20120716 EBM

家庭醫學科
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臨床場景(clinical scenario)分析

- 病人基本資料：
  - 30 y/o man without underlying disease
- 主訴/相關症狀/PE/Lab/image：
  - No fever, general condition well recently
  - Will go to 西藏for traveling
  - No experience for traveling to high-altitude mountain
- 診斷
  - Ask for Prevention for acute mountain sickness
- 治療
  - Acetazolimide 125mg BID, 24hr before and continuing for 1-2 day once reaching the highest altitude

提出background questions

- What is Acute Mountain Sickness
- How to treat Acute Mountain Sickness
- How to prevent Acute Mountain Sickness

What is Acute Mountain Sickness

- AMS diagnosis
  - typical symptoms
    - who lives at low altitude
    - recently ascended to high altitude (generally over 2000 m).
  - headache and at least 1 other symptom of anorexia, fatigue, insomnia, or dizziness
  - If untreated, advanced AMS may progress to its end-stage expression as high altitude cerebral edema

Treatment of Acute Mountain Sickness

- General approach
  - Mild illness can be treated conservatively
  - Moderate to severe symptoms may require medication, supplemental oxygen, and occasionally descent.

Prevention

- Ascending at a slower rate
- Prophylaxis
  - Acetazolamide is the drug of choice
  - Dexamethasone
    - when acetazolamide is not tolerated and in special circumstances.

- Acetazolamide
  - carbonic anhydrase (CA) inhibitor
  - works by a number of mechanisms to accelerate acclimatization and ameliorate hypoxia
  - disinhibiting the central chemoreceptors
    - stimulates ventilation, which rapidly improves oxygenation
  - maintains oxygenation during sleep and prevents periods of extreme hypoxemia
  - diminishes nocturnal antidiuretic hormone (ADH) secretion and cerebrospinal fluid production and volume, and possibly lowers intracranial pressure

