Biomarker-enhanced triage in respiratory infections – a proof-of-concept feasibility trial

W. C. Albrich*#, K. Rüegger*#, F. Dusemund#, P. Schuetz #, B. Arici#, A. Litke#, C. A. Blum#, R. BossartΔ, K. RegezΔ, U. SchildΔ, M. GuglielmettiΔ, A. ConcaΔ, P. SchäferΔ, M. Schubert¶, S. de Geest¶, B. ReutlingerΔ, S. Irani±, U. Bürgi§, A. Huber‡, B. Mueller#

* equally contributing first authors

Medical University Department of the University of Basel, Kantonsspital Aarau, Aarau,

ΔDepartment of Clinical Nursing Science, Kantonsspital Aarau,

¶ Institute of Nursing Science, University Basel, Basel,

± Department of Pneumology, Kantonsspital Aarau, Aarau,

§ Emergency Department, Kantonsspital Aarau, Aarau,

‡ Department of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland

Corresponding author:

Prof. Beat Müller, M.D.

Medical University Department, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland

happy.mueller@unibas.ch ; +41 62 838 6818

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Abstract

Concerns about inadequate performance and complexity limit routine use of clinical risk scores in lower respiratory tract infections (LRTIs). Our aim was to study feasibility and effects of adding the biomarker proadrenomedullin (ProADM) to the CURB65 score on triage decisions and length of stay (LOS).

In a randomised controlled proof-of-concept intervention trial, triage and discharge decisions were made for adults with LRTI according to interprofessional assessment using medical and nursing risk scores without (control group) or with (ProADM group) knowledge of ProADM values, measured on admission, day 3 and day 6. An adjusted generalised linear model was calculated to investigate the effect of our intervention.

On initial presentation the algorithms were overruled in 123 (39.3%) of the cases. Mean LOS tended to be shorter in the ProADM (n=154; 6.3 days) compared to the control group (n=159; 6.8 days; adjusted regression coefficient: -0.19; 95%CI: (-0.41, 0.04); p=0.1). This trend was robust in subgroup analyses and for overall LOS within 90 days (7.2 vs. 7.9 days; -0.18; (-0.40, 0.05); p=0.13). There were no differences in adverse outcomes or readmission.

Logistic obstacles and overruling are major challenges to implement biomarker-enhanced algorithms in clinical settings and need to be addressed to shorten LOS.

Trial registration: ISRCTN62022490

Key words: biomarkers; disease management; length of stay; decision making; respiratory tract infections

Running head: Proadrenomedullin-enhanced triage in LRTI

Introduction

Community-acquired lower respiratory tract infections (LRTIs), including acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and community-acquired pneumonia (CAP), are among the most frequent causes of hospitalisation[1]. Inpatient care of CAP is 8-20 times more costly than outpatient treatment[2, 3] with higher risks of nosocomial complications[4]. Admission rates and length of stay (LOS) are variable in clinical routine and arbitrarily affected by medical, functional, psychosocial factors and patients' and relatives' preferences[2, 5-10]. In this context, scoring systems to quantify medical, nursing and social factors in a standardized way were developed. The self-care index (SPI="Selbstpflegeindex") was developed to assess functional dependence in activities of daily living and predicts the need for social services and [11]. The post-acute care discharge score (PACD) predicts the biopsychosocial risk, requirement for post-acute care and facilitates discharge planning[12]. In the United Kingdom and Scandinavia, nurse-led units (NLU) have become popular institutional settings for patients with low medical but predominantly nursing care needs[13, 14].

To standardise medical risk assessment in CAP the CURB65 score is being propagated [15]. In previous research, we and others validated the feasibility of the CURB65 score in CAP and, importantly, extended it to non-CAP LRTIs, i.e. acute bronchitis and AECOPD. Thereby, the CURB65 score predicts mortality in patients with non-CAP LRTIs with similar prognostic accuracy as in CAP[16-18]. Limitations of clinical risk scores for triage decisions include their static behaviour over time, validation for predefined outcomes, considerable variability of outcomes within given risk categories, and poor memorability[19].

Biomarkers are objective, dynamic and easily measurable. Proadrenomedullin (ProADM) belongs to the calcitonin peptide superfamily and is ubiquitously hyperexpressed during bacterial infections. Of biomarkers, it currently has the best evidence for prognostic assessment in LRTIs[20-23]. We recently showed that ProADM predicted mortality and complications in LRTIs similarly well as the CURB65 score and provided independent prognostic information within each CURB65 risk class[16, 24]. Since biomarkers and clinical scoring systems reflect different aspects of the host response, their combinations demonstrate superior prognostic accuracy[20, 25-27]. Combining ProADM cut-offs with CURB65 classes, we proposed a novel CURB65-A score with improved prognostic accuracy for LRTI[16, 18]. Subsequently, we demonstrated the potential to reduce hospitalisations in patients with low medical risk (OPTIMA I study)[28].

While low CURB65 scores generally indicate the safety of outpatient therapy[29], additional clinical criteria improve its prognostic accuracy[24]. We hypothesized that triage decisions based on CURB65 and medical stability criteria[30] are less effective than if these were

enhanced by ProADM. In this proof-of-concept study we tested the feasibility, possible effects and limitations of adding ProADM to CURB65 and clinical stability criteria and biopsychosocial scores (SPI and PACD) for initial risk stratification and subsequent clinical management for LOS and compared results with the former observational OPTIMA I study (historical control group) [28].

