Validation of a Score for the Detection of Subjects with High Risk for Severe High-Altitude Illness

Jean-Paul Richalet1,2, Fabien Pillard3, David Le Moal2, Daniel Rivière3, Philippe Oriol4,
Mathias Pousset5, Bruno Chenuel5, Stéphane Douitreau6,7, Samuel Verges6,7, Sophie Demanez8,
Michel Vergnion8, Jean-Michel Boulet9, Hervé Douard9, Maryse Dupré10, Olivier Mesland10,
Romain Remetter11, Evelyne Lonsdorfer-Wolf11, Alain Frey12, Louis Vilcoq12, Anne Nedelec Jaffuel12, 
David Debeaumont12, Guy Duperrex14, François Lecoq14, Christophe Hédon15, Maurice Hayot15,
Guido Giardini16, François J. Lhuissier2,17

1Institut National du Sport de l’Expertise et de la Performance (INSEP). Pôle médical. Paris, France;  
2Université Sorbonne Paris Nord, UMR INSERM 1272 Hypoxie et poumon, Bobigny, France;  
3Université Paul Sabatier III, Faculté de Médecine Purpan. UMR INSERM U1048 Institut des maladies  
metaboliques et cardiovasculaires. Hôpital Pierre Paul Riquet. Unité de Médecine du Sport. Toulouse, France;  
4Institut Régional de Médecine et d’Ingénierie de Sport. Médecine du sport et Myologie. CHU Saint-Etienne. Saint-Etienne, France;  
5Centre Hospitalier Universitaire de Nancy, Centre Universitaire de Médecine du Sport et Activité Physique Adaptée, Service des Explorations de la Fonction Respiratoire. Université de Lorraine, EA 3450 Développement, Adaptation et Handicap, Nancy, France;  
6Université Grenoble Alpes. INSERM U1042 Hypoxie-Physiopathologies cardiovasculaires et respiratoires (HP2), Grenoble, France;  
7CHU Grenoble Alpes. UM Sport et Pathologies, hôpital Sud, Echirolles, France;  
8Centre de physiologie de l’effort - CB Move Herve-Julémont, Belgium;  
9Hôpital cardiological. Service malades coronaires, tests d’effort et readaptation, Pessac, France;  
10Institut Régional de Médecine du Sport. CHU Nantes. PHT 10, Hôpital Saint Jacques, Nantes, France;  
11Centre Hospitalier Universitaire de Strasbourg. Service de Physiologie et EFR. Nouvel Hôpital Civil. Strasbourg, France;  
12Centre Hospitalier Intercommunal Poissy/Saint-Germain. Service Médecine du Sport. Site Saint Germain. Saint-Germain en Laye, France;  
13Centre Hospitalo-Universitaire de Rouen, Hôpital Charles Nicolle. CIC-CRB 1404. Unité de physiologie respiratoire et de l’exercice, Rouen, France;  
14Hôpitaux du Pays du Mont Blanc. Consultation de Médecine et Traumatologie du Sport. Montagne, Sallanches, France;  
15UMR INSERM U1046- CNRS 9214- PhyMedExp. Université de Montpellier, CHU Arnaud de Villeneuve, Montpellier, France;  
16Ospedale U. Parini - Azienda USL della Valle d'Aosta. Centro di Medicina e Neurologia di Montagna. Aosta, Italy;  
17Assistance Publique-Hôpitaux de Paris. Hôpital Jean Verdier, Médecine de l’exercice et du sport, Bondy, France

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Jean-Paul Richalet1,2, Fabien Pillard3, David Le Moal2, Daniel Rivière3, Philippe Oriol4, Mathias Poussel5, Bruno Chenuel5, Stéphane Doutreleau6,7, Samuel Vergès6,7, Sophie Demanez8, Michel Vergnion8, Jean-Michel Boulet9, Hervé Douard9, Maryse Dupré10, Olivier Mesland10, Romain Remetter11, Evelyne Lonsdorfer-Wolf11, Alain Frey12, Louis Vilcoq12, Anne Nedelec Jaffuel12, David Debeaumont13, Guy Duperrex14, François Lecoq14, Christophe Hédon15, Maurice Hayot15, Guido Giardini16, François J. Lhuissier2,17

