自己管理法を含む喘息死ゼロ作戦の実行に関する指針

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成人気管支喘息診療のミニマムエッセンス

成人気管支喘息診療のミニマムエッセンス作成ワーキンググループ 編

本書は、平成23年度厚生労働科学研究費補助金で成人気管支喘息診療のミニマムエッセンス作成ワーキンググループ（奥付参照）が作成したものを元に、その後発刊された喘息予防・ガイドライン2012とアレルギー総合ガイドライン2013（一般社団法人日本アレルギー学会作成）の内容を踏まえて改編したミニマムエッセンスです。

1. 診断

診断は、①発作性の呼吸困難、喘鳴、咳、胸苦しさなどの症状の反復、②可逆性の気流制限、③他の心肺疾患などの除外による。過去の救急外来受診歴や、喘息治療薬による症状の改善は診断の参考になる。喘鳴や呼吸困難を認めず、診断に苦慮する場合は、気道過敏性試験を依頼するか、吸入ステロイド薬やβ_2刺激薬による治療的診断を考慮する。

表1. 成人喘息診断の目安

	一般診療	専門診療
1. 発作性の呼吸困難、喘鳴、咳の反復	問診：夜間、早朝に出現しやすい。 聴診：喘鳴は、強制呼気時に頸部で聴取しやすい。	
2. 可逆性の気流制限	問診：無症状期をはさんで、発作が反復	気道可逆性試験
3. 症状が他の心肺疾患によらない（表3）	胸部レントゲン撮影	
4. 気道過敏性の亢進	問診：運動、気道ウイルス感染、アレルゲン曝露、気象変化、精神的ストレス、月経などで症状が惹起される。	気道過敏性試験
5. アトピー素因	血清特異的IgE抗体	即時型皮膚反応
6. 気道炎症の存在	喀痰細胞診や末梢血白血球像における好酸球増多	呼気一酸化窒素濃度測定

1、2、3が臨床診断上重要である。4、5、6は他の所見とともに喘息診断を支持する。

2. 他疾患の鑑別

中高年発症で、喫煙歴を有する場合、COPDの存在を念頭におく。COPDでは、気管支拡張薬吸入後の1秒率が70%未満、高分解能CTで低吸収域、肺拡散能低下などの所見を認める。診断に迷う場合は、専門医へ紹介する。

標準治療に対する反応が十分得られない場合は、**表3**の疾患を念頭に、胸部CT、心機能評価、呼吸器専門医や耳鼻咽喉科医への紹介を考慮する。

表2. COPDとの鑑別のポイント

	COPD	喘息
喫煙歴	ほぼ全例あり	ありうる
40歳未満の場合	稀	多い
呼吸困難	進行性・持続性	発作性・症例により異なる
夜間の咳込み、覚醒	少ない	多い
症状の変動	少ない	多い

COPD診療のエッセンス（日本COPD対策推進会議）より改変

表3. 喘息と鑑別すべき疾患

1. 上気道疾患：喉頭炎、喉頭蓋炎、vocal cord dysfunction（VCD）
2. 中枢気道疾患：気管内腫瘍、気道異物、気管軟化症、気管支結核、サルコイドーシス
3. 気管支～肺胞領域の疾患：COPD、びまん性汎細気管支炎、肺線維症、過敏性肺炎
4. 循環器疾患：うっ血性心不全、肺血栓塞栓症
5. アンジオテンシン変換酵素阻害薬などの薬物による咳
6. その他：自然気胸、迷走神経刺激症状、過換気症候群、心因性咳嗽
7. アレルギー性呼吸器疾患：アレルギー性気管支肺アスペルギルス症、好酸球性多発血管炎性肉芽腫症（Churg-Strauss症候群）、好酸球性肺炎

3. 長期管理における薬物療法プラン

可能な限り呼吸機能を正常化し、QOLを改善し、健常人と変わらない日常生活を送れることが治療の目標である。長期に罹患し、気道リモデリングがある患者では、呼吸機能は正常値まで改善し得ないので、自己最良値に基づいて判定する。コントロール状態は**表4**に基づいて判断するが、短時間作用性β_2刺激薬（SABA）の使用頻度の問診が簡便である。

薬物治療を、**表5**の4つの治療ステップに分ける。未治療患者（**表6**）は、症状が週1回あるかどうかで治療ステップ1と2に分け、連日症状があれば治療ステップ3、さらに治療下でも増悪していれば治療ステップ4とする。治療中の患者は**表4**を参考にコントロール良好を目指し、コントロール不十分であれば、**表5**を参考に治療のステップアップを行う。

