Abstracts from the Fifth American Cough Conference

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The Fifth American Cough Conference was held in Washington D.C. on June 5th, 2015. Dr. Peter Dicpinigaitis assembled a world-class faculty who covered a spectrum of topics of interest for clinicians and educators. There are five state-of-the-art reviews published in this issue of LUNG [1–5]. These reviews provide updates to data on pediatric cough and cough in sarcoid and evaluate neuroplasticity associated with respiratory viral infections and the role of big data analysis in assessing mucoactive drugs. In addition, there is a discussion regarding treatment of acute cough due to the common cold. Finally, this issue contains the following abstracts which were presented at the American Cough Conference. They provide novel data focusing on topics of interest to educators, clinicians and basic scientists.

Abstracts

Effect of Esophageal Acid Infusion on Cough Reactivity in the Guinea Pigs with Chronic Capsaicin Inhalation

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Introduction: Esophageal-bronchial reflex is considered as the main mechanism of cough due to gastroesophageal reflux, and the sensory hypersensitivity in the esophageal mucosa plays an important role. We hypothesized that bronchial-esophageal reflex might be related to pathogenesis of the sensory hypersensitivity in the esophageal mucosa and observed the effect of esophageal acid infusion on cough reactivity and TRPV1 expression in the esophageal mucosa of the guinea pigs with chronic capsaicin inhalation.

Methods: Conscious and ether-anesthetized guinea pigs received a 10^{-4} mol/L capsaicin inhalation through a nebulizer for 2 min, twice a day for 10 days. 24 h after esophageal acid infusion, cough reactivity to inhaled capsaicin was measured, and the TRPV1 expression in the esophageal mucosa was detected by RT-PCR, Western blot, and immunohistochemistry.

Results: Upon chronic capsaicin inhalation, esophageal acid infusion resulted in similar increases, i.e., from 6.3 ± 1.6 to 11.0 ± 5.4 ($P < 0.05$) in the conscious guinea pigs and from 6.6 ± 1.6 to 10.2 ± 4.8 ($P < 0.05$) in the

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ether-anesthetized guinea pigs, in the case of cough counts due to capsaicin challenge. However, the increased cough reactivity was blocked by the pretreatment with 2 $\mu\text{mol/kg}$ of capsazepine esophageal infusion but not by the pretreatment with 0.5 mg/kg of atropine esophageal infusion. Similarly, TRPV1 expression in the esophageal mucosa increased after chronic capsaicin inhalation and esophageal acid infusion in both the conscious and ether-anesthetized guinea pigs. Furthermore, the pretreatment with esophageal infusion of capsazepine but not atropine inhibited the increased expression of TRPV1 in the esophageal mucosa of guinea pigs.

Conclusion: Chronic airway irritation may initiate or aggravate the cough due to gastroesophageal reflux through bronchial—esophageal reflex, and the pathway may be mediated by vagal afferents expressing TRPV1.

Mothers' and School Nurses' Assessment of Cough and Cold Impact on Children's Quality of Life

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Introduction: To understand the quality-of-life impact of cough and cold season on school-aged children as observed by mothers and school. It is well accepted that children suffer from a higher frequency of cough and colds each season; however, the extent to which these illnesses affect their daily functioning has never been validated quantitatively and is not routinely addressed as a mainstream problem. This study looks beyond the cough and cold occurrence rate and focuses on attitudes, as well as emotional and physical impact on children, as evidenced by mothers and school nurses.

Methods: 1002 mothers of children in prekindergarten through eighth grade were surveyed between November 13 and December 8, 2014 using an online survey. 301 school nurses were also surveyed using a mixed-mode methodology; interviewers conducted the survey via phone and completed an online survey. The margin of error among mothers was 3.1 % and among school nurses was 5.7 %. Results from both groups were at the 95 % confidence level.

