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Efficacy and Tolerability of Myrtol Standardized in Acute Bronchitis

A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol

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Summary

Myrtol standardized (Gelomyrtol® forte) is a phytotherapeutic extract (distillate) consisting mainly of three monoterpenes: (+)α-pinene, d-limonene and 1,8-cineole.

Objective: This study describes and compares the efficacy, safety and tolerability of a 2-week treatment with myrtol stand. (4 × 300 mg, day 1–14), cefuroxime (CAS 55268-75-2) (2 × 250 mg daily for day 1–6), ambroxol (CAS 18683-91-5) (3 × 30 mg for day 1–3, 2 × 30 mg for days 4–14) and matched placebo in acute bronchitis.

Patients: 676 male and female outpatients, aged ≥ 18 years, with acute bronchitis of recent onset (within last 5 days), with an FEV_1 > 75 % of the normal EGKS-value and without evidence or suspicion of chronic pulmonary disease or any further confounding illness were included in the study.

Intervention: Patients were randomly assigned to a 2-week treatment course with either myrtol stand. (N = 170), cefuroxime (N = 171), ambroxol (N = 163) or placebo (N = 172) in a double-blind, placebo-matched, parallel-group fashion. Evaluations were at baseline (visit 1), after 1 and 2 weeks of treatment (visits 2 and 3) and at 2 weeks after conclusion of the treatments (visit 4).

Criteria: Responder- and non-responder rates (primary), signs (abnormal auscultation), symptoms (daily diary data on nightly cough, coughing fits during the day, sputum consistence and general well-being; visit data on bronchial hyperreactivity and absence/presence of associated symptoms), FEV_1, overall efficacy, absence of relapse, safety and tolerability (adverse events, laboratory screens, vital signs and physical examination). Criteria were evaluated for the intention-to-treat data-set (ITT) and the 'efficacy evaluable' sample (EAP), i.e. excluding patients with missing values (incl. discontinued non-responders and drop-outs for other reasons) at the time of assessment.

Results: The signs and symptoms of acute bronchitis regressed readily in all treatment groups, but regression was slower and less complete in the patients treated with placebo. In patients treated with placebo, the acute bronchitis was considered to have deteriorated to such an extent that discontinuation was indicated ('non-responder') in 36 patients (ITT: 20.9 %, 95 % CI: 15.1 to 27.8 % and EAP: 21.3 %, CI: 15.4 to 28.3 %) after 1 week (visit 2) and in 19 further patients (ITT: 11.0 %, CI: 6.8 to 16.7 %; EAP: 14.8 %, CI: 9.2 to 22.2 %) after 1 further week (visit 3). In contrast, in the group of patients treated with myrtol stand. the non-re-

sponder rates at visits 2 and 3 were only 5.3 % (ITT, CI: 2.4 to 9.8 %; EAP: 5.4 %, CI: 2.5 to 10.0 %) and 1.2 % (ITT, CI: 0.1 to 4.2 %; EAP: 1.3 %, CI: 0.2 to 4.7 %); the responder rates at visit 2 were statistically significantly higher ($p < 0.001$) for myrtol stand. (ITT: 92.9 %, CI: 88.0 to 96.3) compared to placebo (ITT: 77.3 %, CI: 70.3 to 83.4), and similar to those for cefuroxime (ITT: 92.4 %, CI: 87.4 to 95.9) and ambroxol (ITT: 89.6 %, CI: 83.8 to 93.8 %). The superiority of the active treatments vs. placebo with little difference among the treatments was confirmed for all further criteria of evaluation. There was no evidence of bronchoconstriction or relapse in any treatment group for the patients continuing treatment (i.e. for those who were not discontinued because of non-response). The treatments were safe and comparably well tolerated.

Conclusion: Compared to placebo, treatment with myrtol stand. was well tolerated but evidently superior in terms of efficacy, resulting in a more rapid and more complete recovery; although well comparable with the other active treatments, myrtol stand. tended to be superior to cefuroxime and ambroxol for several ancillary criteria. Myrtol stand. is a well-evidenced alternative to antibiotics for acute bronchitis without specified infective agent, without the risk to promote the development of bacterial resistance.

Zusammenfassung

Wirksamkeit und Verträglichkeit von Myrtol standardisiert bei akuter Bronchitis / Eine randomisierte, Plazebo-kontrollierte, doppelblind geführte Multizenter-Studie im Parallelgruppen-Design versus Cefuroxim und Ambroxol

Myrtol standardisiert (Gelomyrtol® forte) ist ein pflanzliches Destillationspräparat mit den hauptsächlichen Markern 1,8-Cineol, d-Limonen und α-Pinen.

Ziel: Diese Untersuchung beschreibt und vergleicht die Wirksamkeit und Verträglichkeit einer 2-wöchigen Behandlung mit Myrtol standardisiert (4 × 300 mg von Tag 1 bis 14), Cefuroxim (CAS 55268-75-2) (2 × 250 mg täglich für die Tage 1–6), Ambroxol (CAS 18683-91-5) (3 × 30 mg für die Tage 1–3 und 2 × 30 mg für die Tage 4–14) und Plazebo bei akuter Bronchitis.

Patienten: 676 männliche und weibliche ambulante Patienten mit akuter Bronchitis seit weniger als 5 Tagen, mit einer $FEV_1 > 75$ % und ohne klinischen Hinweis auf eine chronische Atemwegserkrankung oder weitere gravierende Erkrankungen nahmen an der Studie teil.

Behandlungsschema: Die Patienten wurden zufallsbedingt, doppel-blind und Plazebo-kontrolliert einer zweiwöchigen Behandlung mit entweder Myrtol standardisiert (N = 170), Cefuroxim (N = 171), Ambroxol (N = 163) oder Plazebo (N = 172) gemäß einem Parallelgruppendesign zugeordnet. Kontrolluntersuchungen erfolgten zu Beginn der Behandlungsdauer (Visite 1), nach einer bzw. zwei Wochen der Behandlung (Visiten 2 + 3) und zwei Wochen nach Behandlungsabschluß (Visite 4).

Endpunkte: Evaluiert wurden Responder und Non-Responder-Raten, klinische Untersuchungsbefunde (pathologische Auskultationsbefunde), Symptome (Tagebuchdaten über das nächtliche Husten, Hustenattacken tagsüber, Sputumkonsistenz und allgemeines Wohlbefinden; klinische Befunde zu den jeweiligen Visiten bezüglich der bronchialen Hyperreaktivität und relevanten Begleitsymptomen), FEV_1, Globalbewertung der Wirksamkeit, Fehlen eines Rezidivs, Verträglichkeit (unerwünschte Arzneimittelwirkungen, Screening von Laborparametern und körperliche Untersuchungsbefunde). Die Parameter wurden sowohl für die intention-to-treat Population (ITT) als auch für die efficacy analysable Population (EAP) bestimmt, d. h. es wurden bei letzterer diejenigen Patienten ausgeschlossen, bei denen keine Daten erhoben werden konnten (einschließlich Non-Responder, die die Studie vorzeitig abbrachen, und Studienabbrecher aus anderen Gründen).