1Institut National du Sport de l’Expertise et de la Performance (INSEP). Pôle médical. Paris, France; 2Université Sorbonne Paris Nord, UMR INSERM 1272 Hypoxie et poumon, Bobigny, France; 3Université Paul Sabatier III, Faculté de Médecine Purpan. UMR INSERM U1048 Institut des maladies métaboliques et cardiovasculaires. Hôpital Pierre Paul Riquet, Unité de Médecine du Sport. Toulouse, France; 4Institut Régional de Médecine et d’Ingénierie de Sport. Médecine du sport et Myologie. CHU Saint-Etienne. Saint-Etienne, France; 5Centre Hospitalier Régional Universitaire de Nancy, Centre Universitaire de Médecine du Sport et Activité Physique Adaptée, Service des Explorations de la Fonction Respiratoire. Université de Lorraine, EA 3450 Développement, Adaptation et Handicap, Nancy, France; 6Université Grenoble Alpes. INSERM U1042 Hypoxie-Physiopathologies cardiovasculaires et respiratoires (HP2), Grenoble, France; 7CHU Grenoble Alpes. UM Sport et Pathologies, hôpital Sud, Echirolles, France; 8Centre de physiologie de l'effort - CB Move Herve-Julémont, Belgium; 9Hôpital cardiologique.
Service maladies coronaires, tests d’effort et readaptation, Pessac, France; \textsuperscript{10} Institut Régional de Médecine du Sport, CHU Nantes, PHU 10, Hôpital Saint Jacques, Nantes, France; \textsuperscript{11} Centre Hospitalier Universitaire de Strasbourg, Service de Physiologie et EFR, Nouvel Hôpital Civil, Strasbourg, France; \textsuperscript{12} Centre Hospitalier Intercommunal Poissy/Saint-Germain. Service Médecine du Sport. Site Saint Germain. Saint-Germain en Laye, France; \textsuperscript{13} Centre Hospitalo-Universitaire de Rouen, Hôpital Charles Nicolle. CIC-CRB 1404. Unité de physiologie respiratoire et de l’exercice, Rouen, France; \textsuperscript{14} Hôpitaux du Pays du Mont Blanc. Consultation de Médecine et Traumatologie du Sport, Montagne, Sallanches, France; \textsuperscript{15} UMR INSERM U1046-CNRS 9214- PhyMedExp, Université de Montpellier, CHU Arnaud de Villeneuve, Montpellier, France; \textsuperscript{16} Ospedale U. Parini - Azienda USL della Valle d’Aosta. Centro di Medicina e Neurologia di Montagna, Aosta, Italy; \textsuperscript{17} Assistance Publique-Hôpitaux de Paris, Hôpital Jean Verdier, Médecine de l’exercice et du sport, Bondy, France

Address for correspondence:

JP Richalet, Université Sorbonne Paris Nord UMR INSERM 1272, 1 rue de Chablis, 93017 Bobigny Cedex, France

Mail: richalet@univ-paris13.fr

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by American College of Sports Medicine. No specific funding was attributed to this study. Each center provided the resources for the routine mountain medicine consultation including the hypoxia exercise test. There is no conflict of interest for any author to declare.
ABSTRACT

Purpose. A decision tree based on a clinico-physiological score (SHAI score) has been developed to detect subjects susceptible to Severe High Altitude Illness (SHAI). We aimed to validate this decision tree, to rationalize the prescription of acetazolamide (ACZ) and to specify the rule for a progressive acclimatization. Methods. Data were obtained from 641 subjects in 15 European medical centers before and during a sojourn at high altitude. Depending on the value of SHAI score, advice was given and ACZ was eventually prescribed. The outcome was the occurrence of SHAI at high altitude as a function of SHAI score, ACZ prescription and use and fulfillment of the acclimatization rule. Results. The occurrence of SHAI was 22.6%, similar to what was observed 18 years before (23.7%), while life-threatening forms of SHAI (High Altitude Pulmonary and Cerebral Edema) were less frequent (2.6% to 0.8%, P=0.007). The negative predictive value of the decision tree based was 81%, suggesting that the procedure is efficient to detect subjects who will not suffer from SHAI, therefore limiting the use of ACZ. The maximal daily altitude gain that limits the occurrence of SHAI was established at 400 m. The occurrence of SHAI was reduced from 27% to 12% when the recommendations for ACZ use and 400 m daily altitude gain were respected (P<0.001). Conclusion. This multicenter study confirmed the interest of the SHAI score in predicting the individual risk for SHAI. The conditions for an optimized acclimatization (400 m-rule) were also specified and we proposed a rational decision tree for the prescription of acetazolamide, adapted to each individual tolerance to hypoxia. Key words: hypoxia, acetazolamide, speed of ascent, acute mountain sickness, exercise, ventilatory response to hypoxia
INTRODUCTION

An increasing number of sea-level residents visit areas above 4000 m of altitude for leisure, sport-base tourism or work. They may suffer from severe acute mountain sickness (AMS), high altitude pulmonary (HAPE) or cerebral (HACE) edema (1). The above clinical outcomes have been aggregated in a clinical entity called Severe High Altitude Illness (SHAI), characterized by a serious negative impact on physical activity. A number of studies have proposed various markers of susceptibility to AMS but failed to demonstrate any predictability of these markers, mainly because they were obtained from a limited number of subjects.

From a cohort of 1,017 sea-level natives, we developed a risk prediction score of SHAI (SHAI score) combining clinical and physiological factors obtained from a hypoxia submaximal exercise test before their stay at high altitude (HA) (Table 1) (2,3). This score was the first to predict the risk of SHAI in a large cohort of sea-level residents visiting HA regions (3,4) and was then used in subsequent studies (5,6,7). A decision tree was designed to standardize the use of the SHAI score 1) to detect high-risk subjects for SHAI, 2) to prescribe advice for acclimatization and eventually acetazolamide (ACZ) for the prevention of SHAI (Figure 1) (8). ACZ is the most efficient drug commonly given for the prevention of SHAI but may have some side effects and contra-indications (9,10,11).

Therefore, the main goal of this decision tree was to minimize the risk of SHAI while also minimizing the use of ACZ. A commonly given recommendation is to climb gradually, but the threshold given for the daily altitude gain in the literature varies from 300 to 600 m (1,12). When an advice is given with a lower and an upper range, people have a clear tendency to conform to
the upper range, putting them at a higher risk. Moreover, the determination of this daily altitude gain is not clear in the literature.