Results: 78 % of mothers reported that health issues during cough and cold season disrupt their child's energy level. 95 % of mothers reported that to address cough and cold symptoms, they encourage their children to get as much rest as possible. Mothers overwhelmingly (58 %) reported a disruption in their child's sleep due to cough and cold symptoms. Additionally, 43 % of mothers noted a marked decrease in the ability to focus. School nurses share the concerns of mothers

regarding insufficient focus, with 84 % reporting that children have focus and participation difficulties during cough and cold season. 51 % of mothers also report that their child's attendance is disrupted during cough and cold season. 63 % of school nurses believe that parents wait until cough and cold symptoms become too severe before seeing a doctor.

Conclusions: The impact of cough and colds in children goes beyond the physical symptoms. Quality of life is impacted in many ways, including sleep disruption and a decrease in the ability to focus. Children are also losing valuable education time from lack of focus, untreated symptoms, or time out of the classroom. Greater attention needs to be paid to management of symptoms in children during cough and cold season to improve their quality of life.

ATP Cough Challenge in Healthy Volunteers

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Introduction: Recent studies have suggested a role for ATP-activated P2X3 receptors in the pathophysiology of chronic cough. ATP has previously been used as an inhalational challenge substance in asthmatics and COPD patients, with the main focus being on bronchospasm. We have considered whether ATP can be used as a cough challenge to provoke a dose-dependent response in healthy volunteers.

Method: The stabilities of ATP and AMP were determined using HPLC analysis. The recognised ERS-standardised cough challenge using the Ko-Ko digidoser was performed with ATP and AMP as substrates. 20 Healthy, non-smoking volunteers were randomised and double-blinded to the order of challenges. C5 (the concentration of substrate causing at least 5 coughs) and total cough response were compared for ATP and AMP. Comparison was also made with the results of a concurrent series of cough challenges using citric acid.

Results: ATP and AMP were stable over 3 days. 6 male and 14 female patients were randomised to receive cough challenges. The age range was 23–62 years. Hull Airways Reflux Questionnaire score range was 0–8. 1 patient had a mild hypersensitivity reaction to ATP with urticaria. No other side effects were reported. 2/19 patients coughed with AMP, neither achieved C5. In total, 152 inhalations of AMP were carried out and only 3 resulted in cough (maximum of 2). 18/20 patients coughed with ATP with 16 achieving C5. All but one patient achieving C5 did so at concentrations of 30 mM or greater.

18 of the same patients were involved in the comparison with citric acid cough challenge. No correlation was detected between the cough responses to ATP and citric acid.

Discussion: Previous research has suggested that ATP plays a role in airways disease. Whilst previous human ATP challenges have documented cough as a symptom, none have objectively measured the cough response in humans. While in guinea pigs it has been suggested that ATP enhances the sensitivity of the cough response, ATP produced a cough response in the majority of our sample of healthy volunteers, suggesting that it may be directly initiating the cough. The lack of cough response to AMP is somewhat at odds with previous studies. However, this supports a role for ATP-driven P2X3 receptors in the initiation of cough. The lack of correlation with the citric acid cough response in the same patients suggests that the mechanism by which ATP causes cough is not the same as that of citric acid.

Further research is required to consider whether ATP-activated P2X3 receptors play a role in chronic cough patients.

Conclusion: Our data support the role of ATP-activated P2X3 receptors in the provocation of cough.

Effect of Female Hormonal Profile on Selected Cough Parameters—Study in Normal Menstrual Cycle and Oral Contraceptives Group

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Introduction: From the literature, it is known that females cough more than males (Fujimura, 1990) and have

heightened sensitivity of cough reflex (Dicpinigaitis & Rauf, 1998). What has not been elucidated yet are the mechanisms of these gender differences, although they are believed to be caused by hormones as they occur at puberty and are highlighted in the late phase of adolescence (Varechova et al., 2006). Chronic cough patients are also more often females, some of them experiencing premenstrual worsening of their symptoms. The aim of our study was to determine the effect of female sexual hormones on cough reflex sensitivity, urge to cough, sound of voluntary and induced coughs, laryngeal sensitivity and FeNO in healthy volunteers with normal menstrual cycle (MC) and females taking oral contraceptives (OC).