Ergebnisse: Obwohl sich die Beschwerdesymptomatik in allen Behandlungsgruppen rasch besserte, war die Rückbildung bei den mit Plazebo behandelten Patienten langsamer und weniger vollständig: unter Behandlung mit Plazebo, zeigten 36 Patienten (ITT: 20,9 %, 95 % CI: 15,1 bis 27,8 % und EAP: 21,3 %, CI: 15,4 bis 28,3 %) eine Verschlechterung der akuten Bronchitis in einem solchen Ausmaß, daß sie die Studie nach 1 Woche abbrechen mußten (Non-Responder); nach einer weiteren Woche (Visite 3) wurden 19 zusätzliche Patienten als Non-Responder betrachtet (ITT: 11,0 %, CI: 6,8 bis 16,7 %; EAP: 14,8 %, CI: 9,2 bis 22,2 %). In der Patientengruppe, die mit Myrtol standardisiert behandelt wurde, lag die Non-Responder-Rate bei Visite 2 lediglich bei 5,3 % (ITT, CI: 2,4 bis 9,8 %; EAP: 5,4 %, CI: 2,5 bis 10,0 %) bzw. bei Visite 3 lediglich bei 1,2 % % (ITT, CI: 0,1 bis 4,2 %; EAP: 1,3 %, CI: 0,2 bis 4,7 %); Die Responderraten waren bei Visite 2 statistisch signifikant höher ($p < 0,001$) für Myrtol standardisiert (ITT: 92,9 %, CI: 88,0 bis 96,3) im Vergleich zu Plazebo (ITT: 77,3 %, CI: 70,3 bis 83,4) und ähnlich zu denen von Cefuroxim (ITT: 92,4 %, CI: 87,4 bis 95,9) und Ambroxol (ITT: 89,6 %, CI: 83,8 bis 93,8 %). Die Überlegenheit der aktiven Behandlungen gegenüber Plazebo mit geringen Unterschieden unter den einzelnen Behandlungsgruppen konnte für alle weiteren dargestellten Parameter bestätigt werden. Es gab keine Hinweise auf Bronchokonstriktion oder Rezidive bei den Responder-Patienten. Die Behandlungen wurden vergleichsweise gut vertragen.

Fazit: Myrtol standardisiert ist hinsichtlich der Verträglichkeit mit Plazebo vergleichbar, jedoch in bezug auf die Wirksamkeit bei der Behandlung der akuten Bronchitis Plazebo klar überlegen; die Besserung des Beschwerdebildes ist unter Myrtol standardisiert schneller und

ausgeprägter. Obwohl mit den anderen Behandlungsformen gut vergleichbar, zeigte Myrtol standardisiert eine geringfügige Überlegenheit gegenüber Cefuroxim und Ambroxol bei mehreren der untersuchten Parameter. Myrtol standardisiert kann als gut belegte Alternative zu Antibiotika bei der Behandlung der unspezifischen akuten Bronchitis betrachtet werden, da es eine nachgewiesene Wirksamkeit besitzt ohne das Antibiotika-typische Risiko einer bakteriellen Resistenzentwicklung.

Key words Acute bronchitis · Ambroxol · Cefuroxime · Gelomyrtol® forte, clinical trial · Myrtol standardized

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1. Introduction

Although mostly of viral origin, acute bronchitis is still often treated with antibiotics [1, 2, 3]. The benefit of antibiotics in this indication is small [4, 5] in relation to the inherent risk to promote the development of bacterial resistance [6, 7], a major threat to public health [8]. In spite of many efforts by expert advisory panels and intensified education, and the discomfort and dissatisfaction of the prescribing physicians themselves, little change in the prescribing habits in this indication has yet been reached. This often is explained by the patients' pressure and expectations [9, 10, 11]. Overall, this demands for better alternatives.

Myrtol standardized[1)] is a phytotherapeutic extract (distillate) consisting mainly of three monoterpenes: (+)α-pinene, d-limonene and 1,8-cineole. Its efficacy in respiratory tract infections is primarily related to its secretolytic and secretomotoric properties and the resulting improvement of bronchoalveolar and/or sinu-bronchial aeration. Further ancillary pharmacological properties might contribute to this, anti-inflammatory [12, 13] and anti-oxidant actions [14], in particular. Both ambroxol [15–19], a further well-established mucolytic agent [20], and myrtol stand. [21] were shown to be efficacious in preventing and alleviating acute exacerbations of chronic bronchitis, but there is little documentation of their efficacy and tolerability in acute bronchitis.

For these reasons the present study was carried out to investigate the course of acute bronchitis under treatment with myrtol stand. and ambroxol, compared to cefuroxime (a 2nd generation cephalosporin often used in lower respiratory tract infections, incl. acute bronchitis) and placebo in an appropriately designed randomised, double-blind, controlled, parallel-group clinical trial.

[1)] Gelomyrtol® forte; Manufacturer: G. Pohl-Boskamp GmbH & Co., Hohenlockstedt (Germany).

2. Methods

2.1. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki (Somerset West, 1996) and the Notes for Guidance on Good Clinical Practice. The study protocol was reviewed and approved by pertinent Ethics Committees. Participation in the study was voluntary. Only subjects who were willing and able to provide informed consent were eligible.

2.2. Design

The study was conducted in a multi-centre, randomised, placebo- and actively controlled, double-blind, parallel-group fashion. Eligible patients with acute bronchitis were randomly allocated to following investigational treatments: 1) myrtol stand. (4 x 300 mg daily for 14 days), 2) cefuroxime (2 × 250 mg daily for day 1–6), 3) ambroxol (3 × 30 mg for day 1–3, 2 × 30 mg for days 4–14) and 4) matched placebo (4 times daily for days 1–14); all patients received investigational medication 4 times daily for days 1–14; treatments were matched by the use of placebo capsules.

2.3. Patients

Six-hundred-forty (640) patients with acute bronchitis were intended to be recruited in approximately 54 centres to obtain at least 592 evaluable cases. Eventually, 681 patients were recruited by 40 active centres, 5 of whom were not randomised. Male and female patients were eligible if they met all of the following criteria: at least 18 years of age, acute bronchitis of recent onset (onset of symptoms within the last 5 days), with nightly cough (at least 4 awakenings due to cough during the night) as main symptom, without reduced FEV_1 (i.e. > 75 % of the normal) and otherwise good physical and mental condition. Furthermore, they had to be willing and able to provide informed consent. Patients with any of the following were to be excluded: chronic bronchitis and/or acute exacerbation of chronic bronchitis, recurrent acute bronchitis (within 4 weeks prior to study admission), bronchial asthma, suspected or evidenced pneumonia, concomitant bacterial infection, fever >39.5 °C (rectally) or ≥ 39 °C (axillary, orally), pregnancy, lactation, relevant allergy or hypersensitivities, lithiasis, gastritis or peptic ulcer disease, evidence or suspicion of drug, medication or alcohol abuse, any relevant associated disease or abnormal finding on extensive pre-study evaluation (including lab. screen), suspicion of likely lack of compliance, recent participation in another clinical trial. Treatment with antibiotics was prohibited

from two weeks prior to the study and during the study. Secretolytics, mucolytics, tussisedatives were prohibited from 5 days before enrolment and during the study. Recent therapy with acetylsalicylic acid (within 12 h prior to inclusion) was not allowed. From the start of the study onwards, therapy with analgesics, except paracetamol, was prohibited. Additionally, inhalation and physical therapy of bronchitis was not allowed from the start of the study onwards. Any other concomitant medication was only allowed if it did not interfere with the eligibility criteria and the evaluation of the study endpoints.

Patients had the right to withdraw from the study at any time and for any reason. Each investigator was entitled to withdraw any patient prematurely if this was deemed to be in the patient's best interest (e.g. in the case of adverse events, need for prohibited medication, intercurrent disease etc.). Additionally, patients were to be discontinued prematurely if they failed to adhere to the treatment schedule, if they were found not to have met the eligibility criteria and/or if they were found not to comply with the protocol directives. In order not to deny patients specific (unblinded) treatment, patients were also to be discontinued in the event of any of the following: 1) deterioration of acute bronchitis (visit 2) and deterioration of acute bronchitis or lack of improvement (visit 3), 2) suspected pneumonia, 3) $FEV_1 < 75\,\%$ of normal, 4) fever above the level of eligibility and relevant changes of safety lab. tests (serum creatinine > 1.8 mg % or SGPT > 3 times upper normal value).