The objective of the present study was to validate the decision tree in a large population of subjects explored in a multicenter network (multiSHAI) gathering 15 centers in France, Belgium and Italy. Our goal was to standardize the use of SHAI score and the advice given to the subjects before their stay at HA. Specific objectives were to propose 1) a validated rule for an optimized prescription of ACZ, and 2) a validated rule for the daily altitude gain.

METHODS

The protocol was approved for all centers involved in the study by the “Comité de Protection des Personnes du Sud-Ouest et Outre-Mer IV » Ethics Committee. All participants provided written informed consent before participation.

Subjects

A total of 1,216 subjects were recruited during a routine mountain medicine consultation performed before their sojourn at HA (for tourism, trekking, expedition or work) in 15 medical centers in France, Belgium and Italy from August 2017 to December 2019. All subjects coming to the routine mountain medicine consultation were invited to participate in the study, as far as their maximal altitude objective was above 4,000m and their minimum duration of stay above 3,500m was two days.
**Study protocol.** Each subject went through a standard medical consultation and performed a Hypoxia Exercise Test, as previously described (2,5). They were given a field questionnaire to fill out on a daily basis during their stay at HA. Among them 655 (54%) sent back their questionnaire after their sojourn at HA.

**Data collection**

*Computation of the SHAI score*

The SHAI score was calculated as previously described (4). Items entering the score are shown on Table 1. The value of the score and the threshold to define high-susceptible and low-susceptible subjects were shown to depend on two specific conditions:

- subjects with previous experience at HA (day-time maximal altitude reached ≥ 4000 m, night-time (sleep) maximal altitude reached ≥ 3500 m), on two occasions

- subjects without such experience

*Analysis of the field questionnaires*

The questionnaires were analyzed in a blind manner by an independent observer who was not aware of the clinical and physiological data obtained during the medical consultation. From the analysis of the questionnaire, the following information were derived:

- highest altitude reached

- highest daily altitude gain in the first two weeks of the stay over 3000 m (after two weeks, the acclimatization process is supposed to be completed). It was calculated as the maximal difference of sleeping altitudes between two consecutive nights, considering the mean of
two successive daily intervals. For example, the following calculation was done for two
given profiles of ascent:

Night 1: 3000 m – Night 2: 3800 m – Night 3: 3900 m. Calculated gain: 450 m/night

Night 1: 3000 m – Night 2: 3800 m – Night 3: 3400 m. Calculated gain: 200 m/night

If the night before the first night above 3000 m (i.e. 3800 m) is lower than 3000 m (i.e. 2500 m),
the value for this night is taken as 3000 m, assuming that up to 3000 m, the climb does
not need a progressive acclimatization. The 400 m-rule is considered fulfilled if the daily
altitude gain is equal or lower than 400 m.

- the Lake Louise Score (LLS) to define AMS (13). LLS was calculated from five items
  (headache, digestive symptoms, fatigue, dizziness, sleep disturbances) quoted from 0 to 3.
The total score is the sum of the 5 items and allows to define three levels of outcome: 0-2:
  no or mild AMS, 3-5: moderate AMS, 6 and above: severe AMS. The functional item (0 to
  3) is used to evaluate the impact of the symptoms on the activity of the subject.

- HAPE was defined by the presence of clinical signs of respiratory distress (dyspnea,
cyanosis, rales), confirmed by a thorax X-Ray upon descent to low altitude. HACE was
declared by clinical signs of neurological deficit (ataxia, mental confusion). The diagnosis of
HAPE or HACE was always confirmed by an expert, either on the spot where the disorder
occurred or later on when hospitalized.

- the presence of localized peripheral edema

- the preventive use of ACZ during the stay.

- the personal feeling of the subject if he or she significantly suffered from intolerance to HA
  and if his/her symptoms led him/her to seek medical advice.
SHAI outcome was defined if the subject had a maximal Lake Louise score of 6 and above or HAPE or HACE.

Quality control.

Independently, the clinical and physiological database as well as the field questionnaires was analyzed for quality control, identifying missing or uninterpretable data and incorrect values for physiological variables. Data from 14 subjects were rejected and therefore 641 subjects were included in the analysis.

Decision tree

From our 20-year experience of mountain medicine consultation and Hypoxia Exercise Test, we designed a decision tree adapted for people aiming to visit HA regions (8). This algorithm is presented on Figure 1. The first part of the tree is the standard medical consultation aiming at identifying cardiovascular risk factors and for medical contra-indications for HA, as proposed by various authors (14, 15). Then, the Hypoxia Exercise Test is performed and the SHAI score is calculated for each individual, integrating the estimated possibility to respect the 400 m-rule for daily altitude gain. If the SHAI score is higher than the susceptibility threshold, ACZ is prescribed (twice 125 mg/day – morning and mid-day - starting the day before reaching 3000 m, and continued until the day when the highest altitude is reached, but not longer than 7 days). The threshold has been previously defined as 5.5 for subjects without previous experience of stay at HA (day altitude ≥ 4000 m, night altitude ≥ 3500 m, on two occasions) and 5 for subjects who have such experience (5). Whatever the score, standard recommendations are given to all subjects: respect of the 400 m-rule, reducing physical activity at the beginning of the stay over
3000 m, good hydration, avoid hypnotics. Patients with history of allergy for ACZ or any sulfonamide are not given ACZ. Caution is taken with pregnant women, patients on diuretics, patients with recurrent kidney stones, and those at risk for retinal detachment.