Methods: 11 healthy females with normal MC and 11 females taking OC underwent ENT exam and lung functions test to meet the inclusion criteria. Cough sensitivity and other parameters were examined in the follicular and luteal phases of MC according to ERS Guidelines (2007). Levels of oestrogen, progesterone, testosterone, prolactin, LH and FSH were determined from blood and the phase of MC was confirmed by USG.

Results: Cough sensitivity expressed as C2 and C5 increased significantly in the luteal phase from 91.2 ± 1.75 to 58.7 ± 1.59 (GM with 95 % CI) for C2 and 364.9 ± 1.90 to 250.0 ± 2.12 (GM with 95 % CI) for C5, $P < 0.05$ for both. FeNO levels and FEV1/FVC also followed the cyclic pattern in the normal MC group, but not in the OC. Urge to cough is similar in both the groups, with premenstrual drop ($P < 0.05$). Correlation analysis showed negative correlation of C2 and C5 with oestrogen levels in the follicular phase and luteal phase ($r = -0.44$) and also negative correlation between C2 and C5 and progesterone in the luteal phase ($r = -0.19$).

Conclusion: Our data document clear hormonal influences on the cough sensitivity measured by capsaicin test and also indicate that premenstrual worsening of chronic cough could be caused by hormonally influenced rise of TRP channels' activity with stronger correlation to oestrogen followed by progesterone.

Extended-Release Guaifenesin/Pseudoephedrine Together with a ‘Wait and See’ Approach to Antibiotic Prescribing for Upper Respiratory Tract Infections

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Introduction: The common cold and most upper respiratory tract infections (URTIs) are caused by viruses, but antibiotic treatment is often expected by patients. The overuse of antibiotics is driving the development of antibiotic resistance, which has now become a serious global threat to public health. A ‘wait and see’ approach or delayed antibiotic prescribing may help manage patients’ expectations and reduce antibiotic use. We aimed at investigating the safety and efficacy of extended-release (ER) guaifenesin/pseudoephedrine in providing symptomatic relief for URTIs, and if symptom improvements reduced the patient desire for, and use of, antibiotics.

Methods: Adults with symptoms of acute URTIs were randomized to 1200 mg guaifenesin/120 mg pseudoephedrine HCl bi-layer tablets or placebo for 7 days. Eligible patients met physician’s criteria for antibiotic therapy but were considered suitable for a ‘wait and see’ approach (withholding antibiotics for ≥ 48 h). Patients recorded seven different symptom ratings (chest congestion, thickened mucus, nasal congestion, runny nose, sinus headache, sinus pressure, post-nasal drip) via an Interactive Voice Response System.

Results: A total of 1179 patients ($n = 591$ guaifenesin/pseudoephedrine, $n = 588$ matching placebo) received at least one dose of study medication and had at least one post-baseline efficacy measure. At Day 8, fewer patients receiving guaifenesin/pseudoephedrine (4.2 %) desired antibiotics compared with patients receiving placebo (8.0 %) ($P < 0.01$). Antibiotic prescribing was lower in the guaifenesin/pseudoephedrine group compared with the placebo group for the per protocol population ($n = 510$ guaifenesin/pseudoephedrine, $n = 523$ placebo) ($P < 0.05$). Significant reductions in URTI symptoms were observed for guaifenesin/pseudoephedrine compared with placebo from Day 1 to Day 8 ($P < 0.05$), with the exception of the afternoon of Day 4. Treatment-related adverse events were reported in 58/593 (9.8 %) guaifenesin/pseudoephedrine-treated patients and 28/591 (4.7 %) placebo-treated patients. There was a higher incidence of gastrointestinal

distress in patients who received placebo and an antibiotic compared with patients receiving only guaifenesin/pseudoephedrine ($P < 0.05$).

Conclusions: This study found that a ‘wait and see’ approach with ER guaifenesin/pseudoephedrine was associated with a decreased patient desire for antibiotics and offers an effective and well-tolerated first-line strategy for the symptomatic management of URTIs.

Ozone Induces a Hypertussive Response to Inhaled Citric Acid in Rabbits

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Introduction: The treatment of chronic cough is currently an unmet clinical need in part due to our poor understanding of the pathophysiology of this condition and also to a lack of a predictive animal model of hypertussive responses. Traditionally, guinea pigs have been used as species to investigate cough, but we were motivated to develop a hypertussive model in the rabbit as this species, like humans, has lungs that are poorly innervated by neuropeptide containing afferent neurons.