表4. コントロール状態の評価

	コントロール良好 （すべての項目が該当）	コントロール不十分 （いずれかの項目が該当）	コントロール不良
喘息症状（日中および夜間）	なし	週1回以上	コントロール不十分の項目が3つ以上当てはまる
発作治療薬の使用	なし	週1回以上	
運動を含む活動制限	なし	あり	
呼吸機能（FEV_1およびPEF）	正常範囲内	予測値あるいは自己最高値の80%未満	
PEFの日（週）内変動	20%未満	20%以上	
増悪	なし	年に1回以上	月に1回以上*

＊増悪が月に1回以上あれば他の項目が該当しなくてもコントロール不良と評価する。

表5. 喘息治療ステップ

		治療ステップ1	治療ステップ2	治療ステップ3	治療ステップ4
長期管理薬	基本治療	吸入ステロイド薬 （低用量）	吸入ステロイド薬 （低～中用量）	吸入ステロイド薬 （中～高用量）	吸入ステロイド薬 （高用量）
		上記が使用できない場合以下のいずれかを用いる LTRA テオフィリン徐放製剤 （症状が稀であれば必要なし）	上記で不十分な場合に以下のいずれか1剤を併用 LABA （配合剤の使用可） LTRA テオフィリン徐放製剤	上記に下記のいずれかを1剤、あるいは複数を併用 LABA （配合剤の使用可） LTRA テオフィリン徐放製剤	上記に下記の複数を併用 LABA （配合剤の使用可） LTRA テオフィリン徐放製剤 上記のすべてでも管理不良の場合は下記のいずれかあるいは両方を追加 抗IgE抗体 経口ステロイド薬
	追加治療	LTRA以外の抗アレルギー薬	LTRA以外の抗アレルギー薬	LTRA以外の抗アレルギー薬	LTRA以外の抗アレルギー薬
発作治療		吸入SABA	吸入SABA	吸入SABA	吸入SABA

LTRA：ロイコトリエン受容体拮抗薬、LABA：長時間作用性β_2刺激薬、SABA：短時間作用性β_2刺激薬

表6. 未治療患者の症状と目安となる治療ステップ

	治療ステップ1 （軽症間欠型相当）	治療ステップ2 （軽症持続型相当）	治療ステップ3 （中等症持続型相当）	治療ステップ4 （重症持続型相当）
喘息症状	週1回未満 軽度で短い	週1回以上だが毎日ではない	毎日	毎日 治療下でもしばしば増悪
夜間症状	月2回未満	月2回以上	週1回以上	しばしば
日常生活の妨げ	なし	月1回以上	週1回以上	持続的

表7. 吸入ステロイド薬、吸入ステロイド薬/長時間作用性β2刺激薬配合剤の治療ステップ別推奨量

商品名	治療ステップ1～2 低用量	治療ステップ3 中用量	治療ステップ4 高用量
キュバール®、フルタイド®エアゾール、オルベスコ®、フルタイド®ロタディスク®、フルタイド®ディスカス®、アズマネックス®ツイストヘラー®	100～200μg/日	200～400μg/日	400～800μg/日
パルミコート®タービュヘイラー®	200～400μg/日	400～800μg/日	800～1600μg/日
パルミコート®吸入液	0.5mg/日	1.0mg/日	2.0mg/日
アドエア®ディスカス®(1吸入2回/日)	100ディスカス	250ディスカス	500ディスカス
シムビコート®タービュヘイラー®	1吸入2回/日	2吸入2回/日	4吸入2回/日
アドエア®エアゾール(2吸入2回/日)	50エアゾール	125エアゾール	250エアゾール
フルティフォーム®	50エアゾール 2吸入2回/日	125エアゾール 2吸入2回/日	125エアゾール 4吸入2回/日
レルベア®エリプタ®(1吸入1回/日)	100エリプタ	100エリプタ または200エリプタ	200エリプタ

●長期管理薬(コントローラー)の使用に関する注意点

①**吸入ステロイド薬(ICS)**：最も効果的な抗炎症薬である。副作用は、口腔･咽頭カンジダ症、嗄声などで全身性の副作用は少ない。妊娠自体に影響しない。喘息患者の呼吸器感染症の頻度を上げる証拠はない。最大呼気位(最大限呼出したところ)から最大吸気位(最大限吸入したところ)まで吸入し、約10秒間息こらえをしてゆっくり吐き出す。デバイス毎に吸入の強さが適切となるように指導する(はやく深く：フルタイド®ロタディスク®･ディスカス®、アドエア®ディスカス®／深く力強く：パルミコート®、シムビコート®、アズマネックス®、レルベア®エリプタ®／ゆっくり深く：キュバール®、オルベスコ®、フルタイド®エアゾール、アドエア®エアゾール、フルティフォーム®)。