Compliance markers

Two compliance markers were assessed: 1) if the physician who prescribed or not ACZ complied with the decision tree and the value of the SHAI score (above or below the threshold); 2) if the patient complied with the prescription of ACZ (if any) by the physician.

Statistical analysis

A sample size calculation was performed. Following previous results obtained with the same methodology (5,7), the mean SHAI score (primary outcome) was 6.4 in subjects who developed SHAI while they took ACZ and 3.8 in subjects who did not develop SHAI without ACZ, with a standard deviation of 2.6. Considering that the expected proportion of subjects developing SHAI with ACZ in a general population was 11.3%, a probability alpha of 1% and the discrimination power of 95%, the minimum number of subjects to be included was 318. Considering that the rate of return of the daily questionnaire was 30%, the minimum number of subjects to be included was estimated as 1060.

Baseline characteristics of subjects were compared according to sex using Student t-test or Pearson chi square-test or Fisher’s exact test, as appropriate.

Two strategies of analysis were then performed.
First, subjects were separated in four groups according to two factors: the preventive use or not of ACZ during their stay at HA and the presence or not of SHAI. The primary outcome was the value of the SHAI score determined during the pre-exposure consultation. Secondary outcomes were the presence of peripheral edema, the maximal altitude reached and the highest daily altitude gain at the beginning of the stay at HA.

Second, subjects were stratified following the value of SHAI score (below or above threshold) and the preventive use of ACZ. The outcome was the occurrence of SHAI at HA.

Quantitative outcomes were compared by analysis of variance (ANOVA) for two factors (ACZ and SHAI). A Tukey’s post-hoc test was then applied when appropriate to compare the extreme groups (no SHAI without ACZ vs SHAI with ACZ). Qualitative outcomes were compared using Pearson’s chi-square or Fisher exact test as appropriate. P value $\leq 0.05$ was considered as significant. A Bonferroni correction for multiple comparisons was used.

The threshold for the acclimatization rule was obtained after a logistic regression between the occurrence of SHAI and the observed daily altitude gain, and then by the calculation of the maximal Youden index = Sensitivity+Specificity-1 (16).

Data were analyzed using STATA software version 12 (Stata Inc., College Station, TX).
RESULTS

General characteristics of the population. Among our cohort, 7% had a previous experience of SHAI, 34% had a previous experience of high altitude without SHAI, and 59% no experience of high altitude. Baseline characteristics of the population studied are shown as a function of sex in Table 2. Women were slightly younger and had a lower body mass index than men. Half of the female population was postmenopausal. Raynaud syndrome and migraine were more prevalent in women and they showed a slightly higher SHAI score. Men presented more frequently systemic hypertension, hypercholesterolemia, and snoring. Men were more frequently endurance trained, had a greater experience of previous stays at HA. At HA, peripheral edema was two-times more frequent in women, but occurrence of SHAI was similar. All other variables were similar between men and women.

SHAI score, ACZ prescription and use, occurrence of AMS, HAPE or HACE (Table 3). Among the 641 subjects, SHAI was observed in 145 cases (22.6%). Only 5 cases (men) of HAPE were observed (0.8%). No case of HACE was reported. SHAI prediction score was higher in the presence of SHAI at HA (P<0.001), and higher in subjects who took ACZ (P<0.001). The highest difference between groups was between those who did not use ACZ and were not severely sick (mean score= 3.84) versus those who were severely sick although they took ACZ (score=6.36, P<0.001). Highest altitude reached and highest daily altitude gain were higher in subjects with SHAI (P<0.001), independently of ACZ use.

Subjects were then grouped following the susceptibility to SHAI (SHAI score ≤ or > threshold) and the preventive use of ACZ. The occurrence of SHAI was evaluated in each subgroup (Figure
2). Altogether, 19% of low-susceptible subjects developed SHAI at HA, while 29% of high-susceptible subjects did (P=0.003). Among the subgroups that did not use ACZ, 20% of low-susceptible and 31% of high-susceptible subjects developed SHAI, (P=0.031). Among those who did use ACZ, 17% of low-susceptible and 28% of high-susceptible subjects developed SHAI at HA (P=0.029). The overall positive predictive value of the SHAI score was 29% while the negative predictive value was 81%.

In each subgroup, the compliance with the 400 m-rule was studied. When the 400 m-rule was respected, in low-susceptible subjects, the occurrence of SHAI was reduced from 28% to 10% (P<0.001), while in high-susceptible subjects, it was insignificantly reduced from 31% to 22% (P=0.22). Among the low-susceptible subjects who did not use ACZ (conforming to the SHAI score), 73% of the subjects who suffered from SHAI did not respect the 400 m-rule. Among the high-susceptible subjects, who took ACZ (conforming to the SHAI score), 83% of the subjects who suffered from SHAI did not respect the 400 m-rule.

Altogether, when both the decision tree (ACZ use if high-susceptible) and the 400 m-rule were respected, only 12% of the subjects suffered from SHAI, as compared to 27% if the recommendations were not respected (P<0.001) (Figure 3).