Methods

Study subjects and study design

This was an interprofessional and pragmatic randomised controlled intervention trial at an acute-care hospital and 2 post-acute centers in Switzerland between September 2010 and July 2011. The study was largely based on routine medical and nursing staff to closely reflect the clinical "real-life" setting in all patients in both groups. We consecutively enrolled patients (≥18 years) with community- or nursing home-acquired LRTI including CAP, AECOPD, acute bronchitis and influenza. Exclusion criteria were inability to communicate in any of 6 commonly spoken languages, intravenous drug use, immediately life-threatening or terminal illness.

Methods

Patients were randomised 1:1 following a computer-generated randomisation scheme, stratified for type of LRTI, into a ProADM or a control group. Patients were triaged by the treating physician according to an interprofessional medical and nursing risk assessment consisting of medical (CURB65 on admission; medical stability criteria during hospitalisation), functional (SPI) and biopsychosocial criteria (PACD), either with (ProADM group) or without knowledge (control group) of ProADM values (**Figure 1**).

Site of care was recommended in both groups: regular hospitalisation or ICU admission in patients at high medical risk; short hospitalisation for 48 hours followed by re-evaluation in patients at intermediate medical risk; and ambulatory care, home health care, health resort, rehabilitation or NLU according to biopsychosocial risk for patients at low medical risk.

Predefined medical, biopsychosocial and organisational criteria and patient's preference could be used to optionally overrule triage decisions and transfer patients to higher risk classes. Biopsychosocial, functional and organisational criteria could increase the level of care up to the NLU. Patient's preference had priority for the final triage decision. Patients remained blinded to study group assignment.

Hospitalised patients were assessed by registered nurses for medical stability criteria[29] three times daily until medical stabilisation. For the functional and biopsychosocial risk, the SPI[11] was assessed once within the first 3 days, and then on day 6 and every 3 days; the PACD[12] score was documented on admission and day 3. Patients were considered appropriate for hospital discharge if they were medically stable without predefined medical, biopsychosocial, functional or organisational overruling criteria. In the ProADM group, medical stability was additionally influenced by ProADM levels on days 3 and 6 (**Figure 1**). Site of care was determined by biopsychosocial and organisational factors in patients who were otherwise appropriate for discharge.

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Treating physicians were given formal introduction into correct application of ProADM values, triage algorithms including CURB65, stability criteria and overruling criteria, and received regular reminders throughout the study. Nursing staff received on-going training on correct use of biopsychosocial and functional criteria. The study team was permanently available for questions regarding the algorithm and oversaw the compliance with the triage pathways. Antibiotic therapy was provided according to previously validated and published PCT cut-off ranges [31].

All patients discharged to home received a phone call within 24 hours by a study nurse to confirm stability and address urgent problems. All patients underwent a standardised phone interview on days 30 and 90 by blinded members of the study team. The trial was approved by the local ethics committee (Kantonale Ethikkommission Aargau, EKAG 2010/045) and supervised by an independent data safety monitoring board.

Methods of ProADM measurement

ProADM was measured in the central hospital laboratory from EDTA plasma with a commercially available immunoassay (MR-ProADM, Thermofisher Scientific-BRAHMS AG, Hennigsdorf, Germany) with a functional assay sensitivity of 0.12µg/L[20]. Results were routinely available within 1.5 hours upon ordering around the clock and reported only for patients randomised to the ProADM group.

Definitions

CAP, AECOPD, bronchitis and severity assessment of COPD were defined as described previously[16, 18]. Medical stability criteria for CAP were applied in all LRTIs[30]. Patients were considered medically stable if all of the following criteria were fulfilled: feasibility of oral intake; stable vital signs for ≥24 hours (temperature <37.8°C, heart rate ≤100/min, respiratory rate ≤24/min, O_2-saturation ≥90% or pO_2 ≥60mmHg on room air; systolic blood pressure ≥90mmHg); mental status at level before LRTI; no evidence of acute co-morbidity necessitating hospitalisation.

Outpatient care was defined as discharge to home (with or without home health care) from the emergency department. Adverse events were defined as any of mortality, ICU admission, recurrent infection and rehospitalisation. LOS was defined as number of physician-led nights spent in hospital, i.e. excluding time spent in the NLU.

Endpoints

The primary endpoint was overall LOS comparing the ProADM with the control group. Secondary endpoints were comparisons with regard to measure of algorithm-adherence, functional status, adverse events and readmission rates.

Statistical analysis

As a proof-of-concept study to primarily assess feasibility, the primary analysis population was the full analysis set, which included all randomised patients following an intention-to-treat principle. The primary analysis was repeated on the per-protocol-population, which excluded non-evaluable cases, violators of exclusion criteria and patients with final diagnoses other than LRTI (**Figure 2**).

