

# Extreme Altitude and illness: How can medical sciences help us achieve the Everest dream?

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## ABSTRACT

Since the first recorded summit of Everest in 1953, medical and technological advances have increased the mountain's accessibility. This has resulted in a commercialisation of Everest expeditions and an underestimation of the challenges the mountain poses. A large proportion of climber mortality on Everest is attributable to controllable and often preventable human factors called subjective hazards, the most prominent being altitude illness. Arguably the biggest cause of death on Everest, altitude illness is a set of conditions resulting from the inability to acclimatise to the hypoxic environment at altitude.

Increasing numbers of climbers on Everest are underprepared, meaning they are at increased risk of developing altitude illness and death. The aetiology of altitude illness is complex and multifactorial, however there are measures which can be taken to reduce susceptibility and treat the condition. Unfortunately due to its complex causation and unspecific symptoms, altitude illness is often hard to foresee and diagnose. Susceptibility to altitude illness is increased massively with a previous history of the illness, fast rate of ascent and certain genetic factors. Knowledge of the causation is being used to construct clinical tests, which can help predict summiting success and produce management plans for those suffering from the illness.

This review identifies the importance of acclimatisation programmes and a slow rate of ascent in reducing the incidence and severity of altitude illness. In addition to examining current best practice for its prevention and treatment, it also aims to produce a conclusive approach to extreme altitude expeditions, by discussing the efficacy of possible screening tests and the best predictors for altitude illness.

## INTRODUCTION

Humanity has long had a fascination with launching expeditions into the world's most hostile environments in a bid to conquer and inhabit them.<sup>1</sup> One such location is the Earth's highest altitude landmass- Mount Everest, standing at 8848 metres above sea level.<sup>2</sup> The first recorded expeditions are dated as early as 1921, with a 1922 team being the first to surpass the 8000-metre barrier.<sup>3</sup> Due to the immense physiological challenges inflicted by the final 500 meters of ascent, the first successful summit did not occur until 32 years later.<sup>3,4</sup>

Arguably, the biggest physiological challenge at extreme altitude is being able to maintain adequate oxygen perfusion for the body's tissues to respire.<sup>5</sup> This is due to the reduced atmospheric pressure, meaning there are fewer molecules of all gas in a given volume.<sup>6</sup> Despite the air composition being similar to sea level, there is less overall oxygen available for the body to inspire leading to hypoxia.<sup>6,7</sup> Studies show hypoxia is so severe at the summit of Everest, the PaO<sub>2</sub> averages at 25 mmHg less

than patients in need of supplementary Oxygen therapy in hospital.<sup>7</sup> Despite a more severe hypoxic state being imposed on the body at altitude, a healthy mountaineer can function better than patients in respiratory stress due to a number of physiological changes.<sup>7</sup> When climbing these changes occur as part of a process called acclimatisation.<sup>5,8</sup> If this process is neglected and climbers do not adequately prepare for altitude, there is a risk they present with similar problems as individuals reliant on oxygen in critical care units within hospitals.<sup>7,9</sup>

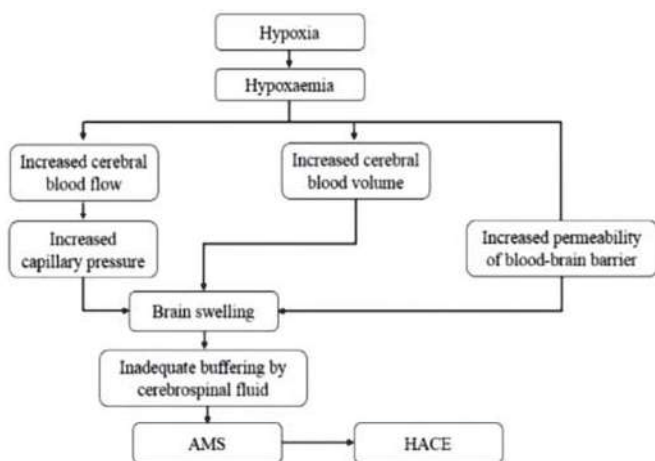
At altitude the body undergoes many hypoxic driven physiological changes because of low arterial oxygen levels, which are detected by the peripheral chemoreceptors.<sup>6,10</sup> This stimulates an adrenergic response whereby impulses sent to the cardio-respiratory system, lead to tachycardia and hyperventilation, resulting in an elevated cardiac output and respiratory alkalosis.<sup>10,11</sup> This is because CO<sub>2</sub> contributes to the acidity of blood and when hyperventilating CO<sub>2</sub> is lost at an increased rate resulting in a raised blood pH.<sup>12</sup> At altitude, the kidneys excrete bicarbonate ions as part of a compensatory metabolic acidosis to try to reduce the progression of alkalosis to hypocapnia.<sup>12,13</sup> In addition a rise in blood pH also increases red blood cells affinity for oxygen, meaning oxygen will not dissociate as readily in ischaemic tissues at altitude.<sup>14</sup> To combat this, the human body produces more<sup>2,3</sup> Bisphosphoglyceric acid, a compound which decreases haemoglobin affinity for oxygen and promotes its release via an allosteric alteration.<sup>15,16</sup>