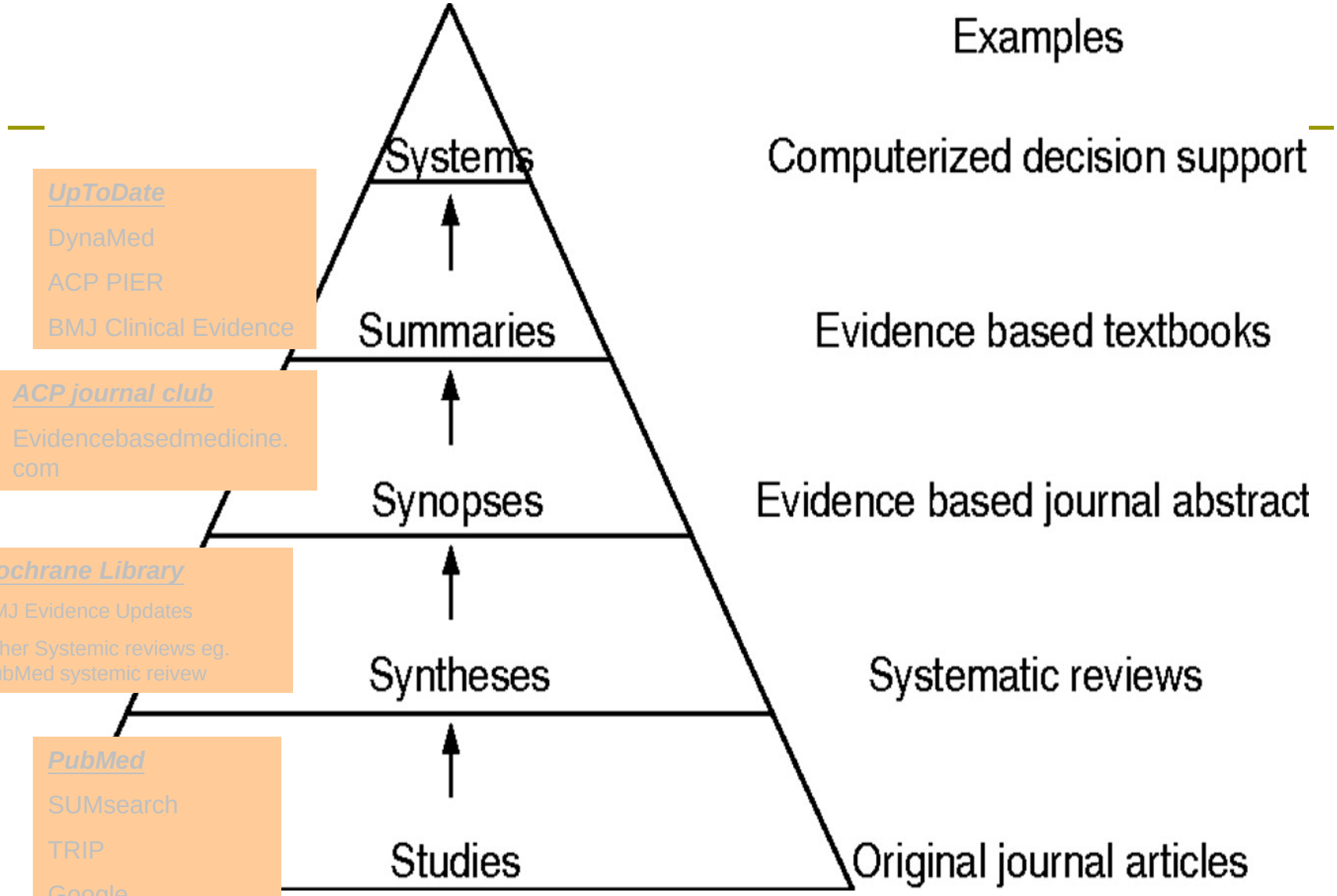
提出foreground questions 及提出此問題的理由

問題描述及提出此問題的理由：病人即將前往西藏旅遊，已建議Acetazolamide為目前最佳預防用藥，病人仍會擔心高山症的發作。希望能了解更多對於高山症發作以及其症狀的預防性的用藥治療。	
P:	30 y/o male person without underlying disease, ask for prevention of AMS
I:	Other medication for prevention
C:	Acetalozamide
O:	symptoms of high altitude sickness
T:	Not defined

搜尋最有用的資料

The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164



EBM ONLINE

搜尋summary

- Key word: Acute Mountain Sickness

搜尋到的文章標題

- **Title:**
  - Acute mountain sickness and high altitude cerebral edema

Acute mountain sickness and high altitude cerebral edema

Authors
Scott A Gallagher, MD
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Section Editor
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搜尋到的文章內容

- Nonsteroidal antiinflammatory medications (NSAIDs)
  - Both **aspirin** and **ibuprofen** have been shown to prevent headache on ascent to high altitude. Since headache is the cardinal symptom of AMS, and required for the research definition of the disease, it follows that these agents "prevent" AMS.
  - For those **going to moderate altitude** (ie, below 3500 m), **aspirin or ibuprofen may be useful agents**. However, it remains ***unclear whether these medications would be useful as prophylaxis, or treatment, in high-risk situations*** (ie, rapid ascent to very high or extreme altitude). The limitations of trials involving NSAIDs make such determinations difficult.