②**長時間作用性β2刺激薬(LABA)**：吸入薬、貼付薬、経口薬があり、必ずICSと併用する(単独使用は禁忌)。ICSにLABAを併用すると相乗効果が得られる。

③**吸入ステロイド薬/長時間作用性吸入β2刺激薬配合剤**：ICSとLABAを個別に吸入するよりも有効性が高い。アドヒアランスを向上させてLABAの単独使用を防ぐ。

④**ロイコトリエン受容体拮抗薬(LTRA)**：気管支拡張作用と抗炎症作用を有し、ICSに併用すると有効性が高い。アレルギー性鼻炎合併喘息、運動誘発喘息、アスピリン喘息患者の管理において有用である。

⑤**テオフィリン徐放製剤**：気管支拡張作用を有する。ICSとの併用で相乗効果が得られる。副作用や過剰投与(中毒)を回避するには100mg錠を2～3回/日で開始し、効果が不十分なら保険診療上の常用量である200mgを2回/日まで増量する。重症例では、専門医と相談の上さらに500～600mg/日へと100mg単位(分2～3)で増量できる(レセプト上の詳記を必要とする場合がある)。血中濃度は5～15μg/mLが目標であるが、患者によっては適正な血中濃度でも、それ以下でも中毒症状が生じることがあるので400mg/日の時点で血中濃度のモニタリングをする。

⑥**抗IgE抗体(オマリズマブ)**：高用量ICSと複数の気管支拡張薬の併用下でもコントロール不十分で総血清IgE値が30～1,500 IU/mL、通年性吸入抗原が証明されている場合に投与する。約60%で奏効するとされる。4か月間投与後に効果判定を行う。

4. 急性増悪(発作)時の対応(成人)

発作強度を呼吸困難症状から判定して遅滞なく治療を開始する。前夜横になれていれば小発作、苦しくて横になれないが歩行可能なら中発作、歩行や会話が困難なら大発作、チアノーゼ、意識障害、呼吸停止を認める場合は重篤症状とする。

中等度以上の発作や、吸入β2刺激薬による初期治療に反応が乏しい場合、十分量のICSや、経口ステロイド薬を常用している症例、挿管の既往例、過去1年間に入院、救急受診があった症例では、直ちに全身性ステロイド薬を投与する。入院や集中治療を要すると判断した場合は、遅滞なく専門施設への搬送を手配する。

表8. 喘息発作の強度に対応した管理のポイント

発作強度	呼吸困難	動作	SpO_2	治療	自宅治療可、入院、ICU管理
喘鳴/胸苦しい	急ぐと苦しい 動くと苦しい	ほぼ普通	96%以上	β2刺激薬吸入、頓用[1] テオフィリン薬頓用	自宅治療可
軽度(小発作)	苦しいが横になれる	やや困難		β2刺激薬吸入、頓用[1] テオフィリン薬頓用	自宅治療可
中等度(中発作)	苦しくて横になれない	かなり困難かろうじて歩ける	91〜95%	β2刺激薬ネブライザー吸入反復[2] 0.1%アドレナリン(ボスミン®)皮下注[3] アミノフィリン点滴静注[4] ステロイド薬点滴静注[5] 酸素投与	救急外来 ・1時間で症状が改善すれば帰宅 ・2〜4時間で反応不十分 ・1〜2時間で反応無し 入院治療→高度喘息症状治療へ
高度(大発作)	苦しくて動けない	歩行不能会話困難	90%以下	0.1%アドレナリン(ボスミン®)皮下注[3] アミノフィリン持続点滴[6] ステロイド薬点滴静注反復[5] 酸素投与 β2刺激薬ネブライザー吸入反復[2]	救急外来 1時間以内に反応なければ入院治療 悪化すれば重篤症状の治療へ
重篤	呼吸減弱 チアノーゼ 呼吸停止	会話不能 体動不能 錯乱、失禁 意識障害	90%以下	上記治療継続 症状、呼吸機能悪化で挿管[7] 人工呼吸[7] 気管支洗浄 全身麻酔を考慮	直ちに入院、ICU管理