2.4. Schedule

The study was to last up to 28 days in each given individual, with investigational treatment regimens lasting 14 days. The study comprised 4 visits: Visit 1 (study day 1): baseline, assessment of eligibility, enrolment, randomisation, start of treatment; Visit 2 (study day 7 ± 2): evaluation after 1 week of treatment, assessment of study criteria; Visit 3 (study day 14 ± 2): evaluation after 2 weeks of treatment; Visit 4 (study day 15–28) final examination and (in those still on study) evaluation at 2 weeks after the regular end of the investigational treatment phase.

2.5. Study medication

Gelomyrtol forte capsules (300 mg) and placebo capsules were provided by the Sponsor; commercially available formulations were used for the treatments with ambroxol and cefuroxime. All medications were encapsulated to allow appropriate matching.

2.6. Treatments

The patients took the medications themselves in ambulatory fashion. Compliance was surveyed by pill-count at visits 2 and 3. The patients were instructed to take 4 capsules per day for 14 days, in the morning, at noon and in the evening – 30 min before meals – and at bedtime. The capsules were to be taken with sufficient cold water. If the patient forgot to take a capsule at the given time, he/she was not to take it at a later time that day, but to leave it in the blister.

2.7. Treatment assignment

For each treatment group, the study medication was assembled in individual subject boxes. These were allocated to the individual participants in accordance with the randomisation list provided by the sponsor. In each centre, the investigator allocated the study medication in ascending order.

2.8. Study criteria and methods

The study evaluated the course of acute bronchitis on the basis of the following criteria:

- Responder- and non-responder rate: at visits 2 and 3, the investigator was to assess whether the condition of the patient had worsened (i.e. making it appropriate to discontinue investigational treatment). Patients considered to suffer a relevant deterioration (visit 2 and 3) or also a relevant lack of improvement (visit 3) were considered 'non-responders' (at that visit). Patients without such relevant deterioration and who were not discontinued prematurely from the study because of other reasons unrelated to the clinical course of the disease were considered 'responders'.
- Diary data on coughing fits during the day, disturbance of sleep by cough, type of cough (sputum consistence) and general well-being as recorded daily by the patient on categorised verbal rating scales (VRS)
- Clinical signs: temperature and lung auscultation (classified as "normal" or "abnormal"; in case of abnormal findings, these were to be specified acc. to predefined categories)
- Clinical symptoms: absence/presence of acute rhinitis, sore throat, difficulty swallowing, hoarseness, headache, pain in limbs and joints, fatigue, others (with specification)
- Overall efficacy: the patient and the physician were to score their overall evaluation of the efficacy on visits 2, 3 and 4 as "very good", "good", "moderate", "bad" and "very bad" (5-point VRS).
- Bronchial hyperreactivity as characterised by coughing when exposed to cold/change of temperatures, during exercise and/or when exposed to noxious substances (e.g. cigarette smoke).
- The change of lung function was assessed by measuring the forced expiratory volume in one second (FEV_1) in relation to the normal reference value (EGK) [22]
- The number of patients with a relapse of the acute bronchitis within 4 weeks after first application of the study drugs

Safety and tolerability were evaluated with regard to the following: adverse events, vital functions (blood pressure and pulse rate), physical examinations and safety laboratory screens (haematology, clinical chemistry and urinalysis).

2.9. Statistical analysis

Two data-sets were assessed:

- ITT (intention-to-treat – 'full sample analysis'): all patients who were treated at least once
- EAP (efficacy analysable population): patients as evaluable for a given criterion at the given timepoint; this excludes ITT-patients discontinued before the given visit because of non-response and those discontinued because of any other reason plus patients who had not been discontinued but for whom data for the given criterion were missing at that time

The EAP accounts for 'informative' drop-outs [23], due to treatment related differences in the discontinuation rates (and resulting exposure) in the absence of procedures to replace missing values [24]. Both data-sets are to be looked at in parallel and are not mutually exclusive. The EAP at a given visit hence represents the sample of the ITT that was not discontinued previously for any reason, lack of response inclusively.

A stepwise testing procedure of a priori ordered hypotheses was established in the study protocol. First myrtol stand. was compared to placebo. In case of a significant

result of this 1st step, myrtol stand. was compared to cefuroxime. For both steps a chi-squared test was used with a two-sided significance level $\alpha = 0.05$. This analysis was based on the ITT responder rates at visit 2. All further analyses were carried out descriptively reporting frequencies, means and the corresponding 2-sided 95 % confidence intervals (CI).

3. Results

3.1. Patient disposition

The study was carried out between March 1998 and January 1999. The time course of enrolment between August and December 1998 is shown in Fig. 1. A total of 681 patients were enrolled, 676 patients were randomised and treated with study medication (= ITT and safety evaluable data-set). Seven patients were discontinued prematurely or withdrew from the study between visit 1 and visit 2 (2 because of re-confirmed non-eligibility, 2 because of adverse events (AE) and 3 because of administrative reasons). A total of 94 patients were discontinued at visit 2, including 69 patients discontinued also because of non-response (s. below); a total of 47 further patients were discontinued at visit 3, including 37 patients discontinued because of non-response (s. below). 17/676 (2.5 %) patients were discontinued because of AE (multiple reasons possible, s. below).

3.2. Protocol deviations

At the blinded report planning meeting, 107 minor and 51 major protocol deviations were identified; the main deviations related to low compliance (23 minor and 18 major) and/or deviations from the time window for visit 2 (24 minor and 16 major). Additionally, patients with relevant deterioration and/or lack of improvement (non-responders) were intended to be discontinued at visit 2 and 3; six patients who were labelled as non-responder either at visit 2 (5 pts.) or visit 3 (1 pt.) were erroneously not discontinued; these patients were not excluded from the efficacy analysis and were categorised as 'non-responder' in spite of the lack of discontinuation.

3.3. Demography

The study patients (N: 676, 58.1 % females), had a mean age of 39 years (range of 18–79 years) and were caucasian. The main demographic data are shown in Table 1. There were no relevant differences in demographic details between the treatment groups. 57.5 % of the patients were non-smokers; a total of 235 previous and/or concomitant diseases were documented in 155 (23 %) patients of the ITT sample; hypertension was the most common diagnosis, i.e. occurring in 71 patients. 296 patients (43.8 %) received at least one concomitant medication; vitamins and minerals were the most often cited. These features were equally distributed across the treatment groups and none meant a relevant confounding factor to the efficacy analysis.

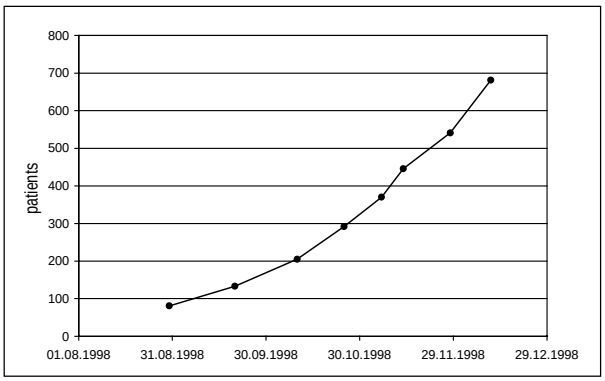

Fig. 1: Time course of the number of enrolled patients with acute bronchitis (cumulatively) between August and December 1998.