將summary搜尋的結果應用到我的病人

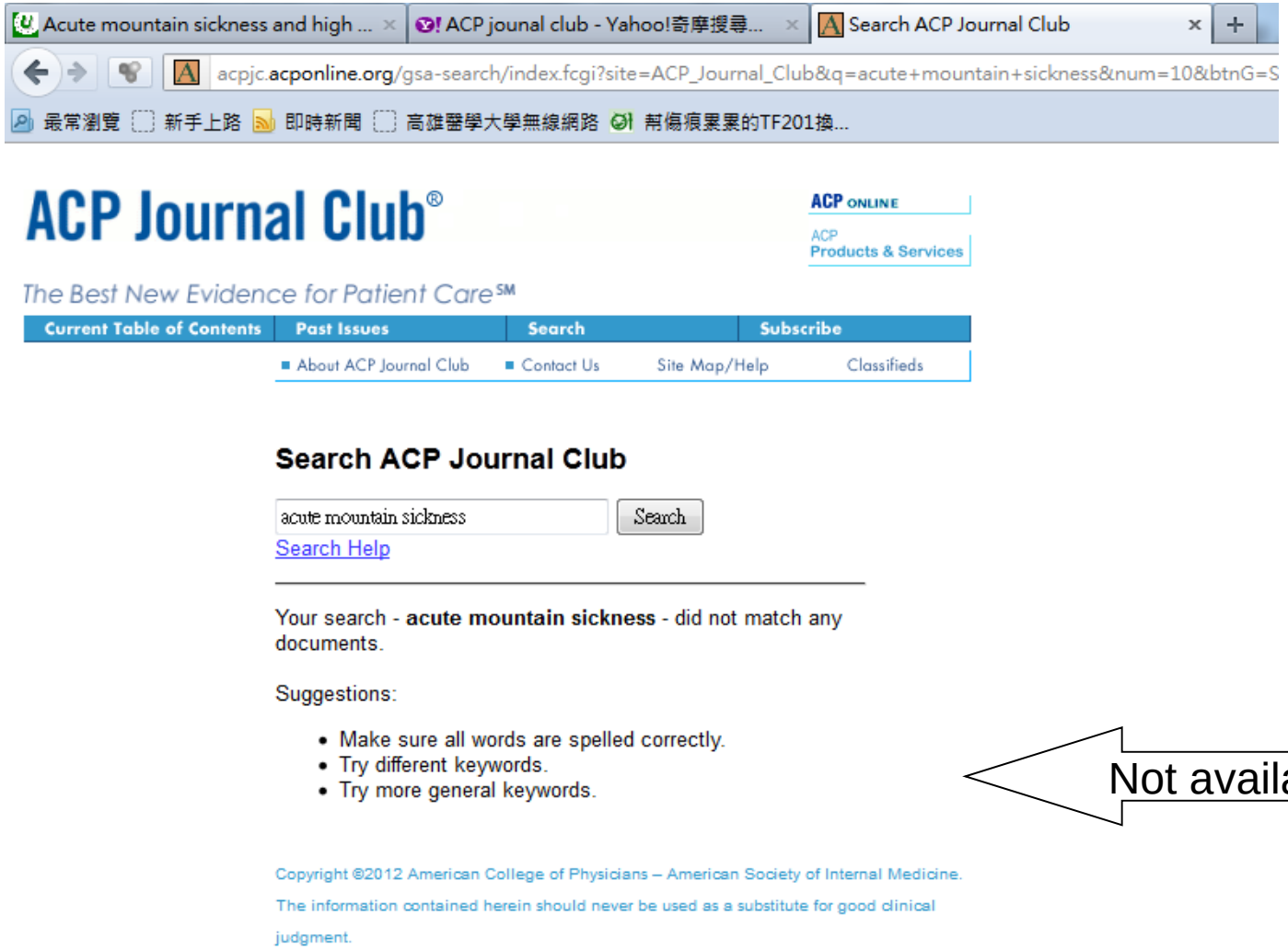
- NSAID類的藥物對於高山症的頭痛是有治療效果；對於可能做為高山症的預防用藥，需要進一步再評估。

搜尋Synopses

ACP Journal Club®
The Best New Evidence for Patient Care℠

- Key word: Acute Mountain Sickness

搜尋到的文章標題



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搜尋synthesis

- Key word: Acute Mountain Sickness

搜尋到的文章標題

Search Results

Show Results in:
Cochrane Reviews [1] | Other Reviews [2] | Trials [158] | Methods Studies [0] | Technology Assessments [0] | Economic Evaluations [0] | Cochrane Groups [0]

There are **1** results out of **7296 records** for: "**acute mountain sickness** in **Title, Abstract or Keywords** in **Cochrane Database of Systematic Reviews**"

View: **1**

Export All Results

Record Information Issue: Current | **All** Restrict to: Reviews | Protocols Sort by: Record Title | **Match %** | Date

Interventions for treating high altitude illness
Arturo J Martí-Carvajal, Daniel Simancas-Racines, Ricardo Hidalgo
May 2012
Protocol

Select All (to export citations)

Export Selected Citations | Export All Results

View: 1

Not available use

搜尋study

PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

- Key word: Acute mountain sickness, Ibuprofen

搜尋到的文章標題

WILDERNESS & ENVIRONMENTAL MEDICINE, **21,** 236–243 (2010)

ORIGINAL RESEARCH

Prospective, Double-Blind, Randomized, Placebo-Controlled Comparison of Acetazolamide Versus Ibuprofen for Prophylaxis Against High Altitude Headache: The Headache Evaluation at Altitude Trial (HEAT)

Jeffrey H. Gertsch, MD; Grant S. Lipman, MD; Peter S. Holck, PhD; Andrew Merritt, MD; Allison Mulcahy, MD; Robert S. Fisher, MD, PhD; Buddha Basnyat, MD; Eric Allison, DO; Keeli Hanzelka, MD; Alberto Hazan, MD; Zachary Meyers, MD; Justin Odegaard, MD, PhD; Benjamin Pook, MBChB; Mark Thompson, MD; Brant Slomovic, MD; Henrik Wahlberg, MBChB; Vanessa Wilshaw, MBChB; Eric A. Weiss, MD; Ken Zafren, MD

WILDERNESS & ENVIRONMENTAL MEDICINE, 21, 236–243 (2010)

搜尋到的文章內容

- **Objective**
  - a prospective, double-blind, randomized, placebo-controlled trial in the Nepal Himalaya designed to compare the effectiveness of ibuprofen and acetazolamide for the prevention of HAH.

