Supplementary data

Inclusion and Exclusion criteria.

The inclusion and exclusion criteria that were used for the CRP-guided Antibiotic Treatment in COPD exacerbations admitted to the Hospital study (CATCH) study were:

Inclusion criteria

- Age 40 years and older. No upper age limit will be employed.
- Written informed consent obtained.
- AECOPD according to the GOLD guideline. An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.
- Criteria for hospital admission according to the GOLD.
  - marked increase in symptoms (i.e. resting dyspnoea)
  - severe underlying COPD
  - onset of new physical signs (cyanosis, oedema)
  - failure to respond to initial medical management
  - significant co morbidities
  - frequent exacerbations
  - newly occurring arrhythmias
  - diagnostic uncertainty
- Former of current smoker with a minimum smoking history of 10 pack years.
- Patients have to be capable of ingesting oral medication.
- Patients have to be mentally capable of participating in the study (able to complete questionnaires and perform lung function tests).
- Life expectancy ≥ 30 days.

Exclusion criteria

- Pregnant or lactating women, or women of childbearing age not using an acceptable method of contraception.
- Pre-treatment with corticosteroids (cumulative dose >210 mg) for the present exacerbation.
- Strong clinical suspicion of pneumonia
- Progression or new radiographic abnormalities on the chest X-ray.
- Cystic fibrosis.
- Tuberculosis.
- Immunodeficiency disorders such as AIDS, humoral immune defect, ciliary dysfunction etc., and the use of immunosuppressive drugs (>30 mg prednisolone/day maintenance dose or equivalent for more than 4 weeks).
- Recent or unresolved lung malignancy.
- Other disease likely to require antibiotic therapy, such as recurrent sinusitis or urinary tract infection.
- Significant gastrointestinal or other conditions that may affect study drug absorption.
- Instable congestive heart failure or recent stroke.
- Newly diagnosed pulmonary embolism

Questionnaire description

LRTI-VAS description:

The Lower Respiratory Tract Infection Visual Analogue Scale(LRTI-VAS) consists of a set of 4 horizontal lines with 2 anchor points, one at each extreme, each line representing a different symptom - dyspnoea, fatigue, cough and sputum colour. Each symptom is scored from 1 to 10, the patients

being unaware of the numbers. Higher scores indicate more severe symptoms. Separate scores were calculated for each symptom, with a total score consisting of all symptom scores added.

CCQ description:

The Clinical COPD Questionnaire is a health-related quality of life questionnaire that has been widely used in both COPD and asthma research and includes 10 items across three domains: symptoms, activity and impact. Higher scores indicate more severe symptoms. It has been validated extensively and can accurately monitor the course of recovery of outpatients as well as that of inpatients with AECOPD

Serious adverse event description

Overall in one year of follow-up, 90 patients had 127 severe adverse events. Events were equally distributed among both groups GOLD 0 (IQR0-1) events compared to CRP 0 (IQR 0-1) events (p=0.720).

Serious adverse event description

29 patients died

10 patients had heart failure

8 patients had cataract

8 patients had a myocardial infarction

5 patients had a lung carcinoma

4 patients had a colon carcinoma

4 patients had a fracture

4 patients had a urinary tract infection

4 patients had a trauma requiring hospitalization

4 patients had unexplained pains requiring treatment/hospitalization

3 patients had a stroke

3 patients had lumbar disc herniation

2 patients had atrial fibrillation

2 patients had an aneurysm of the aorta

2 patients had a depression

2 patients had a cardiac arrhythmia

2 patients had pancreatitis

2 patients had a lung embolus

2 patients had peripheral arterial disease

1 patient had AML

1 patient had diverticulitis

1 patient had acute on chronic kidney failure

1 patient had Barret oesophagus

1 patient had inguinal hernia

1 patient had an exacerbation of rheumatoid arthritis

1 patient had corticosteroid induced diabetes mellitus

1 patient had radiation induced cystitis

1 patient had an ileus

1 patient was admitted to hospital to the geriatric ward because of falling

1 patient had a oesophageal carcinoma

1 patient was admitted to hospital because of hyponatremia

1 patient had laryngeal carcinoma

1 patient had diverticulitis

1 patient was admitted because of an autointoxication

1 patient was admitted due to bowel ischaemia

1 patient was admitted due to unexplained shortnes of breath not explained by COPD or heart failure

Mortality description:

During one year of follow-up 29 patients died. Twenty patients (16.8%) died in the GOLD-group compared to 9 patients (8.9%) in the CRP-group (p=0.082). Median time to death was 153 days (IQR 24-194) in the GOLD-group compared to 199 days (IQR170-239) in the CRP-group (p=0.062)

Cause of death

Fourteen patients died due to COPD/respiratory failure

Six patients died due to cardiac failure/ACS

One patient died of inoperable colon carcinoma

One patient died due to stroke

Seven patients died due to unknown causes.