As expected, subjective appreciation of tolerance to HA was associated with the occurrence of SHAI: difficulties for acclimatization were reported in 55% of subjects who suffered from SHAI, compared to only 14% in subjects without SHAI did (Table 3). Among subjects with SHAI, 13% had a field medical consultation, whereas only 2% of SHAI-free subjects did (Table 3).
**Justification of the threshold for the daily altitude gain rule.**

The highest daily altitude gain in the first two weeks at HA was recorded for each subject and the relative frequency is reported on figure 4A for subjects who suffered (SHAI+) or not (SHAI-) from SHAI. The number of SHAI+ subjects exceeds the number of SHAI- subjects above 400 m (Figure 4A). This threshold was confirmed by the calculation of the cut-off value of the daily altitude gain by maximizing Youden index (Figure 4B). A clear cut-off for daily altitude gain is therefore 400 m.

**Compliance markers.**

Compliance of the physician with the SHAI score to prescribe ACZ was 75%. Compliance of the subject with the prescription of ACZ by the physician was 73%. Among subjects who were prescribed ACZ, 17% did not use it, while 9% of subjects who were not prescribed ACZ, effectively took it (P<0.001). Altogether, the use of ACZ was in accordance with the SHAI score for 70% of all subjects. Compliances to SHAI score and to prescription were not influenced by the occurrence of SHAI. Compliance of the physician to SHAI score was higher when subjects took ACZ (P=0.013), while compliance of the subject to the prescription was higher when ACZ was used (P=0.009). Among high-susceptible subjects (SHAI score > threshold), 16% did not have a prescription of ACZ, and finally 33% did not take ACZ. Among low-susceptible subjects (SHAI score ≤ threshold) 31% had a prescription of ACZ while 29% effectively took ACZ.

**DISCUSSION**

This study is the first multicenter attempt to validate the preventive measures for High Altitude Illness in a large cohort (N=641) of persons planning to visit HA (>4000 m) regions. General
characteristics of the population studied did not evidence obvious differences when compared to a general population. We compared the main characteristics of our population who returned their questionnaire (n=641) with the overall population initially included in the study (n= 1216). There was no difference in age (50±14 yrs vs 46±15 yrs), in sex ratio (M/F) (1.2 vs 1.3), in the proportion of subjects with previous SHAI (7% vs 8%), or in the proportion of high-susceptible subjects (39% vs 36%). Therefore, there was a priori no bias in the analysis of the subgroup that returned the questionnaire. No significant sex effect was found for the occurrence of severe AMS, as found in some studies (4,17) but not in others (2,18,19). All five subjects who presented HAPE were men, however this limited number did not allow us to draw any conclusion. Peripheral edema was approximately two-times more frequent in women than in men, as previously demonstrated (7). When comparing the occurrence of High Altitude Illness in the present study with data previously obtained with the same methodology between 1992 and 2008 (2), the occurrence of SHAI was insignificantly reduced (23.7% to 22.6%), while the occurrence of HAPE (1.7% to 0.8%) and HACE (1% to 0%) was drastically reduced. The overall decrease in life-threatening forms of altitude sickness in these two large cohorts (2.7% to 0.8%, P=0.007) is encouraging, although the small number of affected subjects makes it difficult to attribute to the mountain medicine consultation (i.e. better information about susceptibility given during this medical visit).

The decision tree and the prescription of ACZ. We propose a decision tree based on the individual SHAI score, which had already been proven to detect persons susceptible to Severe High Altitude Illness (4). The efficiency of the decision tree cannot be evaluated by standard indices used in binary classification tests, since it includes a main intervention (prescription of
ACZ depending on the SHAI score) aiming at decreasing the occurrence of the outcome (SHAI at HA). As it was not ethical to compare a treated group (recommendations including ACZ) to an untreated group (no recommendation), the effectiveness of the decision tree was evaluated by studying the occurrence of SHAI in subjects who complied with the protocol. Our main result is that the SHAI score obtained during the pre-sojourn visit is in good agreement with the occurrence of SHAI during the sojourn at HA. Participants who suffered from SHAI in spite of preventive use of ACZ showed a much higher SHAI score (6.36) than those who did not suffer from SHAI without taking ACZ (3.84). The low positive predictive value (29%) is expected since subjects detected as high-susceptible will be given particular advice to limit their risk of SHAI during their stay at HA. Furthermore, these subjects who have identified themselves as being at high risk, will probably be more cautious. The high negative predictive value (81%) confirms that low-risk subjects have a low probability to develop SHAI and that the procedure is efficient to detect subjects who will not suffer from SHAI, therefore limiting the use of ACZ.

Precise value of maximal daily altitude gain. The daily altitude gain is a well-established determinant factor for the occurrence of SHAI (20, 21, 22) although the precise rule to be respected has not been well defined (23). The gap between 300 m and 600 m given in the literature appears much too large if we consider that the great majority of observed altitude gains lie between these values. As shown on figure 4A, the relative frequency of SHAI is reduced only in the strict range 0 to 400m, confirming that the threshold for the golden rule “Do not go too high too fast” should be 400 m. This was confirmed by the Youden index (Figure 4B). In fact, from our first study about risk factors for High Altitude Sickness in 1988 and in the following studies, we used a strict threshold of 400 m (2,4,7,8,24). Thus, we propose the following rule:
“Daily altitude gain should not be higher than 400 m above 3000 m, at the beginning of the stay at HA. This daily altitude gain is computed as the mean between two consecutive day-intervals. In other words, the two-day (three-night) altitude gain should not exceed 800 m”. The limited effect observed in high-susceptible subjects respecting the 400 m-rule suggests that in this high-risk category, respecting the 400 m-rule cannot fully counterbalance individual susceptibility.