We, furthermore, compared the results of the overall cohort to a previously published cohort from a prospective observational quality control study (OPTIMA I, historical control group), where triage decisions were recommended based on CURB65 and medical stability criteria but less strictly enforced by the study team[28]. This allowed us to assess the effect of more strictly enforcing triage pathways in the current intervention study compared to a historic control group, as surrogate for the presence and extent of a Hawthorne effect, i.e. improved triage performance by the treating physicians simply due to the knowledge of being monitored under study conditions.

The primary hypothesis of the randomised study was that knowledge of ProADM values improves interdisciplinary risk-assessment and safely reduces LOS without excess adverse events and patient dissatisfaction. Based on intention-to-treat analysis on the primary outcome, a power of 80%, 2-sided α of 5%, an expected mean length of stay in the acute-hospital setting of 8 days, SD 4 days and expected difference of 1.5 day compared with a historic control[28], we expected to need a sample size of at least 113 patients per group. We planned to screen 350-400 and enroll 250-300 patients.

We used mean and standard deviation, or median and interquartile range to describe the population as appropriate. To investigate for difference between randomisation arms in regard to LOS, we calculated a generalised linear model (GLM) with a gamma distribution as previously suggested for this type of outcome data[31]. We adjusted the model for the main predictors of LOS, namely age, gender, type of LRTI and the CURB65 score. For secondary binary endpoints, we calculated logistic regression models adjusted for the same set of covariates as described above. P-values were reported at the two-sided 5% significance level.

Results

From a total of 430 screened patients with acute LRTI, we enrolled 313 (72.8%) patients (**Figure 2**). Baseline characteristics were balanced in both groups (**Table 1**).

Overall, the algorithms were overruled in 123 (39.3%) of the cases on initial presentation and in 108 (34.5%) after hospital admission. In the control group overruling occurred in 81 (50.9%) patients on initial presentation and 52 (32.7%) after hospital admission; in the ProADM group the algorithm was overruled in 42 (27.3%) patients on initial presentation (p<0.001) and 57 (37.0%) after hospital admission (p=0.42).

Overruling criteria

The reasons for overruling on initial presentation were considered medical in 111 (90.2%), biopsychosocial and functional in 2 (1.6%), organisational in 5 (4.1%) and patient's preference in 5 (4.1%). After reaching medical stability, the triage algorithm was overruled 108 times in the 313 patients (34.5%) with consecutively delayed discharge from hospital. The reasons for overruling were considered medical in 27.8%, biopsychosocial and functional in 6.5%, organisational in 52.8% and patient's preference in 11.1% (**Figure 3**). "Waiting for laboratory results, imaging studies or consultant examinations" was the most frequent organisational overruling criterion (54.4% of organisational reasons and 28.7% of all overrulings). The most frequent medical and biopsychosocial/functional overruling criteria stated were "acute other medical problems" and "deficit of mobility or self-care requiring treatment", respectively.

Patients' preferences

12 patients disliked their initially recommended triage suggestion (5 in the control and 7 in the ProADM group) primarily due to concern about safety at home and were triaged according to their own preferences. Thus, patient compliance with triage suggestions was 96.2%.

Length of hospital stay

Overall, mean (95%CI) LOS was 6.5 (5.8, 7.3) days. 63 patients (20%) were treated as outpatients, with no difference between the control (20.7%) and the ProADM group (19.4%, p=0.78). Mean (95%CI) LOS in the control group was 6.8 (5.7, 7.9) days compared to 6.3 (5.4, 7.2) days in the ProADM group. After adjusting for age, gender, LRTI type and CURB65 score, the ProADM group tended to have a shorter LOS (regression coefficient -0.19; 95%CI: -0.41, 0.04, p=0.1). Results were similar when only considering inpatients treated for ≥1 day in the hospital (-0.12, (-0.29, 0.04), p=0.15). The results were robust in subgroup analyses

without evidence for effect modification (p interaction for each subgroup analysis >0.05; **Figure 4**). A similar trend for lower LOS was found when considering the total number of days hospitalised within 90 days after enrolment: 7.9 (6.7, 9.1) days in the control vs. 7.2 (6.2, 8.2) days in the ProADM group (adjusted regression coefficient: -0.17, (-0.40, 0.05), p=0.13). Results were also robust in a per-protocol analysis excluding non-evaluable cases, violators of exclusion criteria and patients with other final diagnoses than LRTI, and when restricted to patients without organisational, biopsychosocial or preference overruling criteria. The mean time spent in the NLU was 8.1 (range 1 to 25; median 5.5) days in patients in the control group (n=14) and 4.5 (range 2 to 7; median 4.5) days in patients in the ProADM group (n=4) (p=0.11).

Adverse events

Overall, 21.8% and 34.5% of patients experienced an adverse outcome within 30 and 90 days, respectively. There was no difference between the control and the ProADM group for the combined adverse outcome endpoint at 30 days (OR 0.81, (0.46, 1.42), p=0.49) and at 90 days (OR 0.82, (0.50, 1.35), p=0.42). No increased risk was found in regard to mortality, ICU admission and recurrent infection (**Table 2**). Patients' subjective health status on discharge from hospital, measured with the EQ5-D visual analogue scale (VAS), was similar in both groups (61.8% in control vs. 60.3% in ProADM group).