Adverse events description:

Overall in one year of follow-up, 41 patients had 49 adverse events. Events were evenly equally distributed among both groups.

Adverse event description

4 patients had a fracture

3 patients had skin cancer

3 patients had urinary tract infection

3 patients had pain without a medical explanation

3 patients had a gastroenteritis

2 patients had a polyneuropathy

2 patient had arthrosis

2 patients had gout

2 patients had a pressure neuropathy

1 patient had athletes foot

1 patient had a entropion

1 patient had obstipation

1 patient had gastroesophageal reflux disease

1 patient had osteoporosis

1 patient had carpal tunnel syndrome

1 patients had an oral herpes infection

1 patient had an oral candidiasis

1 patient had iron deficiency anaemia

1 patient had steroid myopathy

1 patient had corticosteroid induced myopathy

1 patient had a colonoscopy because of a polyp

1 patient had oesophageal spasm

1 patient had a urinary retention bladder

1 patient had unexplained stomach pain

1 patient had a sore throat

1 patient had an external otitis

1 patient had venous insufficiency of the lower limb

1 patient had impingement of the shoulder

1 patient had a wound of the leg

1 patient had diverticulosis

1 patient had a trigger finger

Adverse event description related to study medication:

Overall during admission 6 patients had an adverse event related to study medication.

3 patients had hyperglycaemia

1 patient had steroid induced myopathy

1 patient had oral candidiasis

1 patient had urinary retention bladder

Table E1 Baseline characteristics per protocol population		
	GOLD (n=109)	**CRP (n=99)**
age (SD) years	71.1(11.8)	68.4(12.1)
Gender male No (%)[a]	65(59.6)	41(41.1)
Current Smoking No (%)	33(30.3)	36(36.4)
Packyears (SD) years	46.9(34.4)	40.5(23.2)
BMI (SD) kg/m²	24.6(5.4)	24.9(5.2)
FEV1 (SD) L [b]	1.23(0.56)	1.14(0.44)
FEV1 (SD) % pred [b]	46(18)	45(16)
FVC (SD) L [ab]	2.91(1.05)	2.64(0.86)
FVC (SD) % pred[b]	85(22)	83(21)
FEV1/FVC ratio (IQR) % [b]	39(31-49)	38(31-52)
Number of exacerbations in the last year(IQR) No	1(1-2)	1(1-2)
Anthonissen type exacerbation.		
Type 1 No (%)	44(40.4)	48(48.5)
Type 2a purulence present No (%)	6(5.5)	12(12,1)
Type 2b purulence not present No (%)	23(21.1)	14(14.1)
Type 3 No (%)	36(33.0)	25(25.3)
Sputum purulence present No (%) [a]	50(45.9)	60(60.6)
Positive sputum culture at admittance No (%)	40(36.7)	37(37.4)
Co-morbidities		
Ischaemic heart disease No (%)	17(15.6)	15(15.2)
Heart failure No (%)	17(15.6)	16(16.2)
Cerebrovasculair disease No (%)	10(9.2)	10(10.1)
Diabetes mellitus No (%)	8(7.3)	10(10.1)
Pre-treatment		
Inhaled corticosteroids usage No (%)	90(82.6)	78(78.8)
Pretreatment with systemic corticosteroids No (%)	54(49.5)	51(51.5)
Pretreatment with antibiotics No (%)	30(27.5)	40(40.4)
Vital parameters		
Respiratory rate (IQR) per minute	20(16-24)	20(18-24)
Temperature (IQR) °C	37.0(36.6-37.6)	37.1(36.7-37.5)
Laboratory results day 1		
WBC (SD) 10x9/L	11.0(4.03)	10.7(4.3)
Blood eosinophil count (IQR) 10x9/L	0.0(0.0-0.2)	0.0(0.0-0.01)
CRP (IQR) mg/L[C]	27(6.7-104)	19(5.6-83)
CRP≥50mg/L No (%)[c]	47(43.1)	32(32.3)
Assisted ventilation		
none No (%)	100(91.7)	91(91.9)
Non-invasisve ventilation No (%)	8(7.3)	7(7.1)
Invasive ventilation No (%)	1(0.9)	1(1.0)

