The total number of blood products transfused at the HealthCity Novena campus was lower in February 2020 and March 2020 as compared to the preceding 12 months. A mean of 1270 PRBC units/month in 2019 was transfused, as compared to 1063 PRBC units/month (16% decrease) in February and March 2020. There was also a reduction in FFP from 245 to 193 units/month (21.2% decrease) and platelet products from 197 to 166 units/month (15.7% decrease). While Tan Tock Seng Hospital still admits non COVID-19 patients, the postponing of elective surgeries and lower bed occupancy rates during February and March 2020 has resulted in decreased demand for blood products. This was also observed from March 2003 to May 2003 during the height of the Severe Acute Respiratory Syndrome (SARS) epidemic, where Tan Tock Seng Hospital was then the designated public hospital in Singapore to manage only patients with suspected and confirmed SARS. The blood transfusion requirements during that period showed a 66.5% decline from a mean 941 monthly red cell units transfused in 2002, to 315 monthly red cell units transfused, and a corresponding decline in mean monthly usage of FFP and platelet transfusions from 500 units FFP and 289 platelet products in 2002, to 211 units FFP (57.8% decrease) and 155 platelet products (46.3% decrease).

The challenges faced by blood banks during an infectious pandemic are securing and protecting the blood supply.[4] While the demand for blood and blood products may decrease during a pandemic due to postponement of elective surgeries, measures such as physical distancing and a complete lockdown of cities, provinces or countries in an attempt to curb the spread of infection may result in a larger decline in blood supply and an overall shortage of blood products. This was observed in April 2003 to July 2003 in Beijing, China during the SARS outbreak where it was necessary to import blood and blood products from other Chinese provinces to ensure availability for clinical use in patients.[5] Hospitals should have in place an emergency blood management plan in preparedness planning for sustainability and safety of blood supply.

In summary, most patients with mild COVID-19 infection do not require blood transfusions. A subset of critically ill patients with severe COVID-19 infection in the ICU, especially those with overt gastrointestinal bleeding, requires mostly PRBC transfusion, with lesser requirements for FFP and platelet products.

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1 | CONFLICT OF INTEREST

All authors declare no competing interests. This study was approved by the National Healthcare Group Domain Specific Review Board (DSRB).

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Incentive spirometry to prevent acute chest syndrome in adults with sickle cell disease; a randomized controlled trial

To the Editor:

Acute chest syndrome (ACS) is a major complication in patients with sickle cell disease (SCD), attributing to up to 25% of mortality.[1] The pneumonia-like complication frequently coincides with hospitalization for vaso-occlusive crisis (VOC) and occurs in approximately 50% of SCD

patients. Besides the acute morbidity and mortality, chronically impaired lung function in patients with recurrent ACS is described.[2] A frequently used definition for ACS is "presence of a new pulmonary infiltrate on a chest X-ray in combination with fever or respiratory symptoms in SCD patients".[1] Multiple factors have been demonstrated to contribute to the development of ACS, including pulmonary fat embolisms, bacterial/viral infections, thromboembolic disease and hypoventilation due to thoracic bone infarction or the use of narcotics, but in more than half of the patients the cause remains unclear.[2] Incentive spirometry is a non-invasive approach to prevent hypoventilation and pulmonary complications by encouraging regular deep inspiration. Two studies have reported this method to be effective as primary prevention of the development of ACS in SCD children hospitalized for VOC.[3,4] In the landmark study of Bellet et al.[3] an absolute risk reduction (ARR) of 36.8% in favor of spirometry was found. Ahmad et al.[4] observed an ARR of 14.1%(CI 1%-28%) by the use of spirometry in a subgroup at high risk for ACS. However, these studies were performed in pediatric patients and no studies have been performed in adult SCD patients so far despite the pathophysiological difference of ACS between these populations.[2]

In the present study, we aimed to evaluate the efficacy of incentive spirometry to prevent ACS during VOC in hospitalized adult SCD patients. Secondarily, we assessed whether specific clinical or laboratory characteristics were associated with an increased risk to develop ACS.

We performed a prospective randomized controlled clinical trial in two hospitals in the Netherlands between January 2010 and August 2015. Patients were randomized to spirometry and standard of care or standard of care only using the online randomization software ALEA (ALEA version 2; 2010, Netherlands Cancer Institute, Amsterdam, Netherlands). Standard of care consisted of pain management and hydration according to local protocols. Blood transfusion, antibiotics and oxygen therapy were considered on clinical indication by the attending physician. The spirometry group was instructed to inhale through the spirometer (RespifloFS, Kendall) every 2 hours between 8 AM and 10 PM. (10 inhalations each time) until at least 24 hours after the pain had subsided. The study protocol was approved by the Medical Ethical Review Committee of the participating centers. Written informed consent was received from all participants.