3.4. Efficacy

3.4.1. Baseline condition

All patients (except one) had acute bronchitis of recent onset (within the last 5 days) with at least 4 awakenings during the night because of cough, 91–94 % reporting at least 4 coughing fits during the day (94–96 % reporting either a dry cough or viscous sputum) and 72–78 % reporting feeling 'bad' or 'very bad' upon entrance in the study. About 36 % had temperature > 37.5 °C; in 72–76 % patients abnormal findings were reported upon auscultation (mainly as sibilant ronchi/buzzing), 49–59 % had associated acute rhinitis, 47–57 % reported associated sore throat, 19–23 % difficulty swallowing and 49–55 % hoarseness; 58–61 % also reported headache, 37–43 % had pain in the limbs and joints and 65–72 % fatigue; in 51–57 % of the patients bronchial hyperreactivity was reported; bronchial obstruction was no common finding (patients with FEV_1 < 75 % of normal were not considered eligible) for the present trial.

Table 1: Descriptive statistics of the main demographic variables.

No. of patients (%)				
Variable	Myrtol stand.	Placebo	Cefuroxime	Ambroxol
N	170	172	171	163
Sex				
Men	65 (38.2)	79 (45.9)	67 (39.2)	72 (44.2)
Women	105 (61.8)	93 (54.1)	104 (60.8)	91 (55.8)
Age (yr)				
Mean	40	39	38	38
SD	14.5	12.9	13.5	13.4
Range	18–77	18–78	18–74	18–79
Height (cm)				
Mean	168.0	169.1	167.7	169.1
SD	8.8	9.3	9.0	9.2
Range	148–186	150–188	140–197	146–192
Weight (kg)				
Mean	70.2	70.3	69.7	71.9
SD	14.3	14.7	13.4	13.8
Range	40–128	42–126	45–110	45–117

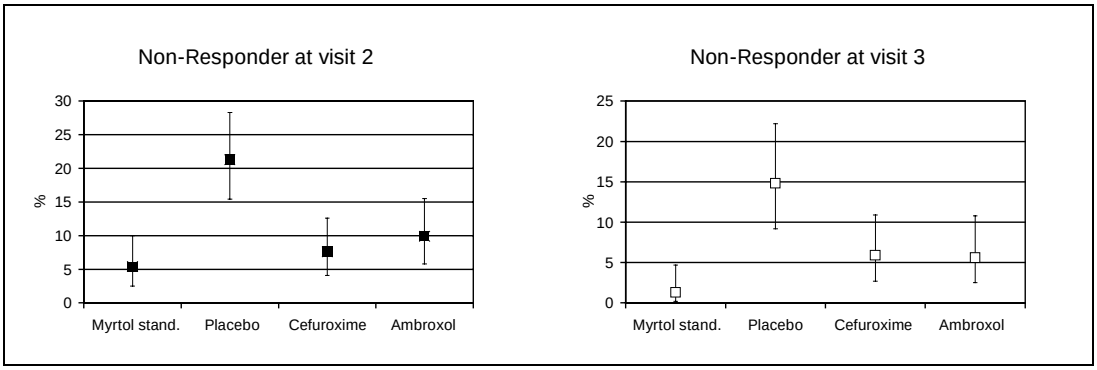

Fig. 2: Non-responder rates [EAP, % plus 95 % CI – non-cumulatively], left: at visit 2 (after 1 week of treatment), right: at visit 3 (after 2 weeks of treatment) (see also Table 2 for related ITT-data).

3.4.2. Natural course of disease under study – placebo treatment

Under treatment with placebo, a clear improvement was seen within one week: there was a clear reduction in cough during the day and during the night (Fig. 3), the sputum was easier to expectorate (37 % reporting filmy or liquid sputum on visit 2 vs. only 5 % on visit 1 [EAP]) and the patients felt generally better (33 % reporting feeling 'good' or very good' at visit 2 vs. none at visit 1 [EAP]). Findings on lung auscultation had improved as well (50 % now having abnormal findings vs. 76 % at visit 1 [EAP], see Fig. 4) and associated symptoms were less frequent (Fig. 5). Nevertheless, after 1 week of treatment (at visit 2) the condition in 36/172 patients (ITT: 20.9 %, CI: 15.1 to 27.8 % and EAP: 21.3 %, CI: 15.4 to 28.3 %) was considered to have deteriorated to such and extent that discontinuation was indicated ('non-responder', Table 2, Fig. 2).

Table 2: Number of patients (upper panel) and responder rates (bottom panel) in the various data-sets and at the different visits.

Number of patients				
	Myrtol stand.	Placebo	Cefuroxime	Ambroxol
N-ITT	170	172	171	163
Visit 2				
N-EAP	167	169	171	162
Drop-outs[a)]	3	3	0	1
Responder	158	133	158	146
Non-Responder	9	36	13	16
Visit 3				
N-EAP	152	128	152	142
Drop-outs[b)]	18	44	19	21[c)]
Responder	150	109	143	134
Non-Responder	2	19	9	8

Responder- and Non-Responder Rates (% and 95 % CI)								
Criterion	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
ITT – visit 2	Myrtol stand.		Placebo		Cefuroxime		Ambroxol	
Responder	92.9	88.0–96.3	77.3	70.3–83.4	92.4	87.4–95.9	89.6	83.8–93.8
Non-Responder	5.3	2.4– 9.8	20.9	15.1–27.8	7.6	4.1–12.6	9.8	5.7–15.5
EAP – visit 2	Myrtol stand.		Placebo		Cefuroxime		Ambroxol	
Responder	94.6	90.0–97.5	78.7	71.8–84.6	92.4	87.4–95.9	90.1	84.5–94.2
Non-Responder	5.4	2.5–10.0	21.3	15.4–28.3	7.6	4.1–12.6	9.9	5.8–15.5
ITT – visit 3	Myrtol stand.		Placebo		Cefuroxime		Ambroxol	
Responder	88.2	82.4–92.7	63.4	55.7–70.6	83.6	77.2–88.8	82.2	75.5–87.7
Non-Responder	1.2	0.1– 4.2	11.0	6.8–16.7	5.3	2.4– 9.8	4.9	2.1– 9.4
EAP – visit 3	Myrtol stand.		Placebo		Cefuroxime		Ambroxol	
Responder	98.7	95.3–99.8	85.2	77.8–90.8	94.1	89.1–97.3	94.4	89.2–97.5
Non-Responder	1.3	0.2– 4.7	14.8	9.2–22.2	5.9	2.7–10.9	5.6	2.5–10.8

ITT: all randomised patients receiving the investigational medication at least once, EAP: all patients evaluable for the given criterion at the defined time point (i.e. excluding non-exposed i.e. dropped-out patients). [a)] Patients discontinued between visit 1 (enrolment) and visit 2 (after 1 week of treatment). [b)] Patients discontinued between visit 2 and visit 3 (after 2 weeks of treatment). [c)] One patient in the ambroxol group was not available for efficacy due to missing values.