Spending extended periods at altitude leads to a range of hormone changes.<sup>16,17</sup> A variety of stress hormones are found to be released at altitude in addition to growth hormone and are thought to play a role in metabolic adaption to hypoxia.<sup>16</sup> Furthermore in response to hypoxic conditions fibroblasts in the kidney release the hormone erythropoietin.<sup>15</sup> This works to increase the oxygen carrying capacity of the blood by raising red blood cell levels.<sup>18</sup> This is done through targeting proerythroblast differentiation and reducing cell turn over with apoptotic protection.<sup>19</sup>

If travelling to extremes of altitude or maintaining residence above 2500 metres for extended periods of time, further changes will occur in the lungs.<sup>20</sup> Normally if parts of the lungs suffer from reduced oxygen flow i.e. due to pneumonia or oedema, the vessels supplying this area will vasoconstrict.<sup>20</sup> This is to reduce the amount of deoxygenated blood leaving the lungs by diverting flow to the areas with richer supply.<sup>21</sup> This is called hypoxic pulmonary vasoconstriction and at altitude can cause pulmonary hypertension due to all areas of the lungs being hypoxic.<sup>20</sup>

Ultimately the physiological changes aim to help the body adapt to extreme altitude by combatting hypoxia.<sup>17</sup> If arterial O<sub>2</sub> concentration is not maintained at the same level as sea elevation, high altitude illness (HAI) may set in, which is one of the biggest causes of morbidity and mortality on Everest.<sup>2,22,23</sup> HAI is the name used for a set of

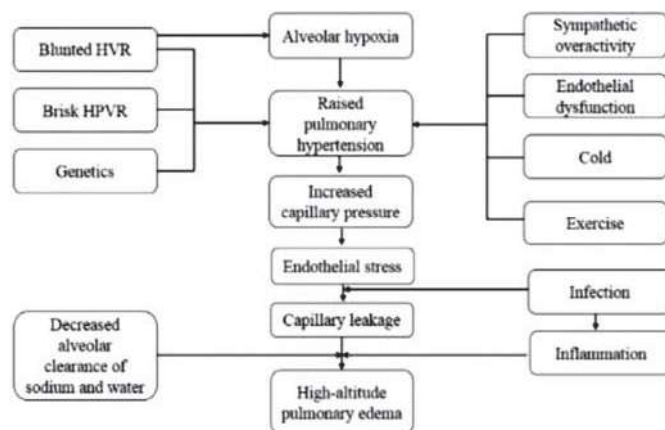
syndromes Acute mountain sickness (AMS), High altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE) which occur with maladaptation to altitudes exceeding 2500 meters.<sup>24</sup> The mildest yet most common of these syndromes is AMS, occurring in 50% of individuals ascending above 4500 meters.<sup>17</sup> This is characterised by a history of headaches, nausea and fatigue with no other obvious cause. The exact pathophysiology of AMS is unclear, but with it usually preceding HACE it is thought they share a similar pathological process, whilst lying on a continuum of varying severity.<sup>25</sup> HACE is a life threatening condition whereby hypoxia leads to increased cerebral blood flow in order to supply the oxygen deprived brain tissue.<sup>25</sup> Consequently, this increases capillary pressure causing elevated permeability of the blood brain barrier resulting in vasogenic oedema.<sup>24</sup> On MRI scans and autopsies of those who have suffered from HACE compressed ventricles, swollen gyri's and reduced cerebellum density are found as a result of the increased intracranial pressure.<sup>26</sup> This leads to damage of the brain tissue, resulting in the associated symptoms of confusion, ataxia and disturbances in consciousness.<sup>25, 26</sup>