Readmission rate

Readmission rates of patients discharged alive for 30 [90] days were similar in the control (8.0% [13.3%]) and the ProADM group (4.9% [10.5%], p=0.29 [p=0.47]).

Effect of ProADM on triage during hospitalisation

In a large proportion of patients in the ProADM group, the ProADM values did not change between categories (i.e. remained <0.75 µg/l or 0.75 to 1.5µg/l or >1.5µg/l) from admission to day 3 (69.9%) and from day 3 to day 6 (72.2%) (**Table 3**). In 22.1% and 22.8%, there was a decrease in ProADM categories, from admission to day 3 and from day 3 to day 6, respectively, and the ProADM category increased in only 8.0% and 5.1%, respectively.

In the ProADM group, 114 and 81 patients were still hospitalized on day 3 and day 6, of which 84.2% and 79.0% were clinically not stable, respectively. For patients meeting all stability criteria, a high ProADM level indicated that ongoing hospitalization was necessary in 9 of 18 (50.0%) on day 3 and in 12 of 17 (70.6%) patients on day 6 in the ProADM group (**Table 4**).

Historic comparison

The results of this study were compared to a historic control patient population (OPTIMA I study) [28]. Compared to historic controls, significantly more patients (20.1% vs. 8.7%; p<0.001) were treated as outpatients during OPTIMA II. The overall LOS (6.5 days) was 1.9 days (22.6%) shorter in this current intervention study OPTIMA II compared to an overall LOS of 9.8 days (corresponding to 8.4 days with the same LOS definition of this study) during the OPTIMA I study, i.e. when triage decisions in the same hospital were recommended based on CURB65 and medical stability criteria but not reinforced[28]. The effect was even more pronounced in the ProADM group (2.1 days, 25.0%).

Discussion

While many studies have evaluated the potential of various clinical disease severity scores and biomarkers to improve prognosis in patients with LRTIs, they all used retrospective or observational designs [32, 33]. However, today's major challenge in view of limited health care resources is to implement these "promising" observational finding into clinical practice. Measuring biomarkers or calculating clinical scores is costly, time-consuming and arguably useless, unless they have a relevant impact on patient care. Based on observational studies, several biomarkers predict adverse outcomes and mortality in patients with LRTIs. These include PCT, which had comparable prognostic accuracy to predict 28 day mortality in CAP as the CURB65 score[34] and particularly helps to estimate the risk for treatment failure and mortality if measured serially[35, 36]. Yet, more investigational biomarkers such as cortisol, proatrial natriuretic peptide, d-dimer, proendothelin-1, copeptin and ProADM have shown a higher prognostic accuracy compared to PCT particularly when measured on admission [32, 37]. Even though these biomarkers are rarely compared head-to-head, currently ProADM is considered the best single prognostic biomarker[22, 23], whereas PCT is currently the best and only systematically evidence-based biomarker to guide antibiotic therapy for patients with LRTI[38].

In this context we undertook a major effort to assess obstacles of implementing a biomarker-enhanced scoring system into daily practice with an adequate and strong control group in a state of the art randomised controlled trial (RCT) in order to inform decision makers. Notably, we used a multimodal triage bundle in both groups for individualised interprofessional risk assessment. Our study is unique in being the first randomised controlled proof-of-concept intervention trial to investigate the feasibility of adding the biomarker ProADM to established and guideline-recommended clinical criteria for site of care decisions in patients with LRTIs. Although we could not show a significant improvement in main outcome between control and intervention group (evidence level 1b), we found a shorter LOS of patients in this intervention study regardless of group assignment and more pronounced for the ProADM- group, compared to historic controls in the same hospital, which was a predefined analysis of evidence level 2b[28].

Indeed, our RCT showed a non-significant trend for reduction of LOS during the initial encounter (point-estimate 0.5 days) and for overall hospitalisations (point-estimate 0.7 days) within 90 days in the ProADM-enhanced compared to the control group. The reduction of LOS was not achieved through a compensatory increase in days spent in the NLU. In fact, our data do not suggest that the LOS in the NLU was increased using ProADM-enhanced triage. The major obstacles were organisational insufficiencies, which are currently typical for many healthcare settings such as the one in Switzerland, e.g. full bed capacity at receiving centers or night and weekends, which prevented better adherence to recommended triage

pathways in both the ProADM and the control group. Patients who had reached medical stability but required additional nursing care or rehabilitation frequently remained hospitalised due to limited capacities at receiving rehabilitative institutions. Furthermore, many patients required hospitalisation for medical problems unrelated to the LRTI. On admission, when 90% of overrulings were for medical reasons, overruling was significantly more frequent in the control than the ProADM group.

While our study apparently was underpowered and the significance level of ProADM-enhanced triage was formally missed, the trend of our findings were robust and unequivocal in all examined subgroups. A reduction of 0.5 to 0.7 days (7.3% and 8.9%, respectively) for the ProADM groups is clinically remarkable as it was embedded in an interdisciplinary risk assessment bundle and compared to a highly competitive, guideline-conform and strictly reinforced control group.

Thus, our results must be interpreted in light of organisational challenges. In such a setting with a strictly reinforced control group and major logistic hurdles we consider the results of this study clinically relevant. The impact of the ProADM-enhanced algorithm is therefore expected in settings with facilitated transition mechanisms to non-acute medical care.