Consecutive adult SCD patients hospitalized for VOC were considered for inclusion. In order to select patients with the highest risk of ACS, only patients with thoracic or back pain above the diaphragm were included according to the study of Bellet et al.[3] Pediatric patients, patients with an ACS at presentation, pregnant women and patients with a blood transfusion 3 months prior to admission were excluded. Patients were allowed to enroll in the study more than once, with a maximum of three enrollments. Hospitalizations of multiple-included patients had to be separated by at least 4 weeks. Note, VOC was defined as musculoskeletal and/or visceral pain that could not be explained otherwise and required hospitalization for pain management. ACS was defined as a new infiltrate on chest radiograph, accompanied by clinical symptoms including fever, pulmonary complaints or desaturation. For this, chest X-rays were performed at presentation and were repeated on day 5 of hospital admission or at discharge, or earlier if clinically indicated. Blood samples were retrieved at day one of hospitalization and were repeated before discharge. Throat swabs were performed at presentation and analyzed for bacterial and viral pathogens by multiplex polymerase chain reaction (PCR). Blood cultures were determined to investigate possible causality of specific pathogens.

The sample size was calculated at 31 patients per group with a statistical power of at least 80%, at an alpha level of 0.05, to detect a 30% lower rate of ACS in the spirometry group, comparable to the study of Bellet et al., using Stata/SE, version 10.1 (Sampsi program, StataCorp LP, Texas, USA). Continuous data are expressed with corresponding means ±1 SD (SD) or with medians and (interquartile range [IQR]). Categorical data were presented as numbers (%). Comparisons between groups for numerical data were performed with the Student *t* test or Mann-Whitney *U* test depending on the distribution of data. All binary variables were compared using the Pearson's chi-Square test (χ^2) or Fisher's exact test as appropriate.

We included 66 hospitalizations of 48 SCD patients. The baseline characteristics are presented in Table 1. Eight patients were included twice and five patients were included three times. Overall, ACS was diagnosed in 11/66 (16.7%) hospitalizations. Laboratory results at admission were comparable, except for leukocyte count: 10.1 [8.0-13.8] $\times 10^9$/L vs 13.2[9.1-16.6] $\times 10^9$/L in the spirometry and control group, respectively ($P = .031$). Although not statistically significant, hydroxycarbamide was used less in the spirometry group; 5/34 (14.7%) compared to controls 10/32 (31.3%; $P = .109$).

ACS developed in 5/34 (14.7%) hospitalizations in the spirometry group compared to 6/32 (18.8%) in the non-spirometry group ($P = .660$) indicating an ARR of 4.1% (CI −14% to 23%) in favor of spirometry. When only unique patients were analyzed (48 individuals), also no difference in ACS incidence between the treatment groups was found (5/25 vs 5/23 in the spirometry and non-spirometry group, respectively; $P = .882$). None of the throat swabs of patients developing ACS tested positive for pathogens. One ACS patient had a positive blood culture (Streptococcus oralis/mitis).

Hospitalizations complicated by ACS had higher baseline LDH levels (577[334-951]IU vs 353[246-553]IU; $P = .004$) and leukocyte counts 15.2[11.1-19.7] $\times 10^9$/L vs 10.8[8.0-13.8] $\times 10^9$/L; $P = .019$) compared with non-ACS hospitalizations (data non shown).

In this prospective randomized controlled trial, we were not able to demonstrate a preventive effect of incentive spirometry on the development of ACS in adult SCD patients. Our findings with a non-significant ARR 4.1% for developing ACS contrast with Bellet et al.[3] (ARR 36.8%) and Ahmad et al.[4] (ARR 14.1%) in pediatric SCD patients. The contrasting findings of our study in adult SCD patients as compared to these previous studies could be explained by the etiological difference in developing ACS between children and adults. This was previously demonstrated in the cooperative study of SCD (CSSCD) in nearly 1000 patients with SCD.[5] Out of 1722 ACS episodes, the authors concluded that, compared to children with SCD, ACS in adults was not only associated with a greater disease severity and higher mortality rate, but also with a different etiology. In this study, which was confirmed in several other studies, the most frequent cause of ACS in children was a viral or bacterial infection, whereas in adults fat emboli were more often reported. In that same study, it was demonstrated that the incidence of

