline), after 3 months and 6 months. The data collection after baseline will be done by phone call from study personal (not part of the treatment team) to the patients. This to ensure that the patient understand the questions and to reduce influence of caregiver in the results.

Annual data on smoking, rehabilitation, MRC, number of admissions are as a national standard collected to a national database (DrKOL).

The secondary endpoints will be collected from electronic journal and national healthcare databases.

Qualitative studies

We will include qualitative studies on central subject of AIR. These questions are

1. ACP conversations
2. The referral from the normal pulmonary ward to palliative care
3. The informal caregiver role in AIR compared to usual care

Inclusion and exclusion criteria

Inclusion

- Diagnosis of COPD by spirometry
- Patients followed in Herlev and Gentofte hospitals' respiratory out-patient-clinics or admitted to Herlev or Gentofte hospital for acute exacerbation
- 2 or more admissions for acute exacerbation of COPD within the last 12 months
- CAT > 19
- Cognitive and linguistic able to understand and give informed consent

Exclusion

- Expected remaining life time less than 6 months due to other disease than COPD e.g. active cancer
- Participating in other studies

Intervention

The AIR intervention – personalized management

- Overall focus on quality of life improvement
- Case-manager nurse
- ACP at baseline and at 6 months
- MDT approach

Intervention group

The AIR concept integrates continuity, accessibility and patient and informal caregiver involvement. We focus our intervention on cooperation with the patient, hence, the treatment goals are defined mostly by the patient. The role of the health care professionals is to educate and inform about prognosis and treatment options, thereby helping the patient and informal caregiver choose the preferred treatment.

The AIR team consists of nurses, physiotherapists, social worker and psychologist and 1 associated pulmonary specialist.

Each patient receives a specially trained nurse who will follow the patient as a case manager. The frequency and type of contact depends on what the patient, caregiver and nurse agree on. Both nurses and physiotherapist have the possibility of home visits or the patient can be seen in the out-patient clinic. When needed the patient can make an appointment with the physician who also has the opportunity of a home visit.

There will be held ACP conversations at baseline and at 6 months, where the informal caregivers are actively invited.

If admitted to hospital the patient will be treated at the pulmonary ward at Herlev or Gentofte Hospital - and will, if possible, receive a visit from the AIR nurse during the admission.

The AIR Nurse

The AIR Nurse has overall responsibility for establishing and maintaining an individualized patient and informal caregiver contact. The relationship between patient, informal caregiver and AIR Nurse should enhance the supporting and promoting of health behavior change and the ability to manage daily life with COPD. The AIR Nurse will also provide advice to the patient in case of periods with worsening of symptoms. The AIR Nurse and patient will together decide the frequency and type of contact. There is shared responsibility to adjust when symptoms become more evident. Contact can be by phone, mail, out-patient clinic visits or home visits.

Advance Care Planning (ACP)

ACP in the AIR study focuses on the process of communication and not necessarily on an end-of-life document. Many patients might wish to die at home but the prognostic uncertainty and severity of exacerbations might result in hospitalizations. The topics discussed in this process-orientated approach are patient driven and when the health care professional wishes to discuss certain topics the “ask and tell”

technique is used. In “ask and tell” the health care professional asks permission to raise a topic - if the patient allows it the discussion can start; if not, the health care professional asks permission to raise it at another time. In this way the conversation is in accordance with what the patient and the informal caregiver find most important in life with severe symptomatic disease. The health care professional is also focused on preparing for a possible future with worsening of disease and possible death.

Intervention key concept.

All patients are assessed individually and the treatment plan will include some or all of the following items

Advance care planning (ACP):

All patients will have an ACP within the first three months, in most cases at the 4-week visit. However, the timing of the ACP depends very much on the individual patient. Most patients will have a formal ACP, but for some participants it will be part of the ongoing doctor patient discussions. Formal ACPs will be with both doctor and case-manager nurse. All patients will have a follow up ACP at least yearly but continue to have scheduled consultations with their physician at least 3 times a year, where also the need for another ACP will be assessed.

Case-manager nurse:

All patients will be assigned a case-manager nurse and a patient responsible physician. The case-manager nurse has a personal cell phone with them at all times during normal working hours (08-15.30), and all patients are given the phone number of the secretary at the department, if the case-manager nurse for some reason is unable to answer the phone, providing the patients with the possibility to leave a message for the case-manager nurse.

Self-management plan:

Some patients will have a self-management plan concerning rescue courses of corticosteroids and antibiotics. Self-management plan will be given to the patients after individual assessment of the case-manager nurse.

If a patient starts treatment with corticosteroid and/or antibiotic, the case-manager nurse will follow the patient closely and inform the doctor.