Our interdisciplinary, multimodal approach led to outpatient treatment in around 20% of patients, which is more than double of our historic control (9%)[28]. This achievement alone confers several advantages: reduction of costs[8] and nosocomial infections[39]. Patients treated at home resume normal activities sooner and experience fewer thromboembolic events[39]. Risk of worsening of pre-existing frailty or delirium is lower in outpatients. A third of elderly patients develop disabilities after hospitalisations for medical reasons such as CAP[40] as 50% of disabilities in elderly persons occur in the setting of hospitalisation[41]. If given the choice, most low-risk patients with CAP prefer outpatient care[42], which is associated with similar outcomes but higher patient satisfaction and lower costs[43].

A 0.5 day shorter LOS was estimated to correspond to $1.37 billion annual savings for CAP patients in the US [44]. Interestingly, this equals our point estimate of shortening of LOS, even though it did not reach statistical significance.

Clinical pathway bundles in the management of pneumonia reduced hospitalisation rate and LOS particularly in low-risk patients, and decreased overall costs while achieving similar quality of life and patient outcomes[45-47]. These interventions were complex and resource-intensive. Recently a 3-step critical pathway (early mobilisation, criteria for switching to oral antibiotics and objective criteria regarding the need for hospital care or discharge, i.e. the core of our algorithm) was found effective and safe to reduce both length of antibiotic treatment and LOS [43]. Our triage algorithm attempts to be both comprehensive and feasible for real-life. It takes medical, functional or social aspects into account and therefore consists of several different risk assessments and predefined overruling criteria. Despite its

complexity, we have been able to implement it in our hospital into clinical routine since the end of this study with the help and dedication of the Medical Department, the Nursing Department and our social workers.

The CURB65 score was previously shown to be applicable to patients with non-CAP LRTI as well[16-18]. While the medical stability criteria[48], which were used in this trial, were not formally extended to patients with non-CAP LRTI, there is little reason to limit their use to CAP considering the fact that many patients are, allegedly unnecessarily, hospitalised without formal infiltrate on chest X-ray but symptoms of LRTI, i.e. acute bronchitis and AECOPD.

Importantly, there was no increased risk for readmissions or serious adverse events and patients reported similar health status on hospital discharge between the two groups. Fear of medical complications was previously shown to be the most important cause for hospitalisation[6]. This was independent of disease severity indicated by clinical risk scores, and it did not correlate with successful procalcitonin (PCT)-guided antibiotic stewardship[49]. A 96.2% patients' agreement with the triage algorithm also confirms that patients feel safe and comfortable with triage decisions. Our ProADM-algorithm was not designed to result in earlier discharges than would be theoretically possible with CURB65 and medical stability criteria alone. Instead, ProADM provided an additional safety tool to increase confidence in readiness for discharge. In fact, high ProADM values on day 3 and day 6 led to ongoing hospitalisations in 50% and 70% of hospitalised patients who otherwise were medically stable and ready for discharge according to clinical criteria alone.

One of the strengths of this study was its innovative design. The functional assessment was evidence-based[12], the biomarker-enhanced risk score was derived and validated based on a large multicenter-RCT (ProHOSP) and an additional observational study (OPTIMA I)[16, 28]. Furthermore, this study is timely and relevant in view of the increasingly wide-spread implementation of DRGs where an effective triage and a timely discharge will be of great importance. It is important to apply evidence-based triage algorithms to prevent unwanted complications. Although the effect of ProADM guidance missed statistical significance, it is noteworthy that the control group had a short LOS due to very efficient triage based on strongly reinforced guideline-recommendations, thus correcting for a Hawthorne limitation, a known limitation of previous projects in biomarker research. Other contributing factors were organisational overrulings as the Swiss health-care system is not yet that well prepared for early discharges. Additional strengths were the high recruitment rate and low loss-to-follow up. Finally, due to the objective triage criteria used, our triage algorithm might be applied to

other healthcare systems. However, its feasibility and utility need to be confirmed in other optimised settings and larger patient populations.

In conclusion, in this proof-of-concept trial we show the feasibility and challenges of an interdisciplinary and biomarker-enhanced triage algorithm to shorten LOS in patients with LRTIs and thereby avoid medically unnecessary days in the hospital. In settings with broader opportunities for outpatient and non-acute hospital care, the benefit of a structured risk assessment might be even larger.

Figure legends:

Figure 1. Algorithm of risk assessment for triage decisions on admission and during hospitalisation

Triage algorithm based on medical and biopsychosocial risk assessment with and without addition of ProADM for patients with lower respiratory tract infection on admission. SPI – "Selbstpflege-Index"; PACD – post acute care discharge score; ProADM – proadrenomedullin; ICU – intensive care unit

Medical overruling criteria:

- admission to ICU, based on respiratory (respiratory rate ≥30/min and/or SO_2<90% with 6L O_2/min) or hemodynamic instability (systolic blood pressure for ≥1h <90mmHg despite adequate volume resuscitation or vasopressor requirement);
- life-threatening co-morbidity, i.e. imminent death; complications (abscess, empyema); for COPD GOLD III & IV; O_2-saturation <90% despite 30 minutes intensive treatment;
- acute illness requiring hospitalisation independent from LRTI;
- comorbidity, i.e. immunodeficiency (neutrophiles <500/µL; if HIV+: CD4 <350/µL, leukemia, lymphoma, myeloma, cytotoxic medications, haemodialysis), pneumonia within last 6 weeks, hospitalisation independent of indication within the last week, other significant lung disease (cancer, fibrosis, bronchiectasis, tuberculosis, pulmonary embolism, cavitary lung disease);
- confusion, delirium or intravenous drug use.