Compliance with decision tree and with prescription. The compliance of the physicians with the decision tree was not perfect since 25% of ACZ prescription was not in accordance with the SHAI score. Some physicians had a clear tendency to prescribe ACZ while the score did not warrant prescription. Similarly, 27% of the subjects did not follow the physician’s prescription. Altogether, the use of ACZ did not conform to the value of the SHAI score in 30% of all subjects. Physicians seem to over-prescribe ACZ, probably because they think it will reduce the risk even in low-risk subjects. Subjects seem to under-use ACZ when prescribed, either for ethical reasons or because they fear side effects.

Limitations. The outcome in field conditions is evaluated through the Lake Louise score, which is a combination of non-specific symptoms. A recent proposal was made to remove the “sleep” item from the total score but major methodological flaws (absence of control of medications) do not allow the validation of this reduced score for field studies (25,26). Moreover, digestive symptoms and fatigue are non-specific symptoms that can be provoked by many other conditions such as gastro-intestinal infections or intense exercise. It was recently shown that dizziness and neurological manifestations can be linked to a ventilatory hyper-response to hypoxia and thus considered as a good marker of acclimatization (27). Therefore, we should accept the Lake
Louise score in its original version for field studies, with all its imperfections and subjective drawbacks. No case of HACE was reported. However, several subjects reported symptoms that may account for starting cerebral edema, such as drowsiness, slurred speech and confusion but these symptoms rapidly disappeared on descent and no participant reported loss of consciousness.

One may argue that the presence of a subgroup of subjects with previous experience of SHAI may have had an impact on our results. However, the proportion of these subjects in our cohort is limited (7%) and comparable to a general population (8%). By re-analyzing our data, it appears that the overall results are not modified after excluding this subgroup. For example, the incidence of SHAI is 19% in low-susceptible subjects and 27% in high susceptible subjects and the difference is still significant (p= 0.023). If we now consider the specific subgroup with previous episodes of SHAI, when both decision tree and 400m-rule were respected, 27% suffered de novo from SHAI while 64% were sick if they did not respect the rules (p=0.04), suggesting that the consultation is even more important for subjects with previous episodes of SHAI.

Another limitation is that the compliance of the physician to follow the decision tree and of the subject to follow the prescription (based on the decision tree) was not perfect, with a tendency for an over-prescription of ACZ by the physician. One of the objectives of this study was to give an objective tool to limit this prescription to those who would really need it, knowing that ACZ may have some side effects (polyuria, dehydration, paresthesias, digestive symptoms, fatigue) (11) and could interfere with current medications, as seen in trekkers in Nepal (28). In spite of
this probable slight over-use of ACZ, a great majority (80%) of persons who were low-susceptible and did not take ACZ did not suffer from SHAI.

Pre-acclimatization (in normobaric or hypobaric conditions) before trekking or expedition has been recently developed to “prepare” the subject to the hypoxic stress and limit the occurrence of SHAI (21,29,30,31). In the present study, no subject had pre-acclimatized, so we cannot evaluate the efficiency of this hypoxic training method. However, based on previous data, it could be suggested as a countermeasure to reduce the risk of SHAI in high-susceptible subjects (30, 31).

In ten years from 2008 to 2018, there is clear tendency for a decrease in the incidence of life-threatening forms of altitude sickness (HAPE, HACE). The incidence of HAPE in our cohort (0.8%) is lower than what is currently observed in the literature (2.5 to 4% in trekkers) (1, 20). However severe AMS is still observed in around one quarter of the population. The advice for a progressive altitude gain (400 m-rule) has been rationalized and documented. Detecting low-susceptible subjects appeared useful to limit and rationalize the prescription of ACZ. Moreover, it allows the detection of high-susceptible subjects for whom, in addition to ACZ prescription, preventive advice (limitation of exercise intensity, proper hydration, respect of the acclimatization rule, avoidance of hypnotics, eventual pre-acclimatization) is particularly important. However, it is clear that the 400 m-rule is sometimes impossible to fulfill because of geographical and practical constraints, such as during the Kilimandjaro climb or when the arrival at HA is abrupt, by flight or by car (Ladakh, Lhassa, La Paz, etc.).
An important aspect of the decision tree based on the SHAI score is that it allows a individualization of the prescription and advice given to the subject, by taking into account his/her personal physiological response to hypoxia (32) as opposed to a simple interview and general advice proposed by others (33). Altogether, the main result comforting the interest of a pre-altitude medical consultation with a hypoxic exercise test leading to the computation of the SHAI score is that the occurrence of SHAI is reduced by more than half (27% to 12%) when the recommendations, in accordance with the SHAI score and the 400 m-rule, are respected by the subjects. The limited cost of the consultation (100 to 120 €) encourages people with no previous experience of high altitude (59% of our cohort) to perform a Hypoxia Exercise Test and evaluate their personal tolerance to hypoxia.