**Figure 1:** A flowchart demonstrating the pathophysiology of AMS and HACE and the continuum in which they both lie.<sup>24</sup>

Oedema at altitude can also present problems in the lungs.<sup>17, 27</sup> This is partly due to hypoxic pulmonary vasoconstriction, which leads to endothelial disruption allowing the leakage of fluid into the extravascular space.<sup>20</sup> Over-activation of the sympathetic nervous system at altitude also stimulates receptors in the lungs that induce further vasoconstriction.<sup>10, 24</sup> The problem is further exacerbated due to reduction of NO synthesis, a potent vasodilator.<sup>24</sup> This is believed to be due to the lack of O<sub>2</sub> within the body, which is required in the reaction to produce NO.<sup>24</sup> Summation of these pathophysiological processes leads to HAPE, characterised by: orthopnoea, productive cough and pink frothy sputum.<sup>17, 24, 27</sup>

Since the first ascent of Everest, evolution in technology and medical advances has led to over 7000 recorded summits of the mountain.<sup>28</sup> This has resulted in a commercialisation of the mountain, allowing individuals with enough money to achieve the "Everest dream".<sup>29</sup> Commercial interests have subsequently resulted in people underestimating the challenges Everest poses.<sup>2</sup> Nearly 300 recorded deaths have occurred on Everest, with 2-3



**Figure 2:** A flowchart demonstrating the pathophysiological mechanism of HAPE.<sup>24</sup>

people dying on its slopes on average each year.<sup>2, 22</sup> An increasing number of these mortalities are inexperienced mountaineers, who have inadequate training for the physiological challenges inflicted on the body at altitude.<sup>28, 29</sup> As commercialisation grows people are calling for more stringent safety rules on Everest, including regulating people's physical and mental preparation.<sup>30</sup> Advances in medical sciences and technology have undoubtedly helped increase the number of people reaching Everest's summit.<sup>24</sup> As part of this advancement, this review aims to investigate how we can prevent HAI and best prepare for an Everest climb, in addition to determining, if there is a way we can predict summiting success.

## RESULTS & DISCUSSION

Hazards and deaths on Everest are often categorised into two broad groups: objective and subjective.<sup>31</sup> Objective hazards are risks which occur regardless of the individual involved and relate to the physical dangers on the mountain, like ice falls and avalanches.<sup>32</sup> Subjective hazards have potential to be controlled, as they are influenced by a mountaineers skills and fitness.<sup>31, 32</sup> Deaths resulting from subjective hazards include hypothermia, fatigue and principally altitude illnesses.<sup>32</sup> When examining the death reports of Everest, climbers die at six times the rate of the Sherpa guides ( native Himalayan people).<sup>20, 32</sup> The majority of climber deaths occur above 8000 meters and result from subjective hazards linked to altitude illness.<sup>29</sup> Comparatively the Himalayan Sherpas are less likely to die from subjective hazards. This is attributable to their increased time spent at altitude resulting in better acclimatisation and development of advantageous evolutionary adaptations.<sup>20, 33</sup> These death reports illustrate the disparities in death rates between non-native climbers and the Sherpa people. This has resulted in investigations into the biological differences between the two groups, in addition to examining the ways subjective hazards can be minimised.<sup>33</sup> Advances in this area will help determine the best preparation for high altitude climbs, in addition to helping predict the likelihood of summiting success.