TABLE 1 Baseline characteristics and characteristics during hospitalization

	Spirometry (N = 34)	Non-spirometry (N = 32)	*P*
Baseline			
Gender, female — No. (%)[aa]	14 (41.2)	15 (46.9)	
Age — yr	25.5 [23.0-32.0]	27 [23.3-41.8]	
Genotype — No. (%)			
-Severe SCD (HbSS, HbSβ^0 thalassemia)	22 (64.7)	24 (75.0)	
-Mild SCD (HbSC, HbSβ$^+$ thalassemia)	12 (35.3)	8 (25.0)	
Medical history — No. (%)			
-Acute chest syndrome	11 (32.4)	10 (31.3)	
-Frequent VOC[bb]	19 (55.9)	20 (62.5)	
Medication use — no. (%)			
-Hydroxycarbamide	5 (14.7)	10 (31.3)	
Blood parameters emergency department			
-Hemoglobin—g/dl	9.7 [8.5-11.0]	8.7 [7.6-10.6]	
-Reticulocytes—%	10.9 [4.1-17.4]	9.8 [4.1-16.5]	
-Platelets—×10^9/L	322.5 [175.5-426.0]	351.0 [270.8-419.3]	
-Leukocytes—×10^9/L	10.1 [8.0-13.8]	13.2 [9.1-16.6]	
-CRP—mg/L	7.3 [2.1-13.4]	6.0 [3.1-15.6]	
-LDH—U/L	342.5 [246.0-517.0]	402.0 [304.0-661.0]	
During hospitalization			
Diagnosis of ACS—% (n)	14.7 (5)	18.8 (6)	.660
Fever—% (n)[cc]	20.6 (7)	31.3 (10)	.322
Treatment with antibiotics—% (n)	41.2 (14)	50 (16)	.472
Treatment with blood transfusion—% (n)[dd]			
All simple transfusions	14.7 (5)	21.9 (7)	.450
Erythropheresis	11.8 (4)	6.3 (2)	.673
Hospital stay—days	6.0 [4.0-7.0]	4.0 [3.0-8.5]	.179
Readmission within 4 wk—% (n)	23.5 (8)	28.1 (9)	.670

Abbreviations: ACS, acute chest syndrome; CRP, C-reactive protein; LDH, lactate dehydrogenase; VOC, vaso-occlusive crisis.

[a]Results are expressed as n (%), means ± SD, or medians [interquartile range].

[b]Frequent VOC was defined as >2 hospital admissions due to VOC per year.

[c]Fever was described as a temperature of ≥38.5°C for a single measurement, or a repeated temperature of ≥38.0°C anytime during hospital admission.

[d]All transfusions contains all hospitalizations during which at least one unit of packed cells was given. Erythropheresis contains all patients from this group that received exchange transfusion.

bacteremia appeared to be the highest in young children with an ACS (14% in infants in comparison with 1.8% in patients between 10-66 years of age).[5] Spirometry has been demonstrated to reduce atelectasis and pneumonia in several studies in post-operative and COPD patients. Although the validity of these studies has been questioned, the fact that infection is a more frequent cause of ACS in children could explain why spirometry seems to be more effective in the pediatric population. As spirometry is not expected to prevent fat emboli, which is considered to be the main cause of ACS in adult SCD patients, this could explain the lack of effectivity we found. Interestingly, none of the throat swabs of ACS patients and only one blood culture became positive in our study, confirming that infection is a rare cause of ACS in adults.

Several limitations should be mentioned. First, our study was powered to detect an effect of 30% reduction in the incidence of ACS. Therefore, the study may have been underpowered to find a more moderate effect as demonstrated in a subgroup of patients in the large study of Ahmad et al.[4] Also the incidence of ACS was lower than observed by Bellet et al.[3] This could be explained by the fact that we used stricter rules to diagnose ACS, for instance requiring a complete lung segment to be affected, which may have led to a lower incidence in our cohort. A second limitation, from a methodological point of view, might be that patients were allowed to be randomized multiple times. However, analyses of only ACS episodes restricted to single randomizations (n = 48) showed similar results. Lastly, there was a trend towards more sparse use of hydroxyurea in the spirometry

group which may have influenced the outcome given the preventative effect of hydroxyurea on ACS. Although a direct effect on the development of ACS cannot be excluded, the preventive effect on ACS is most likely due to prevention of VOC primarily as indicated by the identical rate of effect on VOC and ACS prevention in the landmark study of Charache et al.[6]

In conclusion, our study was unable to demonstrate a preventive effect of incentive spirometry on the development of ACS in adult sickle cell patients. The findings emphasize the need for large prospective studies evaluating the use of incentive spirometry in adults.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

C.v.T. and A.G. contributed equally to this study.
Study concept and design: C.v.T., E.N., B.B.
Acquisition of data: C.v.T., A.G.
(Statistical) analysis of data: C.v.T., A.G.
Interpretation of data: C.v.T., A.G., E.N., A.R., B.B.
Drafting of the manuscript: C.v.T., A.G., E.N., A.R., B.B.
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Increased frequency of the single nucleotide polymorphism of the *DARC/ACKR1* gene associated with ethnic neutropenia in a cohort of European patients with chronic idiopathic neutropenia

To the Editor:

Chronic neutropenia is defined as the reduction of peripheral blood (PB) absolute neutrophil counts (ANC) below the lower limit of the normal distribution for a period exceeding 3 months.[1,2] The investigation of chronic neutropenia in adults comprises rare congenital conditions that involve germline mutations of a variety of genes including *ELANE* and *HAX1*. Also involved are common acquired disorders associated with reduced or ineffective neutrophil production in the bone marrow (BM), increased neutrophil margination to the vascular endothelium, neutrophil sequestration in the spleen, or accelerated neutrophil destruction by immune mechanisms.[1,2] Approximately 30% of patients with chronic neutropenia do not have an apparent underlying cause; the term chronic idiopathic neutropenia (CIN) is used for these cases.[2]

Individuals with African and Near and Middle East ancestry present lower ANCs than individuals of European ancestry, a situation known as ethnic neutropenia (ENP) commonly associated with absence of Duffy