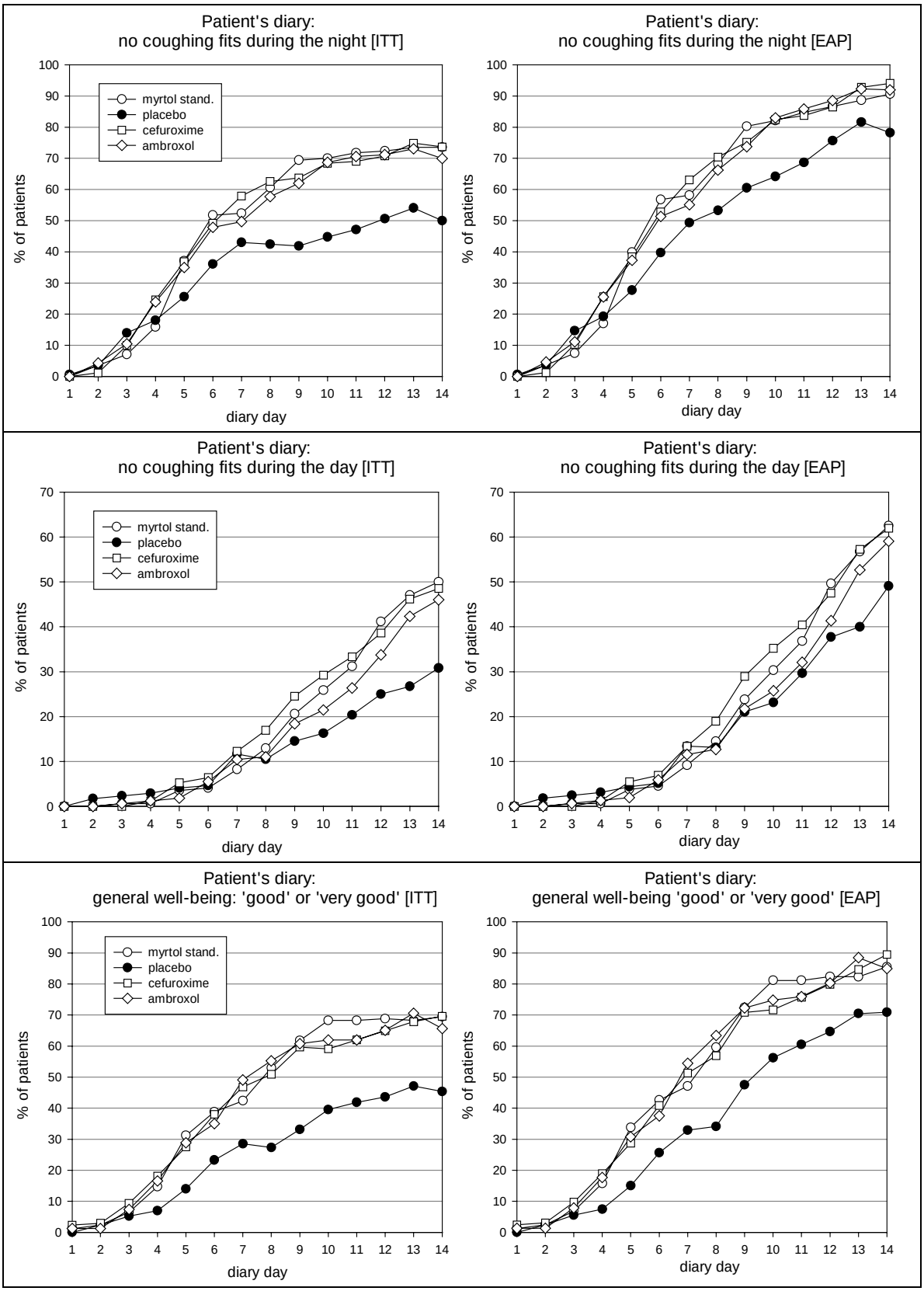

Fig. 3: Percentage of patients with no nightly coughing fits (top), no coughing fits during the day (mid) and % of patients scoring a general well-being at least as 'good' (bottom) during the course of the treatments [patient diary data]; ITT (left): all randomised patients receiving the investigational medication at least once, EAP (right): all patients evaluable for the given criterion at the defined time point (i.e. excluding non-exposed i.e. dropped-out patients).

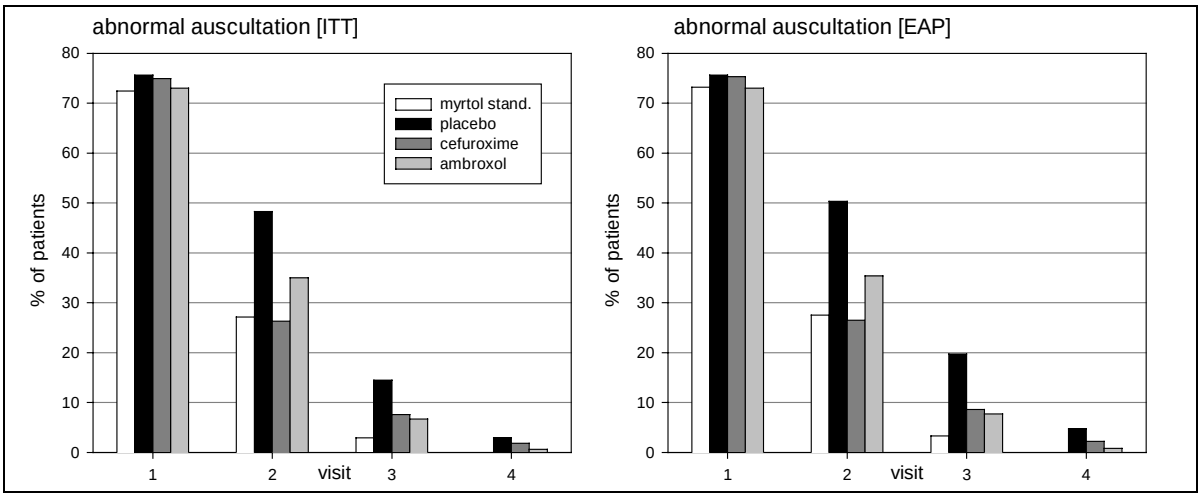

Fig. 4: Percentage of patients with abnormal findings upon auscultation at the various visits (1: enrolment, 2: after 1 week of treatment, 3: after 2 weeks of treatment and 4: 2 weeks after conclusion of the investigational treatments); ITT (left): all randomised patients receiving the investigational medication at least once, EAP (right): all patients evaluable for the given criterion at the defined time point (i.e. excluding non-exposed i.e. dropped-out patients).

After one further week of treatment in the remaining patients [EAP at visit 3], the overall condition in general had improved even further: 49 % had no coughing fits during the day (vs. 13 % and 0 % at visits 2 and 1, respectively), 78 % had no awakening during the night (vs. 49 and 1 % at visits 2 and 1) and 71 % reporting feeling 'good' or 'very good' (vs. 33 % and 0 % at visits 2 and 1); an abnormal auscultation was reported in 20 % [EAP]; associated symptoms had become relatively uncommon (Fig. 5). However, in 19/172 patients originally initiated (ITT: 11 %, CI: 7 to 17 %) i.e. 19/128 patients still under treatment at visit 3 (EAP: 15 %, CI: 9 to 22 %), the treatment had to be discontinued at this time ('non-responders' at visit 3) because of a deterioration or lack of improvement of the acute bronchitis (Table 2, Fig. 2). Of the 172 patients enrolled in the placebo group, 107 completed the study up to visit 4. At that time, the associated symptoms had cleared in most but not all patients and the abnormal auscultation was still present in 4.7 % [EAP]; bronchial hyperreactivity was still present in 21.5 % (CI: 14.1 to 30.5). There was no evidence of bronchoconstriction and/or relapse in the subjects still under study at that time.