### Predicting success and HAI onset

Studies suggest that although preparation and training is essential in high altitude expeditions, there is also a degree



of summiting success linked to genetic components and predisposing risk factors.<sup>34</sup> Identification of these factors in studies could be used to construct screening tests, which help predict individual performance at altitude.<sup>35</sup>

Everest climbs will often involve pre expedition assessments, whereby a medical professional obtains a history from the climbers.<sup>5</sup> This allows for the identification of risk factors which can precipitate HAI.<sup>5</sup> The biggest risk factor for AMS and HAPE is unsurprisingly previous history of HAI.<sup>17</sup> Consequently, those attempting to summit with a history of AMS are less likely to succeed and undoubtedly will suffer from HAI towards the summit.<sup>5,17,36</sup> Chest infections, lung disease (e.g. COPD and cystic fibrosis) and cardiac defects (e.g. atrial septal defect) are also risk factors for HAI especially HAPE.<sup>17</sup> This is because they increase vascular reactivity and pulmonary blood flow leading to pre-existing high pulmonary blood pressure.<sup>17,37</sup> Some studies also suggest being over the age of forty and female are risk factors for HAI.<sup>36</sup> The evidence base for this however is limited and countless people from both these demographics have completed the Everest climb.<sup>2,36</sup> Other risk factors which should be considered include: consumption of alcohol and respiratory depressing drugs, drops in core temperature and fast ascent without acclimatisation.<sup>17</sup>

Certain populations (like the Himalayan Sherpas) are better adapted for life at altitude.<sup>38</sup> This is a result of evolutionary pressures causing genetic selection favourable to the mountain environment.<sup>33</sup> One such genetic advantage is an increased microcirculatory blood flow and capillary density in Sherpas.<sup>34</sup> This allows more oxygen to be delivered to deprived tissues in hypoxic conditions at altitude.<sup>34</sup> Metabolic adaptations also play a role in the Sherpa's success, as they have an increased capacity for lactate production, protection against oxidative stress and reduced capacity for fatty acid oxidation.<sup>33, 38</sup> These adaptations allow for a reduced and more efficient usage of the scarce oxygen supply at altitude, whilst reducing the damage hypoxic conditions inflict on the body.<sup>33, 38</sup> Studies have also found the possession of certain histocompatibility complexes increases the likelihood of HAPE, due to increased pulmonary vasculature reactivity causing a rise in pulmonary blood pressures.<sup>17, 39</sup>

In recent years information obtained from genetic studies combined with known risk factors, has allowed the initial development of screening tests to predict individual susceptibility to HAI.<sup>40</sup> At the most basic level this involves walking tests and hypoxic sensitivity tests, which have unsurprisingly revealed, greater aerobic capacity at sea level better prepares individuals for high altitude expeditions.<sup>41, 42</sup> AMS is a complex diagnosis with a variety of risk factors and as a result, systems are being developed which consider a variety of clinical measurements and algorithms.<sup>40</sup> This includes wearable physiological sensors which track heart rate, blood pressure and SPO<sub>2</sub> etc. in simulated hypoxic conditions.<sup>40, 42</sup> It is found those with lower PO<sub>2</sub> in the blood and higher blood pressure and pulse at a simulated altitude are more likely to suffer from AMS.<sup>40</sup> The development of these monitoring systems mean in addition to helping predict AMS susceptibility, they can also be used on the mountain to aid diagnosis.<sup>40</sup> This will allow for quicker interventions and reduction in symptom severity, increasing the likelihood of summiting success.<sup>40, 42, 43</sup>

## Prevention of altitude illnesses

In order to increase the likelihood of summiting Everest good preparation is required, alongside adequate prevention of subjective hazards.<sup>31</sup> Altitude illness causes significant mortality as individuals develop confusion, ataxia and breathlessness.<sup>24, 25, 31</sup> This means they are more likely to die from falls, fatigue and hypothermia.<sup>32</sup>

Vulnerability to altitude illness is largely determined by four main factors: final altitude, rate of ascent, individual susceptibility and pre-acclimatisation.<sup>44</sup> Primarily, rapid ascent is the most influential factor affecting susceptibility to HAI, as it neglects the vital acclimatisation process.<sup>44</sup> Unsurprisingly, a slow rate of ascent therefore currently serves as the primary prevention strategy for altitude illness.<sup>45</sup> Guidelines currently state rate of ascent should be no more than 500 meters a day, above the 3000 meter mark, with a rest day every 4 days to best avoid altitude illness.<sup>46</sup> This allows for the timely adjustment to hypoxic conditions at altitude, namely through rising haematocrit levels.<sup>46</sup> As time spent at altitude increases, further physiological changes occur, meaning pre-acclimatisation training is paramount for successful functioning.<sup>31</sup> It is found spending time training at altitude for up to 30 days before ascent is protective against altitude illness.<sup>47</sup> This is likely to be due to maintenance of the physiological changes occurring within the body, specifically the high red blood cell count resulting from the 90 day lifecycle.<sup>14</sup>