Biopsychosocial and functional overruling criteria:

- criteria requiring intensive nursing care, i.e. dementia, recurrent falls, pressure ulcer and inability to reliably take medications;
- SPI score<32 points in patients with a low PACD score (<8)[11];
- deficit of mobility or self-care requiring treatment.

Organisational overruling criteria:

- waiting for placement in a non-acute medical care facility (holiday bed, rehabilitation, nursing home, home health care);
- waiting for laboratory results, imaging studies or consultant examinations

Patient's preference: patient's or relative's concerns about safety at home; lack of supporting social network; financial reasons.

Medical stability during hospitalisation[48] included all of the following:

- feasibility of oral intake or need for i.v. therapy;
- stable vital signs for ≥24 hours:
- temperature <37.8°C,

- ▪ heart rate ≤100/min,
- ▪ respiratory rate ≤24/min,
- ▪ O_2-saturation ≥90% or pO_2 ≥ 60 mmHg on room air or, in patients with home O_2 therapy, no higher O_2 flow;
- ▪ systolic blood pressure ≥90mmHg);
- ▪ mental status at level before LRTI.
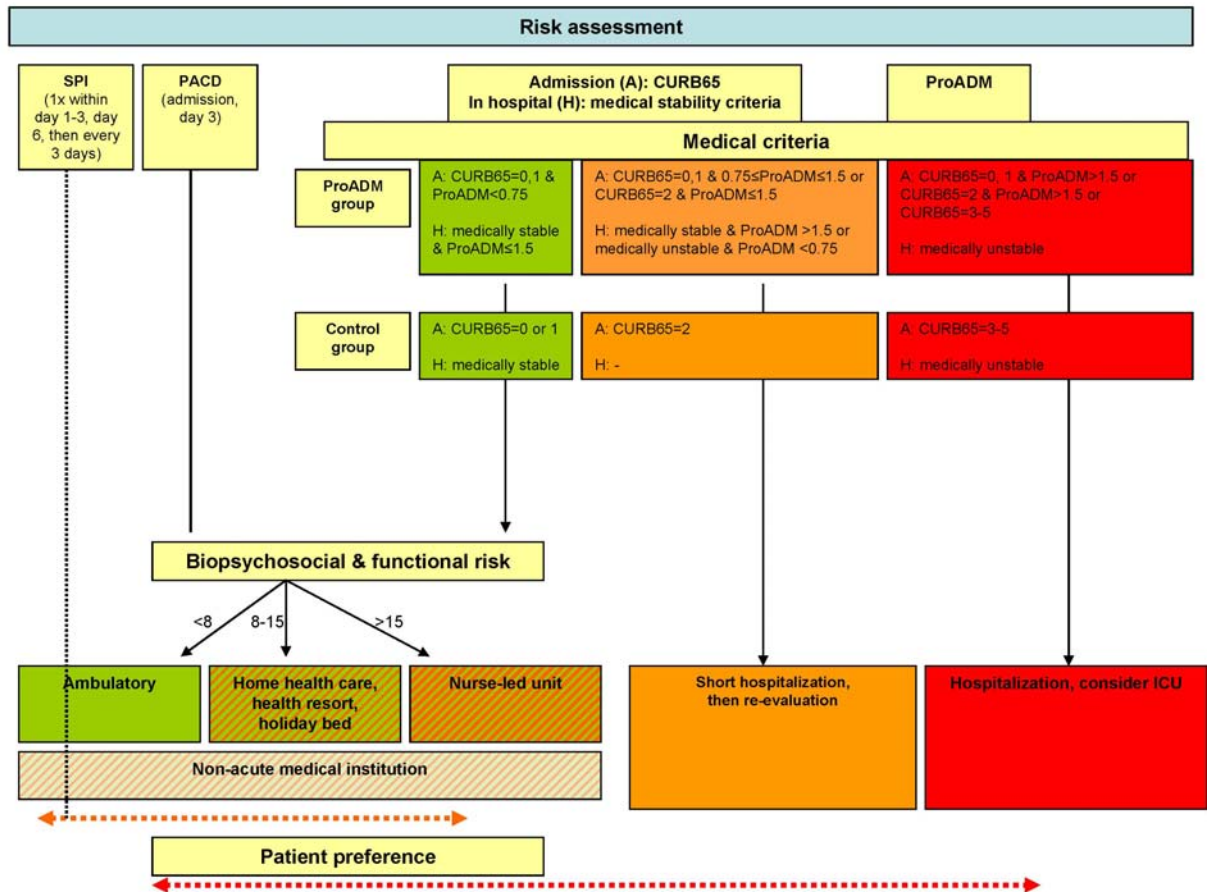
Figure 2. Flow diagram of patients in the trial