Methods

- 343 healthy western trekkers were recruited at altitudes of 4280 m and 4358 m
- assigned to receive ibuprofen 600 mg, acetazolamide 85 mg, or placebo 3 times daily before continued ascent to 4928 m.
- Outcome measures included headache incidence and severity, AMS incidence and severity on the Lake Louise AMS Questionnaire (LLQ), and visual analog scale (VAS).

Inclusion criteria

- specified healthy non-Nepali males and females 18 to 65 years of age
- traveling directly between the baseline villages of Pheriche or Dingboche (4280 m and 4358 m, respectively) and the endpoint in Lobuje (4928 m).

Exclusion

- Had any headache, diagnosis of AMS
- signs or symptoms of a substantial acute infection
- had slept above 4500 m
- had taken any NSAIDs or acetazolamide within 1 day or 3 days prior to enrollment, respectively.

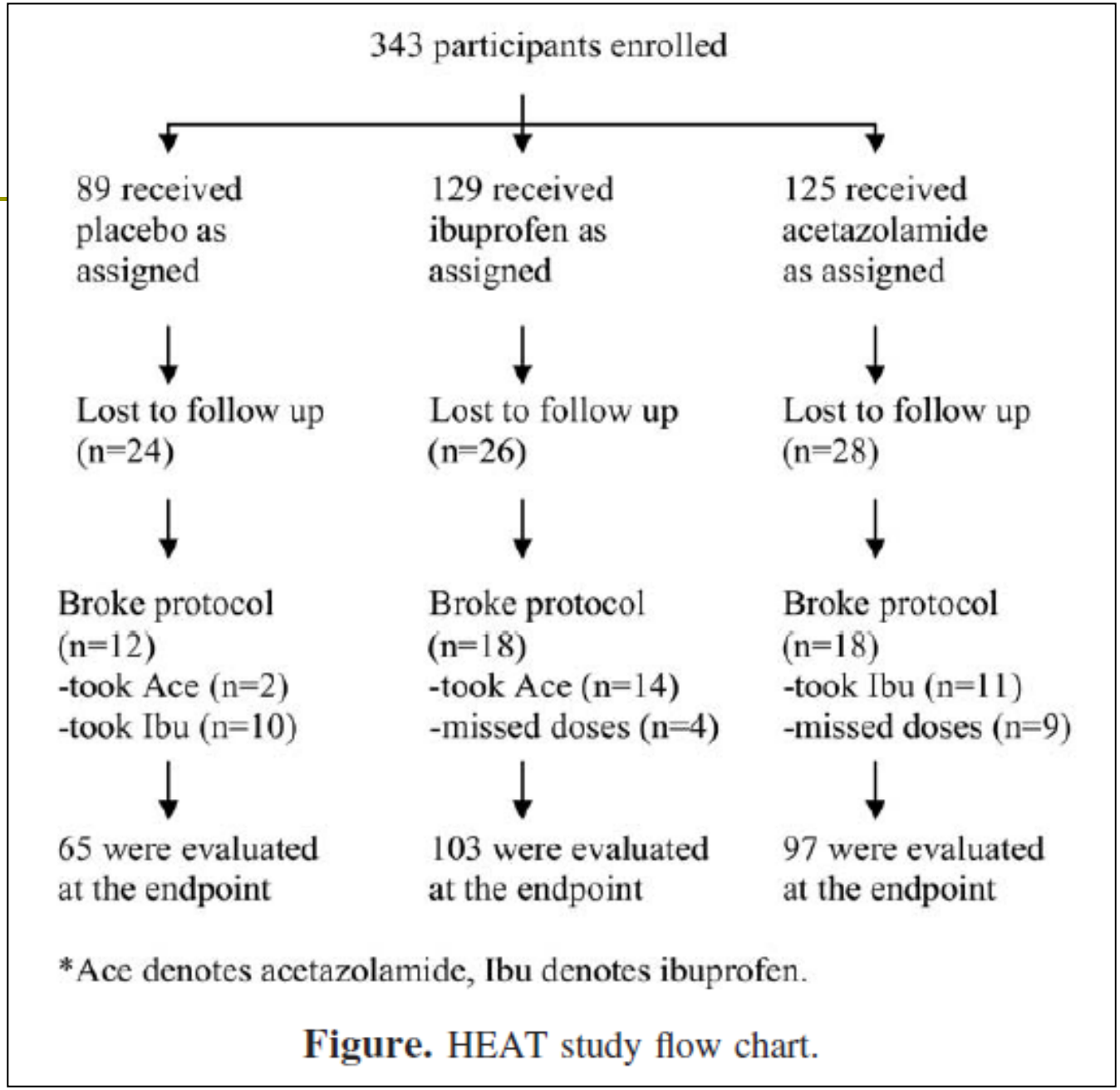


Figure. HEAT study flow chart.

- **Results**
  - 265 of 343 subjects completed the trial.
  - HAH incidence
    - similar when treated with acetazolamide (27.1%) or ibuprofen (27.5%; *P:*0.95);
    - both agents were significantly more effective than placebo (45.3%; *P:0*.01).
  - AMS incidence
    - similar when treated with acetazolamide (18.8%) or ibuprofen (13.7%; *P* .34),
    - both agents were significantly more effective than placebo (28.6%; *P:0*.03).

- In fully compliant participants:
  - moderate or severe headache incidence was similar when treated with acetazolamide (3.8%) or ibuprofen (4.7%; *P*.79),
  - both agents were significantly more effective than placebo (13.5%; *P:0*.03).

Table 2. Main outcome profile (intent-to-treat)

Variables	*Study participants*		*Placebo group*		*Acetazolamide group*		*Ibuprofen group*		*Acetazolamide vs ibuprofen (P)*	*Significance treatment vs placebo (P)*
Endpoint cohort	265		65		97		103			