Follow up after admission:

If the patient is admitted to the hospital, the case-manager nurse will see the patient during admission, if possible. After discharge, the case-manager nurse will be in contact with the patient either by phone contact or home visit within 7 days.

Multidisciplinary team support:

The multidisciplinary team consists of case-manager nurse, contact physician, physiotherapist, and if needed social worker and psychologist, who will support the patients' needs based on the ongoing discussion with the patients.

Informal caregiver support:

As part of the palliative intervention, focus on the informal caregivers will be prioritized. If needed the informal caregiver is offered meetings with case-manager nurse or other members of the multidisciplinary team.

Randomization

After the initial assessment, patients are randomized to either the AIR (intervention group) or "usual care" (control group). The randomization list is compiled by redcap randomization program. The randomization will be 1:1 control versus intervention stratified by the two sites Herlev and Gentofte.

AIR time-schedule

The AIR trial is planned to be conducted over a 6 months period.

Time table for AIR study

1- 12 months for the individual patient

Time months	1	2	3	4	5	6
ACP	X					X
Data collection	X		x			X
Primary endpoint Measured						x

Recruitment procedure

Patients will be identified by regular follow up in the out-patient clinic or at hospital discharge. The identification of patients will be conducted by bed nurses and physicians at the ward and out-patient clinic. If the patient is fulfilling the inclusion criteria they will be asked if they want to participate and given written patient information material. They will give oral consent so that a study nurse can contact them by phone and invite them to another interview. If they still fulfil inclusion criteria, baseline data are collection and randomisation is performed. At this second visit they will give written consent to participation.

Sample size estimation

The minimal clinically significant difference has been estimated to 1.5 units for each scale (HADS-depression (D) and HADS anxiety (A))⁴⁰. We thus decided to aim for a detection limit of HADS change of 3.0 in the total HADS score (HADS A+HADS D). Alfa is set at 0.05 and beta at 0.7. The SD of the patients in the

study is expected to be close to SD for HADS values from patients referred to our palliative unit from our hospitals, which was 6.5 units (total HADS). Using these values, the sample size was estimated to 45+45 = 90 patients.

Ethics and Security

Since we are randomizing between the national standard of COPD out-patient follow ups and a palliative approach with even more close contact we see no risk of harm to either group.

Therefore, we see no ethical dilemmas in this study.

The study will be reported to the local ethics committee.

The Protocol will be registered with ClinicalTrials.gov

The principal investigator will inform the Research Ethics Committee of any serious adverse event and / or major changes in the protocol. Patients are covered by Herlev/Gentofte Hospital's patient insurance.

All data processing complies with the technical requirements set out in the Data Protection Agency safety notice.

Data security

In the randomisation process, the patient data (CPR -social security number) will be linked to a study number. The study number is consecutively number generated by the online program combined with a site specification H or G and the first letter of first and surname entered by the nurse.

The nurse enters the corresponding CPR-number thereby creating a list connecting a specific CPR-number with the study number. This list is stored in a locked safe in a locked office. Access to this data is available to investigators only. No person sensitive data with CPR-number will be saved online.

Economic issues

None external funding is planned for the AIR study.

Time perspective and Publications

The study is expected to start in late 2018, and results are expected to be published in 2020 and early 2021. The AIR study will be enrolled as a PhD project.

AIR-nurses and Palliative unit Herlev Hospital are responsible for the recruitment and data collection. KM is responsible for data analysis. All authors will read and approve the final version of the protocol and future manuscripts prepared for submission in biomedical journals. The results from the study will be submitted for publication whether positive, negative or inconclusive.

The AIR organization

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Strengths and limitations

Strengths

AIR, with its small team, can achieve a high degree of professional agreement in what is meant by MDT-based palliative access. This will enable us to describe the approach in detail.

With our questionnaires, we will get a well-defined picture of how general and COPD-specific symptoms develop during the disease trajectory. With HADS, we will gain important knowledge about the psychological consequences of having COPD and possible differences depending on the organization of outpatient follow ups.

Limitations

The intervention in AIR is complex and multi-faceted as it is significantly individualized. With this study we cannot describe which parts have what effect. This has the strength that it demonstrates the effect of the specialized palliative effort that, in the real world of clinical practice, individualizes treatment additions based on thorough symptom assessment. Although this strength is a limitation in a research set up.

Future perspectives of AIR.

With AIR we will examine long-term consequences of a specific well-defined palliative outpatient follow-up structure.

AIR will provide knowledge in a research field with great international interest currently but so far limited evidence of effect of the palliative approach for other than malignant diseases. If AIR shows superiority over usual care, it potentially has important national and international implications not just in COPD patients but also for other groups of symptomatic chronic diseases with great impact on QOL such as heart- and kidney failure.

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