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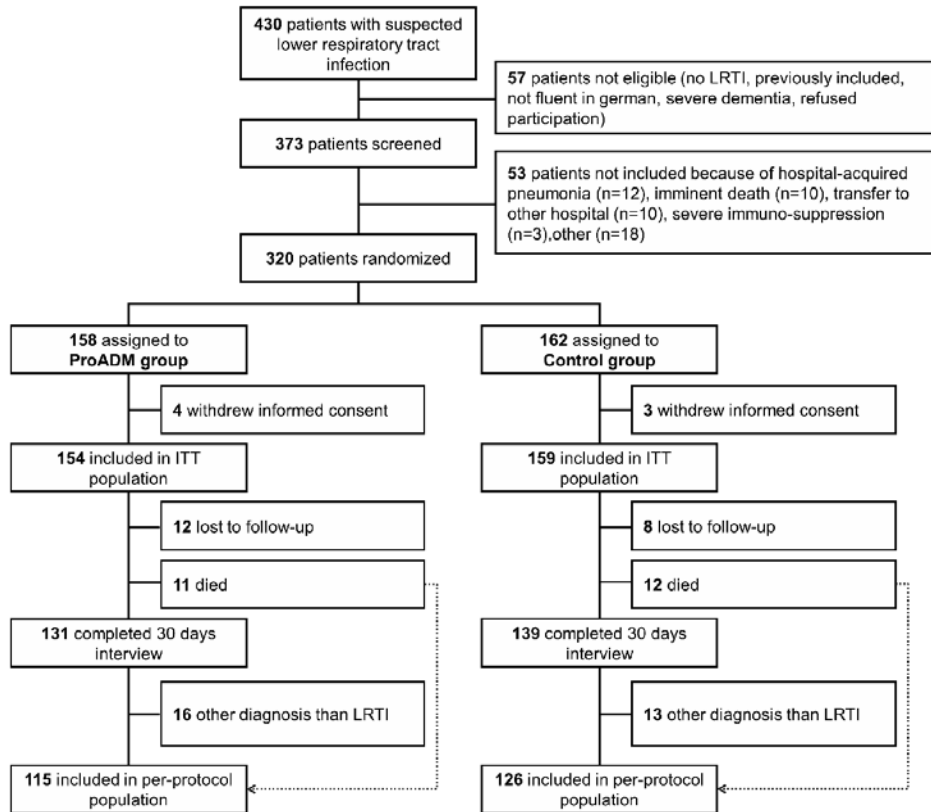
Figure 3. Reasons to overrule triage algorithm after first medical stabilisation

Proportions of reasons indicated by the treating physician, the nurse in charge or the patient as responsible for triage overruling after first medical stabilisation.

Figure 3. Reasons to overrule triage algorithm after first medical stabilisation
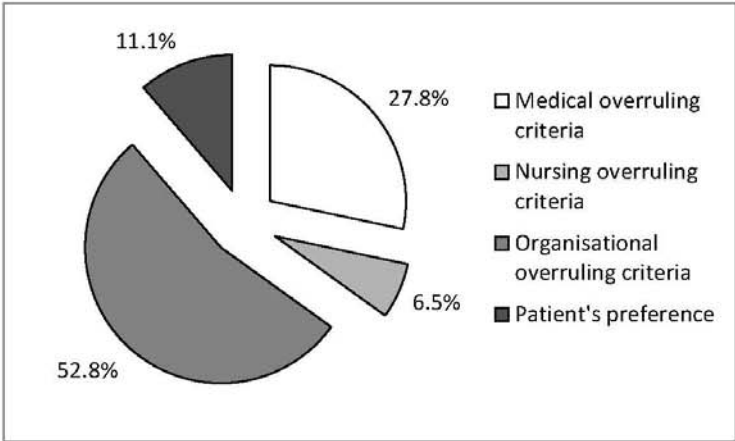
Figure 4. Subgroups analysis for effect of ProADM-enhanced triage

Results from the generalised linear model adjusted for age, gender, type of lower respiratory tract infection and severity (CURB65 score).

CAP – community-acquired pneumonia; LOS – length of stay

Figure 4. Subgroups analysis for effect of ProADM-enhanced triage

Parameter		Regression coefficient (95%CI)
Overall		-0.24 (-0.50, 0.01)
Hospitalised patients		-0.20 (-0.41, 0.02)
Non CAP		-0.22 (-0.60, 0.16)
CAP		-0.26 (-0.61, 0.08)
Male		-0.34 (-0.68, -0.01)
Female		-0.10 (-0.52, 0.31)
Age < 65 years		-0.32 (-0.70, 0.05)
Age ≥ 65 years		-0.14 (-0.52, 0.24)
Charlson ≤3 points		-0.04 (-0.43, 0.35)
Charlson >3 points		-0.24 (-0.65, 0.18)
CURB65 class I		-0.30 (-0.64, 0.04)
CURB65 class II		-0.15 (-0.72, 0.42)
CURB65 class III		-0.07 (-0.75, 0.61)