Headache incidence	83	31.7%	29	45.3%	26	27.1%	28	27.5%	.95	.01
Severe headache incidence[a]	18	6.9%	7	1.9%	6	6.3%	5	4.9%	.68	.14
AMS incidence[b]	50	19.2%	18	28.6%	18	18.8%	14	13.7%	.34	.03
Severe AMS incidence[c]	17	6.5%	4	6.3%	7	7.3%	6	5.9%	.69	.95
Endpoint Sao_2 (%)	81.8	± 4.3	81.0	± 4.9	82.6	± 3.8	81.7	± 4.2	.22	.09
Sao_2 decrease from baseline	−4.3	± 4.1	−5.4	± 4.2	−3.9	± 3.8	−3.9	± 4.1	.99	.03
Headache VAS	5.0	± 1.16	5.6	± 1.06	4.1	± 1.08	5.3	± 1.29	.46	.58
Participants who broke protocol[d]	48	18.1%	12	18.5%	18	18.6%	18	17.5%	.84	.94

Table 3. Main outcome profile excluding those who broke protocol[a]

Variables	*Study participants*		*Placebo group*		*Acetazolamide group*		*Ibuprofen group*		*Acetazolamide vs ibuprofen (P)*	*Significance treatment vs placebo (P)*
Endpoint cohort	217		53		79		85			
Headache incidence	68	31.6%	25	48.1%	18	23.1%	25	29.4%	.36	.01
Severe headache incidence[b]	14	6.5%	7	13.5%	3	3.8%	4	4.7%	.79	.03
AMS incidence[c]	41	19.2%	16	31.4%	12	15.4%	13	15.3%	.99	.01
Severe AMS incidence[d]	13	6.1%	3	5.9%	5	6.4%	5	5.9%	.89	.95
Endpoint SaO_2 (%)	82.0	± 4.0	81.4	± 4.3	82.6	± 3.5	81.8	± 4.2	.28	.25
SaO_2 decrease from baseline	4.4	± 3.8	5.3	± 3.9	4.1	± 3.4	4.2	± 4	.89	.12
Headache visual analog scale (VAS)	4.7	± 1.09	5.9	± 1.13	2.5	± .55	6.0	± 13.8	.04	.34

Limitations of the Study

- First
  - participants had already been exposed to significant altitudes for several days prior to baseline enrollment (4280 or 4358 m)
  - these results cannot necessarily be applied to other high altitude trekking environments
    - where ascent rate, demographics, and final elevation may differ.

- Second
  - Participants in all groups were equally likely to drop out of the study
- Third
  - Increased sample sizes would permit more power to identify small differences between the treatments, should they exist.