CONCLUSION

The present observations obtained in a large multicenter cohort, confirmed the interest of the SHAI score in predicting the individual risk for SHAI, allowed to determine the precise conditions for an optimized acclimatization (400 m-rule) and proposed a rational decision tree for the prescription of acetazolamide.
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Figure captions

Figure 1. Decisional tree used during the mountain medicine consultation. In case of absence of cardiovascular disease or any other medical contra-indication for HA, the Hypoxia Exercise Test is performed and the SHAI score calculated (see text for details). When the score is below the threshold (5 for subjects who have a previous experience at high altitude, 5.5 for those who do not), general advice for prevention of Acute Altitude Illness are given: limit intense exercise, good hydration, respect the 400 m-rule of acclimatization, avoid hypnotics, etc.). When the score is above the threshold, 1) advice are reinforced, insisting on the potential risk of severe manifestations if these advices are not followed, 2) acetazolamide is given for a preventive use: 125 mg B.I.D. (morning and mid-day), starting the day before reaching 3000 m and continuing until the day when the maximal altitude is reached, but not longer than 7 days.

Figure 2. Classification of subjects as a function of the following categories:

- SHAI score below or above the threshold
- Use or not of acetazolamide
- Occurrence of Severe High Altitude Illness (SHAI)

In each block: number of subjects (percentage of above population size)

Figure 3. Classification of subjects following the compliance with the decision tree and the 400 m-rule.

In each block: number of subjects (percentage of above population size)
Figure 4. A. Histogram of observed daily altitude gains in subjects who suffered (SHAI+) or not (SHAI-) from Severe High Altitude Illness. SHAI is more frequent above 400 m of daily altitude gain. See text for the exact calculation of daily altitude gain.

B. Computation of the Youden index (= Sensitivity+Specificity-1) as a function of the threshold for daily altitude gain. The maximal value of the index is observed for a 400 m threshold.
Figure 2
Figure 3

All subjects 641

Compliance with the decision tree

Yes

Compliance with the 400m-rule

No

195 (30%)

446 (70%)

257 (58%)

189 (42%)

Yes

No SHAI 166 (88%)

SHAI 23 (12%)

No SHAI 330 (73%)

SHAI 122 (27%)
Figure 4

A

Relative frequency

SHAI-
SHAI+

Daily altitude gain (m/night)

B

Youden index

Daily altitude gain (m/night)
Table 1. Computation of the SHAI score to define the individual susceptibility to Severe High Altitude Illness (SHAI).

| Item                                              | Subjects with previous experience at high altitude | Subjects without previous experience at high altitude |
|---------------------------------------------------|---------------------------------------------------|-----------------------------------------------------|
| History of SHAI                                   | 2.5                                               |                                                     |
| Planned daily altitude gain (≥400m/night)         | 2                                                 | 2                                                   |
| History of migraine                               | 1.5                                               | 0                                                   |
| Geographical location (Aconcagua, Ladakh-Zanskar, Mont-Blanc) | 1                                                 | 0.5                                                 |
| Age < 46 yrs                                      | 0.5                                               | 0                                                   |
| Female sex                                        | 0                                                 | 0.5                                                 |
| Regular endurance physical activity*              | 0.5                                               | 1                                                   |
| HVRe (L/min/kg) < 0.68                            | 3                                                 | 3                                                   |
| HVRe (L/min/kg) ≥ 0.68 and < 0.94                 | 1                                                 | 1                                                   |
| HCRe (b/min/%) < 0.72                             | 1                                                 | 1                                                   |
| HCRe (b/min/%) ≥ 0.72 and < 0.95                  | 0                                                 | 1                                                   |
| ΔSaO₂Exercise (%) ≥ 24                            | 0                                                 | 2                                                   |
| ΔSaO₂Exercise (%) ≥ 19 and < 24                   | 0                                                 | 1                                                   |
| Threshold to define high susceptibility            | >5                                                | >5.5                                                |

HVRe: ventilatory response to hypoxia at exercise  
HCRe: cardiac response to hypoxia at exercise  
ΔSaO₂Exercise : decrease in arterial O₂ saturation in hypoxia at exercise  
* At least 40 min intense aerobic exercise 3 times/week  
Numerical values of thresholds for HVRe, HCRe and ΔSaO₂Exercise were determined in previous publications (2, 4, 8).
Table 2. General characteristics of the population.