1)β2刺激薬pMDI 1〜2パフ、20分おき2回反復可。
2)β2刺激薬ネブライザー吸入：20〜30分おきに反復する。脈拍を130/分以下に保つようにモニターする。
3)0.1%アドレナリン(ボスミン®)：0.1〜0.3mL皮下注射20〜30分間隔で反復可。脈拍は130/分以下にとどめる。虚血性心疾患、緑内障[開放隅角(単性)緑内障は可]、甲状腺機能亢進症では禁忌、高血圧の存在下では血圧、心電図モニターが必要。
4)アミノフィリン6mg/kgと等張補液薬200〜250mLを点滴静注、1/2量を15分間程度、残量を45分間程度で投与し、中毒症状(頭痛、吐き気、動悸、期外収縮など)の出現で中止。発作前にテオフィリン薬が十分に投与されている場合は、アミノフィリンを半量もしくはそれ以下に減量する。通常テオフィリン服用患者では可能な限り血中濃度を測定。
5)ステロイド薬静注：ヒドロコルチゾン200〜500mg、メチルプレドニゾロン40〜125mg、デキサメタゾン、あるいはベタメタゾン4〜8mgを点滴静注。以後必要に応じて、ヒドロコルチゾン100〜200mgまたはメチルプレドニゾン40〜80mgを4〜6時間ごとに、あるいはデキサメタゾンあるいはベタメタゾン4〜8mgを6時間ごとに点滴静注、またはプレドニゾロン0.5mg/kg/日、経口。
6)アミノフィリン持続点滴：第1回の点滴に続く持続点滴はアミノフィリン250mg(1筒)を5〜7時間(およそ0.6〜0.8mg/kg/時)で点滴し、血中テオフィリン濃度が10〜20μg/mL(ただし最大限の薬効を得るには15〜20μg/mL)になるように血中濃度をモニターし中毒症状の出現で中止。
7)挿管、人工呼吸装置の装着は時に危険なので、緊急処置としてやむを得ない場合以外は専門施設で行われることが望ましい。

アスピリン喘息の場合、40〜60%相当の症例でコハク酸エステル型(サクシゾン®、ソル･コーテフ®、ソル･メドロール®、水溶性プレドニン®など)で発作誘発の危険があるため、リン酸エステル型(ハイドロコートン®、リンデロン®、デカドロン®など)を使用する。リン酸エステル型であっても、急速静注では添加物による発作誘発の可能性がある。初回投与時や、アスピリン喘息の有無が不明の場合は1時間程度かけて点滴投与する。

5. 専門医への紹介を考慮する条件

1. 治療ステップ3で良好な管理ができず、治療ステップ4に変更する場合。
2. 経口ステロイド薬や高用量の吸入ステロイド薬の長期投与が必要な場合。
3. 経口ステロイド薬高用量短期投与を年に2回以上必要とする場合。
4. 症状が典型的でなく、診断や鑑別が困難で、気道過敏性試験、胸部CTなどが必要な場合。
5. 困難な合併症(例：副鼻腔炎、鼻ポリープ、アレルギー性気管支肺アスペルギルス症、COPD合併、心身医学的問題など)や、特殊な原因(職業喘息、アスピリン喘息、食事アレルギーなど)を有する場合。

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アレルギー疾患の予後改善を目指した自己管理および生活環境改善に資する治療戦略の確立に関する研究
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「一般住民に対するダニアレルゲン回避のためのパンフレット

作成：研究分担者　釣木澤尚実

ダニアレルゲン対策

- ✓ 普通に生活していてもアレルギーの主たる原因となりうるダニは日本の温暖・湿潤な気候で増殖しやすく、多くの家がダニアレルゲンで汚染されています
- ✓ **「効果的な掃除」**等の環境整備によりダニアレルゲン量を減らすことができます
- ✓ 特に**「寝室」**と**「寝具」**に対する対策が重要です
- ✓ **「除湿」**は**「カビ対策と共通」**しており、カビをエサにするダニの増殖を抑えることができます
- ✓ 掃除の際は**「窓を開けて換気」**し、**「マスクやタオルで口を覆い」**ながら行ってください

→「アレルゲン」に関する参考情報：http://www.jrmunet.jp/allergy/cause/allergen/index.html

≪寝具のダニアレルゲンを減らす方法≫

- 週に１回以上、家族全員の寝具カバーをはずして寝具そのものに直接掃除機をかける
- 高密度線維でできた布団・枕カバーを使用する
- ベッドメイキング時に窓を開放する
- 布製のソファを寝室に置かない
- 開放型暖房機器を寝室に置かない
- １日に数回窓を開けて換気する
- 掃除機をかける前に床を水拭きする
- 寝室のカーテンを年２回以上丸洗いする