3.4.3. Treatment with myrtol stand.

Under treatment with Myrtol stand., there was a qualitatively similar change over time, but the improvement was more extensive and relatively faster: the percentage of patients with $\geqslant 4$ awakenings during the night due to cough decreased from 100 % (visit 1) to 6 % (visit 2 [EAP]) and patients with $\geqslant 4$ coughing fits during the day from 93 % to 28 % [EAP]; the sputum was easier to expectorate (63 % reporting filmy or liquid sputum on visit 2 vs. only 5 % on visit 1 [EAP]); the patients felt generally better (47 % reporting 'good' or very good' at visit 2 vs. 1 % at visit 1 [EAP], Fig. 3). Findings on lung auscultation had improved as well (28 % now having abnormal findings vs. 73 % at visit 1 [EAP], Fig. 4); associated rhinitis (visit 2: 31 %, visit 1: 49 % [EAP]), sore throat (visit 2: 17 %, visit 1: 57 % [EAP]), difficulty swallowing (visit 2: 4 %, visit 1: 22 % [EAP]), hoarseness (visit 2: 24 %, visit 1: 53 % [EAP]), headache (visit 2: 24 %, visit 1: 58 % [EAP]), pain in joints and limbs (visit 2: 10 %, visit 1: 43 % [EAP]) and fatigue (visit 2: 36 %, visit 1: 72 % [EAP]) all improved (Fig. 5). Bronchial hyperreactivity improved similarly. Only in 9/170 patients (ITT: 5.3 %, CI: 2.4 to 9.8 %, EAP: 5.4 %, CI: 2.5 to 10.0) the condition was considered to have deteriorated to the extent of requiring discontinuation ('non-responder', Table 2, Fig. 2). The responder rate for myrtol stand. (ITT: 92.9 %, CI: 88.0 to 96.3) was significantly ($p < 0.001$) larger than for placebo (ITT: 77.3 %, CI: 70.3 to 83.4), but not statistically significantly different (p: 0.85) from that for cefuroxime (ITT: 92.4 %, CI: 87.4 to 95.9, Table 2, Fig. 2). After one further week of treatment with myrtol stand. in the remaining patients [EAP at visit 3], the overall condition in general had improved even further: 63 % had no coughing fits during the day (vs. 9 % and 0 % at visits 2 and 1, respectively), 91 % had no awakening during the night (vs. 58 and 0 % at visits 2 and 1) and 86 % reporting feeling 'good' or 'very good' (vs. 47 % and 1 % at visits 2 and 1; Fig. 3); an abnormal auscultation was reported for only 3 % [EAP] (Fig. 4); associated rhinitis (5 % [EAP]), sore throat (3 % [EAP]), difficulty swallowing (1 % [EAP]), hoarseness (5 % [EAP]), headache (7 % [EAP]), pain in joints and limbs (5 % [EAP]) and fatigue (11 % [EAP]) all had become relatively uncommon (Fig. 5). In only 2/170 patients originally initiated (ITT: 1.2 %, CI: 0.1 to 4.2 %) i.e. 2/152 patients still under treatment at visit 3 (EAP: 1.3 %, CI: 0.2 to 4.7 %), the treatment had to be discontinued at this time ('non-responders' at visit 3) because of a deterioration or lack of improvement of the acute bronchitis (Table 2, Fig. 2).

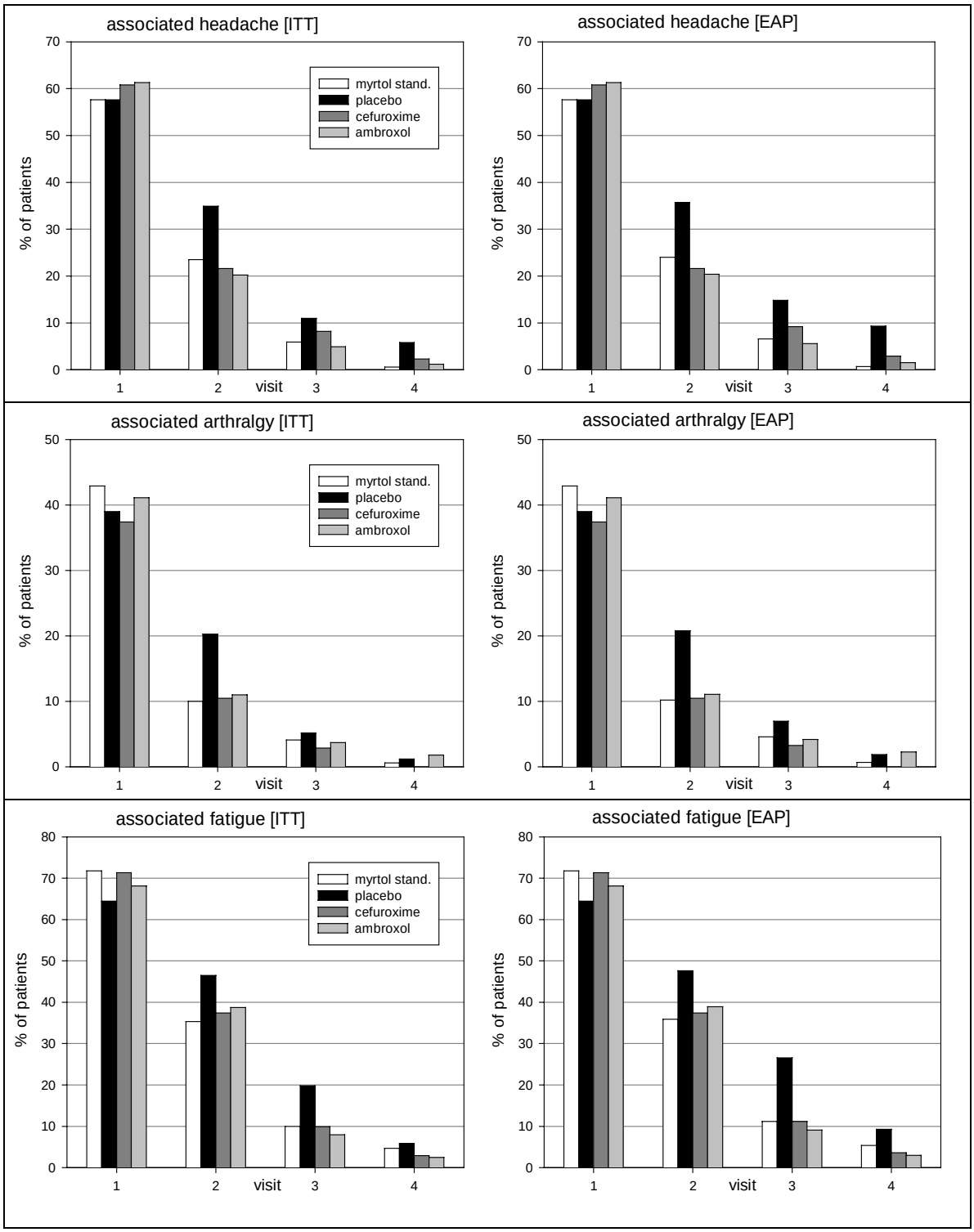

Fig. 5: Percentage of patients with associated headache (top), pain in joints and limbs (mid) and fatigue (bottom) at the various visits (1: enrolment, 2: after 1 week of treatment, 3: after 2 weeks of treatment and 4: 2 weeks after conclusion of the investigational treatments); ITT (left): all randomised patients receiving the investigational medication at least once, EAP (right): all patients evaluable for the given criterion at the defined time point (i.e. excluding non-exposed i.e. dropped-out patients).