Conclusions

- Ibuprofen and acetazolamide were similarly effective in preventing HAH.
- Ibuprofen was similar to acetazolamide in preventing symptoms of AMS
  - an interesting finding that implies a potentially new approach to prevention of cerebral forms of acute altitude illness.

Appraisal

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	www.cebm.net	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

Item	AAMPICOT for therapy- Criteria	Comments(評論並說明你的根據)
Answer	此文獻有沒有回答我的問題	有，這篇Paper比較Acetazolamide和Ibuprofen在AMS和Headache方面治療的效果
Authors	作者群是這領域的專家嗎？	是
	有沒有利益衝突？	沒有，No potential conflicts of interest relevant to this article were reported
Method	本文獻研究設計是屬於以下那一類 SR, RCT, Cohort, Case-contro, Case series or report, Expert opinion	是 Prospective, Double-Blind, Randomized, placebo-controlled
Population	取樣是否為隨機取樣？	是
	取的樣本是否具代表性？其特性是否接近我的病人？	是
	分組是否是隨機分組？	是
	分組是否採用盲法？	是
Intervention	給予實驗組的處置是否描述清楚，並且是臨床可行的？	是
Comparison	給予對照組的處置是否描述清楚，並且是臨床可行的？各種可能比較皆有了？	是

Outcome	測量了那些結果？是否用客觀的方式測量？請問NNT,NNH各是多少？	1. headache incidence- (LLQ) Lake Louise AMS Questionnaire 2. headache severity by Visual Analog Scale (VAS) 3. Pulse oximetry 4. NNT= 5.5 (HAH) 5. NNT= 8.1 (AMS)
	這些結果是否有統計學上的重要性？	是
	這些結果是否有臨床上的重要性？	是
	是否呈現結果的「數值」，「p值」，「信賴區間」，「檢力」？	只有呈現數值和P值
	是ITT analysis還是PP analysis	ITT analysis
Time	測量結果的時間點是否合宜？	是，追蹤登山至endopoint隔天早上
	追蹤時間是否夠長？	無後續追蹤
	文獻發表時間？	2010 Sep

實證醫學結果小結

- 對於高山症頭痛的預防除了使用acetalozamide之外，使用Ibuprofen有類似的效果
- 高山症的預防上，Ibuprofen有和acetalozamide類似的效果，但確定機轉仍未明

將EBM結果應用到病人身上

Compare the clinical question with the article's question

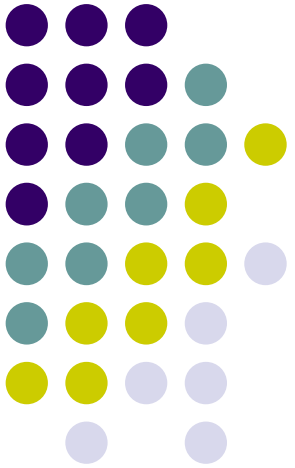
Clinical question	Article's question
P: health male	P: Heath people
I: other treatment	I: Ibuprofen
C: Acetalozamide	C: acetalozamide
O: symptoms of high altitude sickness	O: symptoms of HAH, AMS
T: not defined	T: after the endpoint

醫療現況	病人意願
目前第一線預防藥物仍為Acetazolamide。其它藥物的預防效果仍繼續研究中。	即使知道Acetazolamide為目前第一線預防用藥，病人會擔心高山症的發作。希望能了解更多預防性的用藥。
生活品質	社會脈絡
要對於高山症的症狀了解，並使用預防性藥物，如果有任何不舒服，立刻下山送醫治療。	台灣登山人口日益增多，2500公尺以上的高山亦不少，需對高山症的預防治療需有相當程度的了解。

總結

- 目前第一線預防用藥物仍是使用Acetazolamide。Ibuprofen仍在研究之中。
- 病人會擔心高山症的發作。衛教病人高山症的症狀以及治療方式。如有嚴重症狀須立刻送醫治療，仍是不變的原則。

Audit（自我評估）



在「提出臨床問題」方面的自我評估

- 我提出的問題是否具有臨床重要性？
  有，目前高山旅遊的人口越來越多
- 我是否明確的陳述了我的問題？
  - 我的foreground question 是否可以清楚的寫成PICO？是
  - 我的background question是否包括what, when, how, who等字根？有
- 我是否清楚的知道自己問題的定位？（亦即可以定位自己的問題是屬於診斷上的、治療上的、預後上的或流行病學上的），並據以提出問題？知道
- 對於無法立刻回答的問題，我是否有任何方式將問題紀錄起來以備將來有空時再找答案？有