All data are represented as mean (SD) unless specified otherwise.
Definition of abbreviations: BMI: body mass index (kg/m2),
FEV1: forced expiratory volume 1 second, FVC: Forced Vital Capacity,
WBC: white blood cell count, CRP: C-reactive protein SD: standard deviation, IQR: inter quartile range

[a]: <0.05, [b]: Last recorded postbronchodilator value in a stable state before admission, [c]: Highest level recorded in the first 24 hours

Table E2 Primary & secondary outcomes per protocol population						
Primary outcome		**GOLD (n=109)**	**CRP (n=99)**	**Difference**	**95% CI bootstrap interval**	**p-value**
Patients treated with antibiotics No (%)		50(45.9)	32(32.2)	-13.7	-1.4;-26.9	0.046
Secondary outcome						
30-day treatment failure rate No (%)		46(42.2)	45(45.5)	3.3	-10.8;16.2	0.637
Time to next exacerbation (IQR) days		28(5-210)	34(0-328)	6	-54.6;22.6	0.916
Length of stay(IQR) days		6(4-8)	7(4-9)	1	-0.1;2.7	0.157
CCQ score change on day 30		-1.0(-2.0;-0.2)	-0.9(-1.40;-0.1)	0.1	-0.53;0.16	0.655
LRTI-VAS score change on day 30, (IQR)		-9(-14;-5)	-7(-15;-2)	2	-3.3;2.2	0.540

All data are represented as mean (SD) unless specified otherwise. Differences are represented as percentages or differences in medians.

Definition of abbreviations: CCQ: Clinical COPD Questionnaire,
LRTI-VAS: Lower Respiratory Tract Infection Visual Analogue Scale

Table E3 Symptom score LRTI-VAS and CCQ at admission		
	GOLD (n=100)	**CRP (n=90)**
LRTI-VAS score t=0(IQR)	24(18-27)	23(21-28)
Dyspnea t=0(IQR)	7(6-9)	8(7-9)
Fatigue t=0(IQR)	8(5-9)	8(6-9)
Cough t=0(IQR)	5(4-7)	6(5-8)
Sputum purulence t=0(IQR)	3(1-5)	3(1-5)
Clinical COPD Questionnair total t=0(IQR)	3.55(3.00-4.05)	3.80(3.10-4.20)
CCQ symptoms t=0(IQR)	4.00(3.00-4.50)	3.75(3.25-4.5)
CCQ mental t=0(IQR)[a]	2.00(1.00-3.00)	2.50(1.50-3.50)
CCQ functional t=0(IQR)	4.00(3.25-4.75)	4.25(3.00-4.75)

Definition of abbreviations: CCQ: Clinical COPD Questionnaire,
LRTI-VAS: Lower Respiratory Tract Infection Visual Analogue Scale

[a]: p=<0.05

Table E4 Symptom score change on day 30 LRTI-VAS and CCQ			
	GOLD (n=80)	**CRP (n=78)**	**p-value**
LRTI-VAS score change on day 30(IQR)	-8.5(-14.0--3.0)	-7.5(-15.0--2.0)	0.831
dyspnoea change on day 30(IQR)	-2.0(-5.0-0.0)	-2.0(-5.0-0.0)	0.856
fatigue change on day 30(IQR)	-2.0(-4.0-0.0)	-1.0(-3.5-0.0)	0.104
cough change on day 30(IQR)	-3.0(-4.5-0.0)	-2.0(-5.0-0.0)	0.611
sputum purulence change on day 30(IQR)	-1.0(-3.0-0.0)	-1.0(-3.0-0.0)	0.696
Clinical COPD Questionnaire total change on day 30(IQR)	-1.00(-1.95--0.20)	-0.90(-1.40;-0.10)	0.289
CCQ symptoms change on day 30(IQR)	-1.25(-2.13-0.00)	-0.75(-1.75;-0.25)	0.289
CCQ mental change on day 30(IQR)	-0.50(-1.50-0.00)	-0.50(-1.50;-0.00)	0.728
CCQ functional change on day 30(IQR)	-1.00(-2.13--0.13)	-0.75(-1.25;-0.00)	0.192