Methods: Naïve rabbits were exposed to citric acid (0.4 M and 0.8 M), and were then exposed to either air or ozone (2 ppm) for 1 h after 1 week. The number of coughs was counted during the 10-min exposure to citric acid and for a further 5 min. We used crossover designs and exposed rabbits to either air or ozone at weekly intervals in drug- or vehicle-treated animals. Data are expressed as mean with confidence interval.

Results: In rabbits, the cough counts on exposure to citric acid (0.4 M and 0.8 M) and those on 1 h exposure to ozone (2 ppm) increased by 4.86 (2.21–7.54, 95 % CI, $n = 8$) and by 6.88 coughs (5.12–8.64, 95 % CI $n = 40$) in number, respectively ($P < 0.05$). This increase in cough frequency was associated with a significant ($P < 0.0001$) decrease in the time-to-cough to citric acid, from 58.1 s (52.7–63.5, 95 % CI) in the control group to 22.9 s (21.4–24.4, 95 % CI) in the ozone-sensitised group. Ozone also sensitised rabbits to cough without citric acid as a tussive stimuli in 74 % of the rabbits studied (38 out of 52) which had an average of 16 coughs (7.15–20.51, 95 % CI) during the 1-h ozone-sensitization period. Pretreatment of rabbits with the anti-inflammatory PDE4 inhibitor roflumilast (1 mg/kg, i.p. –30 min) or the bronchodilator B2 agonist salbutamol (100 mg/mL, aerosol, 2 min at 3 L/min,

–5 min) did not significantly alter the ozone-induced hypertussive response to citric acid in rabbits ($n = 8$). However, treatment with codeine (10 mg/kg, i.p., –5 min) significantly reduced the ozone-sensitised response by a factor of 2 from 14.8 (10.2–19.4, 95 % CI) to 6.25 (0.97–11.53, 95 % $P < 0.05$). This dose of roflumilast was sufficient to significantly reduce the infiltration of neutrophils into the airways of rabbits exposed to ozone and this dose of salbutamol reduced methacholine-induced bronchospasm (% baseline RL) to 30.3 % (8.1–52.5 %, CI 95 %). Treatment with the muscarinic receptor antagonist tiotropium bromide (0.025 mM, $n = 12$) for 10 min, 2 h prior to ozone exposure, did not significantly alter the hypertussive cough to citric acid (0.8 mM), even though this dose of tiotropium bromide provided significant bronchoprotection in anaesthetised rabbits 4 h after drug exposure. In contrast, the ozone-induced hypertussive response to citric acid was abolished in animals chronically treated with capsaicin.

Conclusion: Ozone induces a hypertussive response in rabbits which is secondary to a neuronal reflex, but not secondary to inflammation or bronchoconstriction. We anticipate that this model will be of value in investigating novel drugs for the treatment of cough.

Effect of Flurbiprofen 8.75 mg Lozenge on Coughing in Patients with Upper Respiratory Tract Infection

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Introduction: Cough and sore throat are common linked symptoms of the upper respiratory tract infection (URTI). The mechanism of URTI-associated cough and sore throat is thought to include the action of inflammatory mediators on sensory nerve endings in the oropharynx; therefore, a locally applied anti-inflammatory drug may have beneficial effects on both symptoms. We have previously shown that a lozenge containing 8.75 mg of the anti-inflammatory drug, flurbiprofen, is effective for the treatment of sore throat. Here we report some preliminary findings of an apparent effect of flurbiprofen 8.75 mg lozenge on

coughing in patients with concurrent sore throat due to URTI.

Methods: We enrolled adults with recent onset sore throat due to pharyngitis (≥ 5 on the Tonsillo-Pharyngitis Assessment) and at least one symptom of URTI on the URTI Questionnaire. Patients were randomly assigned to one identically flavoured flurbiprofen (FL) 8.75 mg ($n = 101$) or placebo ($n = 21$) lozenge (for double-blind). They reported the presence or absence of coughing and other URTI symptoms by completing the URTI Questionnaire at baseline and 3 h post dose while under observation in the clinic. The mean age of patients was 19.5 years, 58 % were female, and the mean TPA score was 9.9.