在「搜尋最佳證據」方面的自我評估

- 我是否已盡全力搜尋？有
- 我是否知道我的問題的最佳證據來源？知道
- 我是否從大量的資料庫來搜尋答案？是
- 我工作環境的軟硬體設備是否能支援我在遇到問題時進行立即的搜尋？是
- 我是否在搜尋上愈來愈熟練了？是
- 我會使用「斷字」、布林邏輯、同義詞、MeSH term，限制（limiters)等方法來搜尋？較生疏
- 我的搜尋比起圖書館人員或其他對於提供病人最新最好醫療有熱情的同事如何？搜尋的技巧仍然很不純熟，需要多加練習

關於「嚴格評讀文獻」方面的自我評估

- 我是否盡全力做評讀了？是
- 我是否了解Number need to treat 的意義？是
- 我是否了解Likelihood Ratios的意義？是
- 我是否了解worksheet每一項的意義？是
- 評讀後，我是否做出了結論？是

關於「應用到病人身上」的自我評估

- 我是否將搜尋到的最佳證據應用到我的臨床工作中？是
- 我是否能將搜尋到的結論如NNT, LR用病人聽得懂的方式解釋給病人聽？可
- 當搜尋到的最佳證據與實際臨床作為不同時，我如何解釋？須考量當下的治療方式並且評估病人條件是否能夠使用最佳證據的治療。每一項治療的必須以病人目前身體狀況去進行評估是否合宜。

改變「醫療行為」的自我評估

- 當最佳證據顯示目前臨床策略需改變時，我是否遭遇任何阻止改變的阻力？

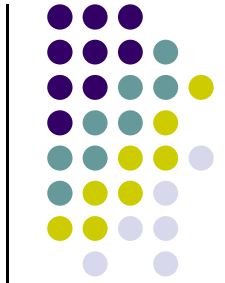
  未知

- 我是否因此搜尋結果而改變了原來的治療策略？做了那些改變？

  會參考搜尋的結果，並評估這項治療對病人是否有明顯幫助。

效率評估

- 這篇報告，我總共花了多少時間？
  十幾個小時。
- 我是否覺得這個進行實證醫學的過程是值得的？
  值得，對查詢EBM有概念多了。
- 我還有那些問題或建議？技巧尚待加強。



Thank You

ciception.[10–14] Multiple studies show the NSAID aspirin

(LLQ), a validated field standard for diagnosis of AMS, which includes a question on headache presence and severity.[25,26]

A predetermined secondary endpoint included evaluation of headache severity by Visual Analog Scale (VAS).[27,28] Other secondary measures included pulse oximetry (Nonin Medical Products, Minneapolis, MN), as well as AMS incidence and severity as measured by the LLQ. Demographics, ascent profile, compliance, and side effects data were collected to adjust for potential confounders.

Study Design

Commercial pharmaceutical grade acetazolamide and ibuprofen were packed in visually identical capsules by Deurali-Janta Pharmaceuticals (Kathmandu, Nepal). Study medications were randomized via computer-generated code. Participants were sought out on a daily basis in all baseline village hotels and sequentially enrolled in order to minimize selection bias.

All trekkers newly arrived at the baseline altitude were screened daily. Interviewers gathered demographics, ascent profile data, LLQ, VAS, and pulse oximetry. All trekkers were given information on methods for reducing the risk of AMS, thereby meeting the minimum standard of care. They were then randomized in a double-blind fashion to receive 3 times daily dosing of placebo, ibuprofen 600 mg, acetazolamide 85 mg (total daily dose of 255 mg to approximate a cumulative 250 mg daily dose given for AMS prophylaxis). Participants took a mini-

from modulation of carotid body activity, and inhibition of cerebrospinal fluid production.[22,23] While intuitive that ac-

place between October and November 2005 along the approach trail to Mount Everest in the Nepali Himalaya. The study was conducted in accordance with the Decla-

- 1. Commercial pharmaceutical grade acetazolamide and ibuprofen were packed in visually identical capsules
- 2. Study medications were randomized via computer generated code.

1. Interviewers gathered demographics, ascent profile data, LLQ, VAS, and pulse oximetry
2. randomized in a double-blind fashion to receive 3 times daily dosing of placebo, ibuprofen 600 mg, acetazolamide 85 mg

mum of 3 doses at the baseline altitude before proceeding on their trek.