≪寝室のダニアレルゲンを減らす方法≫

- 室内に植物や水槽、洗濯物、加湿器を置かない
- 週に１回以上寝室を含むすべての部屋に掃除機をかける
- 掃除機をかける前に床の拭き掃除をする
- 床はフローリングである
- 床を化学雑巾やモップで乾拭きする

厚労科研費補助金難治性疾患等克服研究事業「気管支喘息に対する喘息死の予防や自己管理手法の普及に関する研究」
主任研究者：大田　健　分担研究者：〃　国立病院機構相模原病院　釣木澤尚実　提供資料

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Association of Asthma Education with Asthma Control Evaluated by Asthma Control Test, FEV_1, and Fractional Exhaled Nitric Oxide

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Background. Asthma education is an important adjunct for asthma control although the way asthma education affects asthma outcomes is poorly understood. The asthma control test (ACT), forced expiratory volume in 1 s (FEV_1), and fractional exhaled nitric oxide (FeNO) have all been used as markers of asthma control. However, the use of FeNO as a surrogate marker remains controversial. *Objectives.* (i) To examine whether asthma education is associated with asthma control; (ii) to compare absolute levels and changes of ACT, FEV_1, and FeNO over a year; and (iii) to evaluate whether FeNO can be used as an additional marker of asthma control. *Methods.* Fifty asthmatics with poor adherence (12 mild, 21 moderate, and 17 severe) received asthma education at study entry. Medications were unchanged for the first 3 months, and ACT, FEV_1, and FeNO measurements were recorded at entry, 3, 6, and 12 months. Asthma control was assessed at each visit and patients were categorized as either "stable" or "unstable" asthmatics according to the global initiative for asthma (GINA) guidelines. *Results.* A significant decrease in FeNO and increase in ACT score were noted in the stable asthmatic group at 3 months ($p < .001$), and this persisted over 12 months. Significant correlations were seen between changes (Δ) in FeNO, ACT, and FEV_1 over time. However, significant correlations between the absolute levels were not maintained over 12 months. A decrease of $\geq$18.6% in FeNO and a $\geq$3-point increase in ACT score (sensitivity: 80% and 73.3% and specificity: 83.3% and 87.5%, respectively) were associated with stable asthma control although the absolute levels were not. *Conclusions.* Asthma education may be useful to achieve stable control. In addition, changes rather than absolute levels of FeNO and ACT may be better markers of asthma control.

Keywords asthma control, asthma control test questionnaire, asthma education, fractional exhaled nitric oxide

INTRODUCTION

Interventions that aim to enhance medication adherence have recently been developed (1), although studies of adults and children with asthma show that approximately 30%–50% of those on asthma therapy are nonadherent to therapy at least for part of the time (2–4). Therefore, educating patients on how to manage their asthma more effectively should be used to improve patients' knowledge and influence their decision-making process regarding disease management, resulting in greater treatment adherence. However, the way asthma education affects asthma control remains poorly understood.

Asthma symptom questionnaires, spirometry, sputum eosinophil cell counts, and airway hyperresponsiveness (AHR) are potential ways of monitoring asthma control. Of these, the global initiative for asthma (GINA) guidelines recommend asthma symptom questionnaires and spirometry as conventional approaches for managing asthma. These are easy to perform and are considered to be an indirect marker of underlying airway inflammation (5). However, directly monitoring airway inflammation may be a better and more reliable method. Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible, and noninvasive marker for directly detecting allergic airway inflammation (6–9). However, the use of FeNO as a surrogate marker of asthma control remains controversial (6, 10).

The aims of this study were to examine whether an intensive asthma educational program is associated with asthma control, to compare changes of predictive markers for asthma control [asthma control test questionnaire (ACT), forced expiratory volume in 1 s (FEV_1), and FeNO] over a 12-month period following asthma education and finally to evaluate whether FeNO measurements could be used as an additional marker of asthma control compared with ACT and FEV_1.