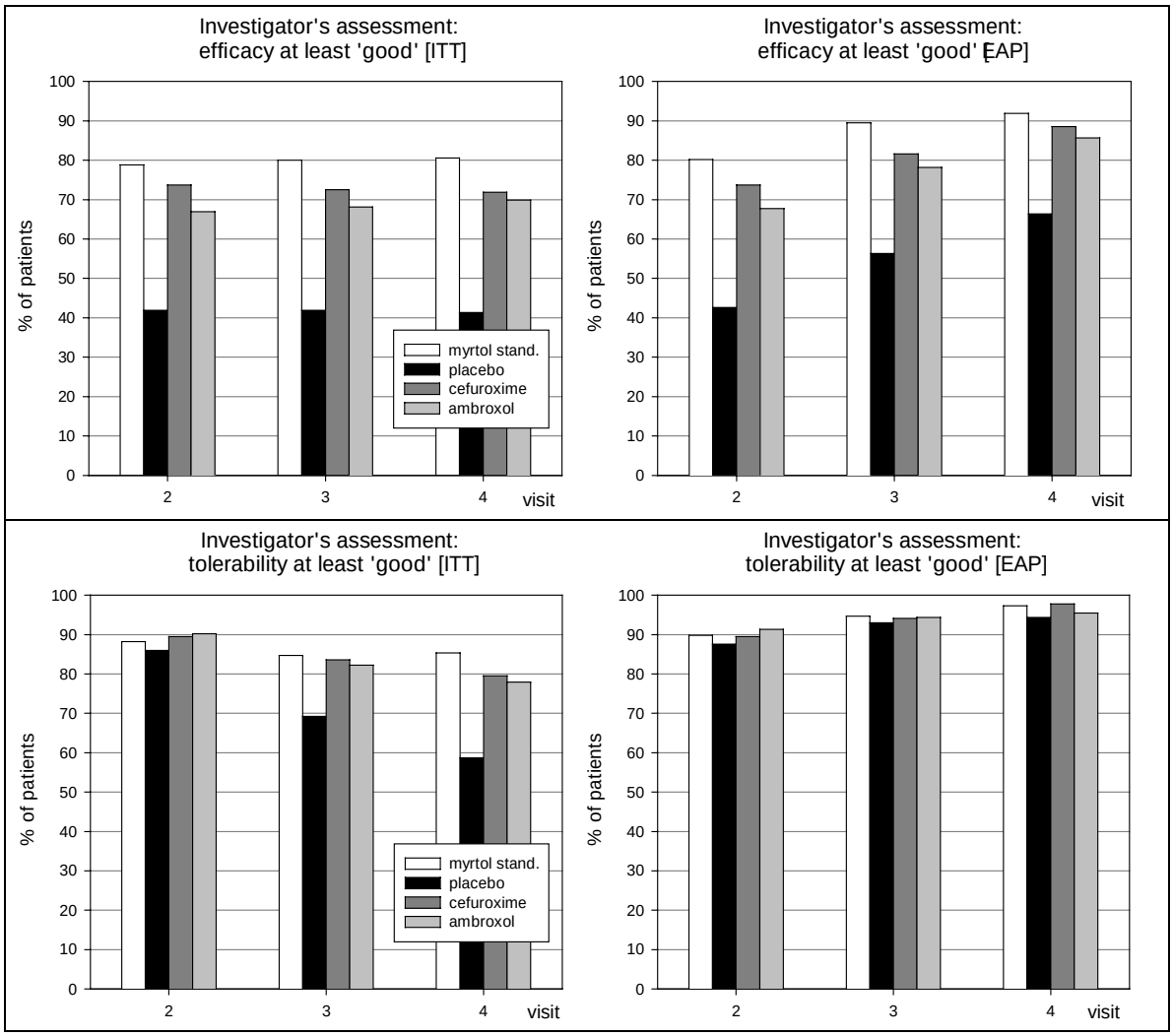

Fig. 6: Percentage of patients for whom the physicians scored the overall efficacy (top) and overall tolerability (bottom) at least as 'good' at the various visits (2: after 1 week of treatment, 3: after 2 weeks of treatment and 4: 2 weeks after conclusion of the investigational treatments); ITT (left): all randomised patients receiving the investigational medication at least once, EAP (right): all patients evaluable for the given criterion at the defined time point (i.e. excluding non-exposed i.e. dropped-out patients).

Of the 170 patients enrolled in the myrtol stand. group, 149 completed the study up to visit 4. At that time, the associated symptoms had cleared in most but not all patients and no abnormal findings on auscultation were present in any of the subjects [EAP] who completed the study. Bronchial hyperreactivity was present in only 13.4 % (CI: 8 to 20 %). There was no evidence of bronchoconstriction and/or relapse in the subjects still under study at that time.

3.4.4. Treatments with ambroxol and cefuroxime

In general, cefuroxime and ambroxol had a similarly beneficial effect, clearly superior to that of placebo, with little difference vs. myrtol stand., although the latter tended in general to score slightly better.

3.4.5. Overall efficacy

The superiority of the active treatments is also well demonstrated by the scores of both patients and physicians for the overall evaluation of efficacy (Fig. 6): for 42 %, 79 %, 74 % and 67 % (ITT) the efficacy was scored as 'good' or 'very good' by the physicians (41 %, 78 %, 74 % and 66 % for the scores by the patients) at visit 2 for the treatment groups with myrtol stand., placebo, cefuroxime and ambroxol, respectively. For 92 %, 66 %, 89 % and 86 % of the patients who remained under study, i.e. for those who had not to be discontinued (incl. drop-outs for non-response – EAP), the physicians scored similarly high at visit 4 (91 %, 65 %, 89 % and 87 % for the patient scores).

3.4.6. Safety and tolerability

There was a total of 131 AEs in 104/676 subjects: 15.9, 16.3, 14.0 and 15.3 % of the subjects treated with myrtol stand., placebo, cefuroxime and ambroxol (respectively) experienced at least one AE. There was one serious AE (mild increase in serum hepatic enzymes requiring hospitalisation for clarification) in a patient treated with placebo; no AE

was labelled as severe, 48 AE as of moderate intensity (myrtol stand.: 12, placebo: 10, cefuroxime: 12, ambroxol: 14 AE) and 83 as of mild intensity. Fifty-six AE (41 of mild and 15 of moderate intensity) were considered at least possibly treatment related: 18, 4, 15 and 19 AE under treatment with myrtol stand., placebo, cefuroxime and ambroxol respectively. 17/676 (2.5 %) patients were discontinued (also – multiple reasons possible) because of AE (24): 5, 2, 8 and 2 pts. treated with myrtol stand., placebo, cefuroxime and ambroxol, respectively.

There was no evidence or indication of relevant changes with regard to the findings upon physical examination, vital functions (blood pressure and pulse rate) and safety laboratory screens (haematology, clinical chemistry and urinalysis).

The treatments scored comparably well upon evaluation of tolerability by patients and physicians: for 88 %, 86 %, 90 % and 90 % (ITT) the tolerability was scored as 'good' or 'very good' by the physicians (85 %, 86 %, 84 % and 87 % for the scores by the patients) at visit 2 for the treatment groups with myrtol stand., placebo, cefuroxime and ambroxol, respectively. For 97 %, 94 %, 98 % and 96 % of the patients who remained under study, i.e. for those who had not to be discontinued (incl. drop-outs for non-response – EAP), the physicians scored similarly high at visit 4 (93 %, 95 %, 96 % and 95 % for the patient scores).

4. Discussion

Although mostly of viral origin, and in spite of well-evidenced expert advice against it, acute bronchitis still is often treated with antibiotics. This usually is explained by the patients' pressure and expectations. This latter factor might be challenged if appropriate alternatives were available. In patients with acute bronchitis and wheezing (or other evidence of bronchoconstriction), bronchodilators might be an alternative [25, 26, 27]; but their safety margin is low, especially because of tremor and – although less frequently – because of untoward cardiovascular extension effects [28, 29]. Additionally, this approach might be less appropriate for patients with acute bronchitis without evident bronchoconstriction [30]. Muco-secretolytic drugs are a further alternative. Their efficacy in preventing and alleviating acute exacerbations of chronic bronchitis has been extensively investigated and confirmed, but little is known about their efficacy and tolerability in acute bronchitis in patients without chronic respiratory disease. The present study was carried out to address this question.

The present study confirmed that acute bronchitis is a bothersome disease with a broad variety of symptoms at onset and a clear impairment of well-being. The observations in the group treated with placebo clearly showed that the condition is self-limiting as it regresses readily – albeit not completely – in many patients. But it also showed that there is room for improvement by appropriate therapeutic intervention.