|                          | Female   | Male    | \(P\)  |
|--------------------------|----------|---------|--------|
| Number of subjects       | 292      | 349     |        |
| Age (yrs)                | 48.8 ± 14.6 | 51.8 ± 13.9 | 0.008  |
| Body Mass Index \((\text{kg.m}^{-2})\) | 22.2 ± 3.0 | 24.4 ± 2.9 | <0.001 |
| Coronary diseases        | 1        | 6       | 0.13   |
| Systemic hypertension    | 15 (5.1) | 42 (12.0) | 0.002  |
| Raynaud syndrome         | 28 (9.6) | 3 (0.9)  | <0.001 |
| Hypercholesterolemia     | 16 (5.5) | 41 (11.7) | 0.005  |
| Asthma                   | 14 (4.8) | 20 (5.7) | 0.59   |
| Bronchopulmonary diseases| 7 (2.4)  | 6 (1.7)  | 0.54   |
| Allergy                  | 90 (30.9)| 93 (26.6)| 0.23   |
| Perinatal events         | 2 (0.8)  | 8 (2.6)  | 0.11   |
| Migraine                 | 35 (12.0)| 25 (7.2) | 0.037  |
| Menopause                | 148 (53.4)|        |        |
| Smoking                  | 28 (9.6) | 29 (8.3) | 0.57   |
| Sleep apneas syndrome    | 6 (2.1)  | 14 (4.0) | 0.16   |
| Snoring                  | 40 (13.7)| 106 (30.4)| <0.001 |
| Regular endurance training| 94 (32.2)| 154 (44.1)| 0.002  |
| Previous stay at HA      | 106 (36) | 157 (45) | 0.026  |
| Previous SHAI if previous stay | 21 (20) | 24 (15) | 0.34   |
| Planned altitude (m)     | 5250 ± 753 | 5366 ± 777 | 0.06   |
| SHAI score               | 5.1 ± 2.3 | 4.7 ± 2.0 | 0.03   |
| Lake Louise score        | 4.0 ± 2.5 | 3.8 ± 2.6 | 0.42   |
| Presence of SHAI         | 64 (22.0) | 81 (23.0) | 0.70   |
| Peripheral edema         | 59 (20.2) | 34 (9.7)  | <0.001 |
| Subjective feeling of intolerance | 71 (24.3) | 80 (22.9) | 0.68   |
| Medical consultation     | 9 (3.1)  | 20 (5.7) | 0.11   |
| **Highest altitude reached** | 5178 ± 738 | 5223 ± 744 | 0.46   |
| **Highest daily altitude gain** | 420 ± 163 | 418 ± 182 | 0.88   |
| Preventive use of ACZ    | 141 (48) | 138 (40) | 0.026  |
| Compliance to prescription| 217 (74) | 253 (73) | 0.60   |

Values presented are mean ± standard deviation or number (percentage).

SHAI: Severe High Altitude Illness; AMS: Acute Mountain Sickness; HA: High Altitude.

\(P\) value is calculated via unpaired Student t-test for continuous variables and via chi square or Fisher’s exact test for categorical variable.
Table 3. Outcomes in the four groups of subjects according to ACZ use and occurrence of SHAI.

|                              | No preventive use of ACZ | Preventive use of ACZ | P               | P               |
|------------------------------|--------------------------|-----------------------|-----------------|-----------------|
|                              | No SHAI | Presence of SHAI | No SHAI | Presence of SHAI | ACZ effect | SHAI effect |
| Number of subjects           | 282     | 80              | 214     | 65              | 0.72       |             |
| SHAI score                   | 3.84 ± 1.92 | 4.64 ± 2.18      | 5.83 ± 1.90 | 6.36 ± 1.67*** | <0.001     | <0.001     |
| Lake Louise score            | 2.92 ± 1.58 | 7.69 ± 1.54      | 2.70 ± 1.52 | 7.40 ± 1.93*** | 0.075      | <0.001     |
| Functional item              | 0.37 ± 0.65 | 1.43 ± 1.00      | 0.52 ± 0.77 | 1.80 ± 1.06*** | 0.001      | <0.001     |
| No or mild AMS               | 107 (38) | 0 (0)           | 103 (48) | 0 (0)           | NA         |            |
| Moderate AMS                 | 175 (62) | 0 (0)           | 111 (52) | 0 (0)           | NA         |            |
| Severe AMS                   | 0       | 80              | 0       | 65              | NA         |            |
| HAPE                         | 0 (0)   | 2 (2.4)         | 0 (0)   | 3 (4.7)         | NA         |            |
| HACE                         | 0 (0)   | 0 (0)           | 0 (0)   | 0 (0)           | NA         |            |
| Peripheral edema             | 32 (11) | 19 (24)         | 25 (12) | 17 (26)**       | 0.73       | <0.001     |
| Subjective feeling of severe AMS | 39 (14) | 45 (56)         | 32 (15) | 35 (54)**       | 0.81       | <0.001     |
| Medical consultation         | 6 (2)   | 8 (10)          | 5 (2)   | 10 (15)**       | 0.36       | <0.001     |
| Maximal altitude reached (m) | 5097 ± 747| 5424 ± 678      | 5212 ± 749 | 5352 ± 688*** | 0.21       | 0.001      |
| Maximal daily altitude gain (m) | 388 ± 184| 493 ± 170      | 413 ± 152 | 478 ± 160*** | 0.26       | <0.001     |
| Compliance to SHAI score     | 217 (77) | 67 (84)         | 146 (68) | 49 (75)         | 0.013      | 0.10       |
| Compliance to prescription   | 197 (70) | 54 (68)         | 171 (80) | 48 (74)         | 0.009      | 0.36       |

Values presented are mean ± standard deviation or number (percentage); SHAI: Severe High Altitude Illness; Functional item: functional item (0 to 3) of the Lake Louise score (LLS); AMS: Acute Mountain Sickness (no or mild: LLS<3, moderate: LLS 3 to 5, severe: LLS>5); HAPE: High Altitude Pulmonary Edema; HACE: High Altitude Cerebral Edema.; Compliance to SHAI score: prescription of acetazolamide by the physician conforms to SHAI score vs threshold; Compliance to prescription: use of acetazolamide by the subject conforms to the prescription by the physician; **,***: P<0.01, P<0.001 SHAI with ACZ vs no SHAI without ACZ. NA: not applicable.

P value is calculated as indicated in the Statistics section (ANOVA or Chi square when appropriate.)