Individual susceptibility is predominantly determined by a person's genetics, meaning little can be done to influence this factor. However, there are some Prophylactic pharmacological interventions, which can be taken to reduce susceptibility of contracting altitude illness.<sup>31</sup>

Acetazolamide is widely accepted as the preferred pharmacological prevention for AMS.<sup>13</sup> Guidelines suggest a 125mg dose of Acetazolamide twice daily, with scope to double this as a treatment following the onset of symptoms.<sup>13, 46, 48</sup> Acetazolamide works by inhibition of carbonic anhydrase resulting in less resorption of bicarbonate ions in the kidneys.<sup>46</sup> Increased excretion of the bicarbonate ions within the urine, leads to increased acidity of the blood resulting in metabolic acidosis.<sup>12, 46</sup> The body counteracts this by offloading CO<sub>2</sub> through tachypnoea and deeper breathing, consequently increasing PaO<sub>2</sub>.<sup>12</sup>

Dexamethasone is also used as a form of AMS prevention, often appropriated for individuals who cannot tolerate the preferred Acetazolamide regimes.<sup>46, 49</sup> As a corticosteroid, Dexamethasone has anti-inflammatory effects.<sup>24, 46</sup> Its inhibition of the inflammation pathways and reduction of vascular permeability, leads to a reduction in cerebral oedema.<sup>24</sup> However there is a distinct lack of consistency within studies surrounding Dexamethasone usage in AMS prevention.<sup>13</sup> This is largely due to it masking the symptoms of AMS by reducing inflammation.<sup>46, 49</sup> Consequently ischaemic changes imposed by hypoxia are still likely to occur just with later onset, explaining the current preference for Acetazolamide within guidance.<sup>48</sup>

Nifedipine is a calcium channel blocker used in the prevention of HAPE.<sup>13</sup> Calcium ions (Ca<sup>2+</sup>) are required for the smooth muscle contraction found in hypoxic pulmonary vasoconstriction.<sup>45</sup> Nifedipine prevents the influx of Ca<sup>2+</sup> into cells allowing for smooth muscle relaxation and vasodilation.<sup>24</sup> This reduces the pressure in pulmonary vessels resulting in reduced leakage and oedema at altitude.<sup>46</sup>

Traditional remedies such as the consumption of coca are used in the Andes for HAI prophylaxis; however, there is a lack of evidence supporting its efficacy.<sup>49, 50</sup> There is some research, which shows increased oxygen saturations and better symptom control in those who consume coca remedies.<sup>50</sup> This could be attributable to the stimulant effects of the coca alkaloid within the leaves increasing heart and breathing rates whilst lifting mood.<sup>24, 50, 51</sup> A distinct lack of research however means, before being suggested as a suitable treatment for AMS, more definitive studies are required.

## Treating altitude illness

The extreme altitude challenge Everest presents means the onset of HAI is inevitable.<sup>49, 52</sup> The single best intervention is descent until symptoms resolve, usually requiring at least a 300m decline in altitude.<sup>49</sup> Descent however is not always feasible due to summit ambitions or physical problems i.e. the terrain and weather.<sup>49</sup> Therefore mountaineers should be aware of the therapeutic options available.

Supplementary oxygen therapy is widely used first-line along with bed rest until symptoms subside or oxygen saturations are above 90%.<sup>48, 49</sup> Studies suggest oxygen therapy and bedrest alone are adequate for resolution of HAPE, without the need for further interventions.<sup>53</sup> Unfortunately Oxygen supply at altitude is limited, and hazardous conditions do not always allow for bedrest acclimatisation.<sup>17, 49</sup> This often necessitates rationing of this therapy in remote situations and the use of complimentary interventions to relieve HAI symptoms.<sup>49</sup>

When HAI is severe, hyperbaric chambers are an effective form of treatment, which simulate descent by increasing barometric pressure in an enclosed space.<sup>17</sup> Hyperbaric chambers are useful to stabilise individual's suffering from severe HAI, but require intermittent pumping to maintain pressure and allow CO<sub>2</sub> clearance.<sup>17</sup> The effects are also not long-standing after removal, meaning it should not be used to replace descent.<sup>17, 49</sup>