Results: At baseline, 24 patients in the flurbiprofen group reported the presence of coughing. After 3 h, cough was absent in 11 (46 %) of the FL-treated patients ($P = 0.01$ compared with baseline). There were no serious AEs and no patients discontinued due to an AE.

Conclusions: This study suggests that flurbiprofen 8.75 mg lozenge may have antitussive effects, possibly due to the local anti-inflammatory activity of flurbiprofen in the pharynx.

Obstructive Sleep Apnea in Patients at a Voice Disorders Clinic and Its Relationship to Cough Intensity in Patients with Irritable Larynx Syndrome

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Introduction: Patients with irritable larynx syndrome/laryngeal hypersensitivity, a spectrum disorder, may present with chronic cough, functional dyspnea/vocal cord dysfunction (VCD), and dysphonia. Significant relationships between VCD and chronic cough and between chronic cough and obstructive sleep apnea (OSA) have been shown. However, relationships between OSA and laryngeal disorders are not well understood despite significant trauma sustained to the upper airway during episodes of apnea/hypopnea and findings of impaired sensation at multiple upper airway sites in OSA.

Methods: Patients seen at the University of Utah Voice Disorders Center during the years 2013–2014 were screened with the Leicester Cough Questionnaire (LCQ) and the STOP-BANG screening questionnaire. The STOP-BANG questionnaire is a validated OSA screening tool with a PPV of 76 % and sensitivity of 92 %. Patients were divided into three groups: (1) *Functional* group with cough and dyspnea and/or dysphonia without any upper airway structural abnormalities or neurological disease. (2) *Structural* upper airway group with cough with findings of subglottic or tracheal stenosis or vocal cord paralysis. (3) *Neurological* group with cough in patients with Parkinson's disease, amyotrophic lateral sclerosis, etc. Patients with any pulmonary function or chest radiologic abnormalities, usage of oxygen, or known OSA were excluded.

Results: 25 patients in the functional group (15 females and 10 males) and 6 patients in the structural group (unilateral vocal cord paralysis—4/6) were evaluated. In the functional group, 80 % of patients had a STOP-BANG screening score of 3 or more indicating a significant likelihood of OSA, whereas none had STOP-BANG scores of 3 or more in the structural group. Only a small number of patients met the objective criteria for VCD, such as paradoxical vocal fold motion visualized during laryngoscopy. The mean age and BMI of patients in the functional group was 56.2 ± 18.2 years and 30 ± 8.14 , respectively. 4/25 were current smokers and 9/25 patients were on inhaled bronchodilators. Correlations between STOP-BANG scores and LCQ scores (total, physical, psychological and social) showed a negative correlation between STOP-BANG and LCQ-physical domain score ($r = -0.59$; $P = 0.001$) but no relationship between psychological, social and total LCQ scores and STOP-BANG scores ($r = -0.35$).

Conclusion: OSA is highly prevalent in patients with functional upper airway complaints of cough, dyspnea and dysphonia. While some correlations between STOP-BANG questionnaire scores and cough intensity based upon LCQ scores can be demonstrated, further studies to examine the effect of OSA therapy on other validated VCD severity tools will help understand relationships between irritable larynx syndrome/laryngeal hypersensitivity and OSA.

Patterns of Inappropriate Antibiotic Use in Cough

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Introduction: Inappropriate use of antibiotics, e.g. for viral conditions, is fuelling antibiotic resistance, an

expanding global health threat that may render some conditions untreatable in the near future. More than 90 % of acute coughs are non-bacterial in origin but many are treated inappropriately with antibiotics. Acute cough can last up to 3 weeks although the key factors leading patients to consult a physician remain unclear. We therefore conducted a multinational survey to determine the proportion of acute cough episodes treated with antibiotics and to better understand the reasons why patients sought medical advice.