On their ascent from baseline, a minority of participants stopped overnight at a lodge at 4595 m, but all were expected to arrive at the endpoint altitude for data collection. VAS and LLQ scores were self-reported the night of arrival and the morning after arrival, at which point the study was complete. Endpoint data collection represents morning-after-arrival data (unless missing, then replaced with night-before data) in order to emphasize specificity in the diagnosis of HAH and AMS.

In order to minimize morbidity from high altitude illness, participants were discouraged, but not actively prevented, from using unblinded analgesics or acetazolamide. In the event of a severe illness that might be attributable to altitude or a reaction to medications, administrators were at the baseline and endpoint sites with appropriate steroid medication available.

1. VAS and LLQ scores were self-reported the night of arrival and the morning after arrival, at which point the study was complete

2. Endpoint data collection represents morning-after-arrival data to emphasize specificity in the diagnosis of HAH and AMS

at the endpoint at the endpoint at the endpoint

*Ace denotes acetazolamide, Ibu denotes ibuprofen.

Figure. HEAT study flow chart.

Statistical Analysis

1), characteristics that could potentially provide a pro-

opment of acute mountain sickness (AMS). HAH is the requisite cornerstone symptom of AMS, defined at alti-

1. primary outcome measure
   - headache incidence at the study endpoint as calculated on the Lake Louise AMS Questionnaire (LLQ)

2. secondary endpoint included evaluation of headache severity by Visual Analog Scale (VAS)

3. Pulse oximetry (Nonin Medical Products, Minneapolis, MN)

studies have suggested that the related NSAIDs naproxen and calcium carbasalate are ineffective for prevention of AMS, whereas a preliminary observational report suggests a protective effect.[18–20]

Acetazolamide is a diuretic and carbonic anhydrase inhibitor used as the standard prophylactic agent against

Participants and Outcome Measures

Trekkers completed questionnaires after giving signed informed consent. Inclusion criteria specified healthy non-Nepali males and females 18 to 65 years of age traveling directly between the baseline villages of Pheriche or Dingboche (4280 m and 4358 m, respectively) and the endpoint in Lobuje (4928 m). Potential participants were excluded if they had any headache, diagnosis of AMS, signs or symptoms of a substantial acute infection, had slept above 4500 m, or had taken any NSAIDs or acetazolamide within 1 day or 3 days prior to enrollment, respectively.

The predetermined primary outcome measure was presence of headache incidence at the study endpoint as calculated on the Lake Louise AMS Questionnaire (LLQ), a validated field standard for diagnosis of AMS, which includes a question on headache presence and severity.[25,26]

A predetermined secondary endpoint included evaluation of headache severity by Visual Analog Scale (VAS).[27,28] Other secondary measures included pulse oximetry (Nonin Medical Products, Minneapolis, MN), as well as AMS incidence and severity as measured by the LLQ. Demographics, ascent profile, compliance, and side effects data were collected to adjust for potential

1. No significant difference between treatments in preventing HAH incidence (acetazolamide 27.1%, ibuprofen 27.5%; P:0.95)

2. Combining treatment group revealed a decrease in HAH incidence when compared to placebo at 45.3% (P: 0.01)
   - NNT: 5.5

3. combined groups were efficacious in prevention of AMS incidence (acetazolamide 18.8%, ibuprofen 13.7%, placebo 28.6%, P:0.03) ; NNT: 8.1.

life-threatening altitude sickness). Ibuprofen was not associated with a higher incidence of gastrointestinal upset or nausea after multiple statistical evaluations were performed.

Intent-to-Treat Analysis

Intent-to-treat data analysis revealed several key findings (see Table 2). For the primary endpoint, there was no significant difference between treatments in preventing HAH incidence (acetazolamide 27.1%, ibuprofen 27.5%; $P = .95$). Combining treatment groups revealed a decrease in HAH incidence when compared to placebo at 45.3% ($P = .01$), resulting in a number needed to treat of 5.5. Headache severity was not significantly reduced either between treatments or compared to placebo by several measures (see below). The combined treatment groups were efficacious in prevention of AMS incidence (acetazolamide 18.8%, ibuprofen 13.7%, placebo 28.6%, $P = .03$), resulting in a number needed to treat of 8.1. Participants taking placebo had a greater oxygen desaturation on ascent than those in the treatment arms ($P = .03$).

Secondary Analysis

Analysis with fully compliant participants (defined as those who took all study medications and did not take off-study