Pharmacological interventions for HAI treatment are similar to the preventative treatments and includes Acetazolamide at higher doses.<sup>46</sup> Although the role of Dexamethasone in preventing HAI is dubious, it is well established as a treatment for alleviating HAI symptoms.<sup>49</sup> This is usually given as an 8mg loading dose followed by 6 hourly 4mg preparations.<sup>25, 54</sup> Further ascent should not occur until symptoms subside without the medication due to the minimal effect Dexamethasone is thought to have on acclimatisation.<sup>25, 48, 49</sup> Nifedipine can also be used as an adjunctive therapy alongside oxygen in treating HAPE, however evidence is limited so should not replace descent where possible.<sup>49</sup>

## CONCLUSIONS AND SUGGESTED APPROACH FOR ALTITUDE EXPEDITIONS

In conclusion HAI is the leading contributor to mortality on Everest but is a complex and multifactorial diagnosis. In order to reduce the likelihood of HAI and increase the chances of summiting success the following should be considered.

Firstly, it is important to complete pre expedition assessments to identify risk factors prior to ascent. These

should be treated and minimised where possible and acetazolamide prescribed as first line preventative therapy for HAI in at risk climbers. Where possible screening for advantageous genetic traits should be implemented, to assist with preparation and obtain realistic ideas of summiting success. On the mountain, these technologies can be implemented to aid with the diagnosis of HAI, allowing for earlier intervention to improve prognosis.

The most important aspect of preparation for altitude is a good acclimatisation program with a slow rate of ascent. This is paramount for success on Everest and should be further supplemented with pre-acclimatisation stays at altitude up to 30 days prior to the expedition. Future work should concentrate on continuing the development of screening tests to identify those susceptible to altitude illness. This will help produce tailored acclimatisation programs and reduce the incidence of HAI on Everest, so it becomes a safer and more attainable dream for future generations.

## REFERENCES

(A full list is available on request)

1. Daly N. Pushing Extremes: 10 Grueling National Geographic Expeditions (internet) Washington D.C: National Geographic; 2015 [Available from: <https://www.nationalgeographic.com/adventure/features/best-adventure-picturesmountain-climbing-volcano/>].
2. Bisharat A. Recent Everest Summits, Tragedies Mark Return of 'Normal' Climbing Season (Internet) Washington D.C: National Geographic; 2016 [Available from: <https://www.nationalgeographic.com/adventure/adventure-blog/2016/05/22/after-threeyears-of-disaster-everest-returns-to-business-and-death-as-usual/>].
3. Rodway GW. George Ingle Finch and the Mount Everest expedition of 1922: Breaching the 8000-m barrier. *High Alt Med Biol.* 2007;8(1):68-76.
4. Ward MP. Everest 1953, first ascent: A clinical record. *High Alt Med Biol.* 2003;4(1):27-37.
5. Brants A, Metcalfe T. Practical Tips for Working as an Expedition Doctor on High-altitude Expeditions. *High Alt Med Biol.* 2017;18(3):193-8.
6. Grissom CK, Jones BE. Respiratory Health Benefits and Risks of Living at Moderate Altitude. *High Alt Med Biol.* 2018;19(2):109-15.
7. Wagner PD. Operation Everest II and the 1978 Habeler/Messner ascent of Everest without bottled O<sub>2</sub>: what might they have in common? *J Appl Physiol.* 2017;123(6):1682-8.
8. Parati G, Agostoni P, Basnyat B, Bilo G, Brugger H, Coca A, et al. Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions. *Eur Heart J.* 2018;39(17):1546-+.
9. Cumpstey AF, Milledge JS, Grocott MPW. Anesthetists (and Physicians) at Altitude. *Int Anesthesiol Clin.* 2018;56(2):47-64.
10. Richalet JP. Physiological and Clinical Implications of Adrenergic Pathways at High Altitude. In: Roach RC, Wagner PD, Hackett PH, editors. *Hypoxia: Translation in Progress. Advances in Experimental Medicine and Biology.* 903. New York: Springer; 2016. p. 343-56.
11. Ronen R, Zhou D, Bafna V, Haddad GG. The Genetic Basis of Chronic Mountain Sickness. *Physiology.* 2014;29(6):403-12.

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