Methods: Fifteen-minute online interviews were conducted in November/December 2014 with approximately 500 adults in each of 33 different countries in Europe, Asia, Africa, Australasia, South America and North America. For up to 6 ailments suffered in the previous 12 months, they answered questions on where they sought advice, their reasons for visiting a healthcare practitioner (HCP) and what happened as a result of that visit. They were also asked where they met the HCP and if it was the first time they had suffered the ailment.

Results: Across all countries and conditions surveyed, cough-related conditions were the most common reason for primary care visits, accounting for 9 % of all encounters. Data on the concerns prompting patients to seek medical advice will also be presented. Antibiotic prescription was made on the following cases:

- 34 % of 3510 consultations for dry/tickly cough
- 39 % of 2415 consultations for chest congestion/chesty cough
- 36 % overall of 5925 consultations for cough-related conditions

Of 13,306 consultations where an antibiotic was prescribed, 16 % (2121) were for dry cough or chest congestion/chesty cough, accounting for a greater proportion of antibiotic prescriptions than any other conditions. As fewer than 1 in 10 acute coughs are susceptible to antibiotics, these data suggest that approximately 1/4 to 1/3 of patients with cough-related conditions may receive antibiotics incorrectly. Across all conditions, the greatest number of encounters resulting in antibiotic receipt occurred in Indonesia (37 %), UAE (35 %), and Malaysia (35 %).

Conclusion: Inappropriate prescription of antibiotics for upper respiratory tract infections (URTIs) needs to be reduced to mitigate the growth of antibiotic-resistant infectious diseases. The above results demonstrate that many patients with non-bacterial URTIs still receive antibiotics. Further education is needed for healthcare providers on how best to address patients' concerns and desire for symptomatic relief, as well as changes in reimbursement policies to discourage inappropriate antibiotic use.

Association of Esophageal Dysfunction with Therapeutic Efficacy of Baclofen in Patients with Refractory Gastroesophageal Reflux-Induced Chronic Cough

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Introduction: To investigate how the changes of esophageal function in patients with refractory gastroesophageal reflux-induced chronic cough (GERC) influence the efficacy of treatment with baclofen.

Methods: Pressure, length and relaxation in lower esophageal sphincter (LES), and esophageal peristaltic contractive amplitude, time and wave velocity were recorded by manometry procedure in 83 consecutive patients with refractory GERC. Moreover, the effects of the changes in esophageal function on the efficacy of treatment with baclofen were analyzed.

Results: In 83 patients with refractory GERC, there was a positive correlation between LES pressure and esophageal peristaltic contractive amplitude ($r = 0.413$, $P = 0.000$). 46 patients responsive to baclofen had a lower LES pressure (9.03 ± 4.18 vs. 13.05 ± 5.57 mmHg, $t = -3.759$, $P = 0.000$) or esophageal peristaltic contractive amplitude (30.76 ± 11.00 vs. 39.78 ± 14.10 mmHg, $t = -3.276$, $P = 0.002$) and shorter LES length (2.31 ± 0.54 vs. 2.62 ± 0.56 cm, $t = -2.606$, $P = 0.011$) but similar LES relaxation, esophageal contractive time and peristaltic wave velocity when compared

with 37 patients failed to the treatment with baclofen. The optimal cut-off point of LES pressure for predicting effectiveness of baclofen was defined as 11.5 mmHg according to the highest Youden index of 0.497, with a sensitivity of 64.9 %, specificity of 84.8 %, positive predictive value of 83.3 %, and negative predictive value of 66.0 %. The AUC of LES length was 0.736. A sub-analysis for LES length showed less improvement in the predictive accuracy, corresponding to sensitivity of 62.2 %, specificity of 78.3 %, positive predictive value of 77.8 %, and negative predictive value of 61.7 %. Furthermore, a meaningful cut-off point of esophageal peristaltic wave velocity for prediction of effectiveness of baclofen could not be determined.

Conclusions: Esophageal dysfunction may be an underlying mechanism for refractory GERC. Baclofen is probably more effective in refractory GERC with the LES pressure of ≤ 11.5 mmHg.

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