-1.0   -.5   0   0.5   1

Intervention has shorter LOS   **Intervention has longer LOS**

Table 1. Baseline characteristics

Demographic characteristics	Control group (n=159)	ProADM group (n=154)	All (n=313)
Mean age (years)	61.3	63.7	62.5
Sex (male), no. (%)	94 (59.1)	96 (62.3)	190 (60.7)
Initial treatment site, no. (%)			
Inpatient treatment	126 (79.3)	124 (80.6)	250 (79.9)
Outpatient treatment	33 (20.7)	30 (19.4)	63 (20.1)
Risk assessment			
CURB65 (mean; median)	1.2; 1	1.4; 1	1.3; 1
CURB65 I	102	93	195
CURB65 II	33	37	70
CURB65 III	24	24	48
CURB65-A class (mean; median)	2; 2*	2; 2	2; 2*
CURB65-A I (no.)	48*	36	84*
CURB65-A II (no.)	63*	73	136*
CURB65-A III (no.)	48*	45	93*
Confusion	11	17	28
Urea > 7mmol/L	62	59	121
Respiratory rate >= 30/min	22	17	39
Blood pressure sys. < 90mmHg	4	6	10
Age > 65 years	74	87	161
Final diagnosis (%)			
Bronchitis	31 (19.5)	33 (21.4)	64 (20.4)
AECOPD	22 (13.8)	21 (13.6)	43 (13.7)
CAP	90 (56.6)	75 (48.7)	165 (52.7)
Influenza	1 (0.6)	5 (3.2)	6 (1.9)
other	15 (9.4)	20 (13.0)	35 (11.1)
Coexisting illnesses, no. (%)			
Lung cancer	7.5	1.3	4.5
Other cancer<1year	10.1	7.8	8.9
Coronary heart disease	9.4	10.4	9.9
Charlson comorbidity index (mean)	3.7	3.6	3.7
Anamnestic findings, (%)			
Cough	78	89	83.4
Sputum	49.1	55.5	50.4
Dyspnea	57.9	55.5	56.5
Tachypnea	23.3	25.8	24.6
Chest pain	25.2	28.4	26.8
Clinical findings			
Auscultatory findings, (%)	59.7	54.8	57.2
Fever, (%)	49.7	60	54.6
Shivering, (%)	17.6	23.9	20.4
Leukocytosis / Leukopenia, (%)	47.8	44.5	46.3
Heart rate (bpm)	95	94	95
Temperature (°C)	37.6	38	37.8
Laboratory findings (mean)			

Proadrenomedullin (nM) (admission)	1.311*	1.599	1.456*
Proadrenomedullin (nM) (d3)	1.171*	1.285	1.241*
Proadrenomedullin (nM) (d6)	1.215*	1.396	1.293*
Procalcitonin (ug/l) (admission), median	0.16	0.18	0.18
PCT <0.25 (in %)	62.3	63.6	62.9
PCT 0.25 - 0.5 (in %)	14.5	12.3	13.4
PCT >0.5 (in %)	23.3	24	23.6
C-reactive protein, mg/l	108.8	107.5	107.2
Leukocyte count, cells/ul	12.3	11.5	11.8

* values determined by batch analysis post-hoc; not known at time of enrolment and not available for medical care

Table 2. Adverse events within 30 and 90 days after enrolment

	Control group (n/total, %)	ProADM group (n/total, %)	Adjusted OR (95%CI)	p value
Short term outcomes (30 days)				
Any adverse event	35/159 (22.1%)	31/154 (20.1%)	0.81 (0.46, 1.42)	0.458
Mortality	12/159 (7.6%)	11/154 (7.1%)	0.75 (0.3, 1.85)	0.526
ICU admission	8/159 (5.0%)	10/154 (6.5%)	1.25 (0.47, 3.34)	0.650
Recurrent infection	5/159 (3.1%)	5/154 (3.3%)	1.11 (0.31, 3.95)	0.877
Rehospitalisation	16/159 (10.1%)	13/154 (8.4%)	0.80 (0.37, 1.73)	0.569
Long-term outcomes (90 days)				
Any adverse event	57/159 (35.9%)	51/154 (33.1%)	0.81 (0.50, 1.31)	0.384
Mortality	14/159 (8.8%)	16/154 (10.4%)	0.99 (0.44, 2.22)	0.978
Recurrent infection	15/159 (9.4%)	13/154 (8.4%)	0.91 (0.41, 1.99)	0.810
Rehospitalisation	30/159 (18.9%)	27/154 (17.5%)	0.88 (0.49, 1.57)	0.663

Of note, patients may experience more than 1 adverse outcome, thus outcome my sum up to more than 100%

Table 3. Change in ProADM categories over time in the ProADM group

	Day 1 to day 3	Day 3 to day 6
No change in ProADM category	79 (69.9%)	57 (72.2%)
ProADM decreasing category	25 (22.1%)	18 (22.8%)
ProADM increasing category	9 (8.0%)	4 (5.1%)

Table 4. Influence of high ProADM values on triage decisions in the ProADM group

	Day 3	Day 6
Patients hospitalized	114	81
Patients medically stable	18/114 (15.8%)	17 (21.0%)
High ProADM indicates non-stable in otherwise medically stable patients	9/18 (50.0%)	12/17 (70.6%)

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