Indeed, in the actively treated patient groups, the non-responder rates (i.e. the frequency of patients with a deterioration and/or lack of improvement to such an extent that discontinuation from the study was to be considered) at visit 2 (after 1 week of treatment) and 3 (after 2 weeks of treatment) were clearly lower than for placebo. The superiority of the active treatments vs. placebo, with little difference among the active treatments, was evident also for the cough data, and the associated signs and symptoms: there was a rapid, treatment dependent regression of the frequency of abnormal auscultation, and associated hoarseness, headache, pain in joints and limbs and fatigue, but not for associated rhinitis and sore throat (which cleared similarly fast for all treatments). This was confirmed by the patient's and investigator's valuation of efficacy: at visit 3, the investigators considered the efficacy at least good for 80.0 % (ITT – 89.5 % for EAP) and 41.9 % (ITT – 56.3 % for EAP) of the patients treated with myrtol stand. and placebo, respectively; this was similar on the basis of the patient's valuation.

The extent of discomfort due to coughing fits during the day and the night reflected the treatment effects differently, whereby the latter are less confounded and more suitable to evaluate treatment effects [31, 32].

Additionally, the active treatments were in general very well tolerated; AE were relatively few and mostly of mild-to-moderate intensity. There were no treatment related changes upon physical examination, for vital functions and for the safety lab. data.

It is concluded therefore, that treatment with myrtol stand. is as well tolerated as placebo but evidently superior in terms of efficacy when treating acute bronchitis, resulting in a more rapid and more complete recovery; in general, although well comparable with the other active treatments, myrtol stand. tended to be superior to alternative active treatments for several criteria. In view of this, myrtol stand. ought to be considered as a well-evidenced alternative to antibiotics for acute bronchitis, as it is evidently efficacious but carries no risk to cause bacterial resistance.

5. References

[1] Macfarlane, J. T., Holmes, W. F., Macfarlane, R. M. et al., Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in primary care in the UK: implications for developing management guidelines. Respir. Med. **91,** 427 (1997)

[2] Macfarlane, J., Holmes, W., Macfarlane, R. et al., Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. BMJ **315,** 1211 (1997)

[3] Verheij, T. J. M., Kaptein, A. A., Mulder, J. D., Acute bronchitis: aetiology, symptoms and treatment. Fam. Pract. **6,** 66 (1989)

[4] Becker, L., Glazier, R., McIsaac, W., Smucny, J., Antibiotics for acute bronchitis (Cochrane Review). In: The Cochrane Library, Issue 3 (2000); Update Software, Oxford

[5] Orr, P. H., Scherer, K., Macdonald, A., Moffatt, M. E. K., Randomized Placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. J. Fam. Pract. **36,** 507 (1993)

[6] Belongia, E. A., Schwartz, B., Strategies for promoting judicious use of antibiotics by doctors and patients. BMJ **317,** 668 (1998)

[7] Huovinen, P., Cars, O., Editorials – Control of antimicrobial resistance: time for action. BMJ **317,** 613 (1998)

[8] Wise, R., Hart, T., Cars, O. et al., Streulens, M., Helmuth, R., Houvinen, P. et al., Antimicrobial resistance is a major threat to public health. BMJ **317,** 609 (1998)

[9] Webb, S., Lloyd, M., Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. Br. J. Gen. Pract. **44,** 165 (1994)

[10] Rapaport, J., Patients' expectations and intention to self medicate. J. R. Coll. Gen. Pract. **29,** 468 (1979)

[11] Butler, C. C., Rollnick, S., Pill, R. et al., Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. BMJ **317,** 637 (1998)

[12] Juergens, U. R., Stöber, M., Vetter, H., Steroidartige Hemmung des monozytären Arachidonsäuremetabolismus und der IL-1ß-Produktion durch 1.8-Cineol. Atemw.-Lungenkrkh. **24,** 3 (1998)

[13] Beuscher, N., Kietzmann, M., Bien, E. et al., Interference of Myrtol standardized with inflammatory and allergic mediators. Arzneim.-Forsch./Drug Res. **48 (II),** 985 (1998)

[14] Beuscher, N., Bien, E., Elstner, E. F. et al., Phytotherapiekongreß Würzburg, 1997, Z. Phytother., Abstractband 8, S. 9–10

[15] Barattini, D. F., Daniotti, S., Pierfederici, P., Prevention of chronic bronchitis exacerbations with Ambroxol (mucosolvan retard). An open long-term, multicenter study in 5,635 patients. Respiration **55** (Suppl. 1), 84 (1989)

[16] Cegla, U. H., Long-term therapy over 2 years with Ambroxol (Mucosolvan) retard capsules in patients with chronic bronchitis. Results of a double-blind study of 180 patients. Prax. Klin. Pneumol. **42,** 715 (1988)

[17] Olivieri, D., Zavattini, G., Tomasini, G. et al., Ambroxol for the prevention of chronic bronchitis exacerbations: long term multicenter trial: protective effect of Ambroxol against winter semester exacerbations: a double-blind study versus Placebo. Respiration **51** (Suppl. 1), 42 (1987)

[18] Germouty, J., Jirou-Najou, J. L., Clinical efficacy of Ambroxol in the treatment of bronchial stasis: clinical trial in 120 patients at two different doses. Respiration **51** (Suppl. 1), 37 (1987)

[19] Ericsson, E. C., Juhasz, J., Jonsson, E. et al., Ambroxol therapy in simple chronic bronchitis: effects on subjective symptoms and ventilatory function. Eur. J. Respir. Dis. **69,** 248 (1986)

[20] Disse, B. G., The pharmacology of Ambroxol – review and new results. Eur. J. Respir. Dis. Suppl. **153,** 255 (1987)

[21] Meister, R., Wittig, Th., Beuscher, N. et al., Efficacy and tolerability of myrtol standardized in long-term treatment of chronic bronchitis: a double-blind, placebo-controlled study. Arzneim.-Forsch./Drug Res. **49 (I),** 351 (1999)

[22] Quanjer, P. H., Standardised lung function testing: Report Working Party standardisation of Lung Function tests of the European Respiratory Society and the European Community for Coal and Steel. Eur. Respir. J. **6** (Suppl. 16), 1 (1993)

[23] Billingham, L. J., Abrams, K. R., Jones, D. R., Methods for the analysis of quality-of-life and survival data in health technology assessment. Health Technol. Assess. **3,** 1 (1999)

[24] Touloumi, G., Pocock, S. J., Babiker, A. G. et al., Estimation and comparison of rates of change in longitudinal studies with informative drop-outs. Stat. Med. **18,** 1215 (1999)

[25] Hueston, W. J., A comparison of albuterol and erythromycin for the treatment of acute bronchitis. J. Fam. Pract. **33,** 476 (1991)

[26] Hueston, W. J., Albuterol delivered by metered-dose inhaler to treat acute bronchitis. J. Fam. Pract. **39,** 437 (1994)

[27] Melbye, H., Aasebo, U., Straume, B., Symptomatic effect of inhaled fenoterol in acute bronchitis: a Placebo-controlled double-blind study. Fam. Pract. **8,** 216 (1991)

[28] Littenberg, B., Wheeler, M., Smith, D. S., A randomized controlled trial of oral albuterol in acute cough. J. Fam. Pract. **42,** 49 (1996)

[29] Nelson, H. S., ß-Adrenergic bronchodilators. N. Engl. J. Med. **333,** 499 (1995)

[30] Williamson, H. A., Pulmonary function tests in acute bronchitis: evidence for reversible airway obstruction. J. Fam. Pract. **25,** 251 (1987)

[31] Matthys, H., Expektorantien, Pharmakotherapie mit mukoaktiven Substanzen, in: F. Kummer, N. Konietzko Medici (Hrsg.), Pharmakotherapie bronchialer Erkrankungen, 1. Aufl., S. 133–137, Springer Verlag, Wien (2000)

[32] Matthys, H., Erhardt, J., Rühle, K. H., Objektivierung der Wirkung von Antitussiva mittels Tussometrie an Patienten mit chronischem Husten. Schweiz.-med.Wschr. **115,** 307 (1985)

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