METHODS

Subjects

Asthmatic patients with persistent disease and poor adherence were recruited. All subjects had attended the outpatient clinic at the Department of Pulmonary Medicine, Fukushima Medical University Hospital for more than 6 months. Asthma was diagnosed according to a clinical history of characteristic symptoms (i.e., dry cough, wheezing, chest tightness, and breathlessness) and the presence of either bronchial hyperresponsiveness to methacholine or bronchodilator reversibility $\geq$12% (5). Subjects were excluded if they were current smokers, had other respiratory diseases, or had a respiratory tract infection within 6 weeks of study entry. Poor adherence was defined as the

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presence of at least one of the following in the previous 6 months: (i) failure to follow treatment by missing any prescribed asthma medications more than 1–2 times per week; (ii) a missed follow-up appointment for more than 4 weeks without taking appropriate medications; (iii) difficulty in using prescribed inhalers evaluated by observing and assessing the patient's demonstration of a sample inhaler device, and (iv) the requirement of high-dose inhaled corticosteroid (ICS) due to uncontrolled symptoms. Adherence to therapy and current medications was assessed by respiratory consultants in our department following a patient interview, review of medical records, and asthma diaries. Asthmatic patients attending our hospital's outpatient clinic are seen every 4–8 weeks and medications can only be prescribed at these appointments.

All subjects provided written informed consent, and the Ethics Committee of Fukushima Medical University approved the study.

Study Design

This was a prospective, single-center, observational study. Subjects were reviewed at entry and at intervals of 3, 6, and 12 months (four visits). At study entry, all subjects received an intensive educational program using an illustrated guide. ACT, FeNO measurements, and spirometry [FEV_1 and forced vital capacity (FVC)] were performed, and asthma control, based on the GINA guidelines, was assessed at each subsequent visit in order to evaluate the most appropriate treatment (5). Treatment remained unchanged during the first 3 months to evaluate the association of the intensive asthma educational program with asthma control. Following this 3-month period, the treatment could be changed if the subjects needed to step-up or step-down their treatment in line with the GINA guidelines (5). During the follow-up period, subjects were divided into two groups: (i) stable control group: asthmatic subjects whose treatments had not been changed or had been decreased over the study period and (ii) unstable control group: asthmatic subjects who had to increase their ICS dose or add other antiasthmatic drugs during the study period. These groups categorized as "stable" and "unstable" were used to assess ACT, FeNO, and FEV_1 as outcome predictors in this study.

Intensive Asthma Educational Program

The Ministry of Health and Welfare of Japan has developed a specific educational intervention program for asthma management according to the GINA guidelines. It provides information about asthma pathogenesis, diagnosis, severity, medications (including side effects), differences between reliever and controller agents, importance of asthma treatment, inhaler device instructions, exacerbation management, peak expiratory flow (PEF) monitoring, and a self-management plan. All subjects received a 30-min educational intervention program from a respiratory physician. The program included a detailed explanation and a demonstration of inhaler technique.

The Online FeNO Measurement Methods

FeNO measurements were made prior to spirometry at a constant flow of 50 mL/s according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines (11) using a chemiluminescence analyzer (Kimoto, Osaka, Japan). Three measurements were performed and the mean value was documented (coefficient of variation $\leq$10%).

Lung Function Tests

Spirometry was performed using rolling seal spirometers (CHESTAC-11; Chest M.I., Inc., Tokyo, Japan) according to the ATS guidelines (12). Three tests were performed and the highest FEV_1 was recorded. Results of FVC and FEV_1 were presented as percentages of the predicted level for statistical analysis.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 17.0; SPSS, Chicago, IL, USA). Data are shown as means and 95% confidence interval (95% CI). Changes in FeNO, ACT, and FEV_1 are shown as ΔFeNO, ΔACT, and ΔFEV_1, respectively.

The association between intensive asthma education and asthma control was evaluated using a comparison of ACT scores, FeNO levels, and FEV_1 %predicted at study entry and at the 3-month visit using a paired *t* test. The one-way analysis of variance was used to compare changes in FeNO levels, ACT scores, and FEV_1 %predicted over 12 months in the stable and unstable asthmatic groups. Correlations of changes (Δ) and absolute levels between FeNO, ACT, and FEV_1 were evaluated using the Spearman rank correlation coefficient analysis. A receiver operating characteristic (ROC) curve was constructed and the area under the curve (AUC) for each parameter was compared with 0.5 to estimate the optimal cutoff levels for detecting stable control of asthma. Sensitivity, specificity, positive predicted value (PPV), negative predicted value (NPV), positive likelihood ratio (LR(+)), and negative likelihood ratio (LR(−)) were calculated. A two-tailed *p*-value of $<.05$ was considered significant.

RESULTS

Characteristic of Subjects

The study population consisted of 50 asthmatic patients with poor adherence (18 males and 32 females) (Table 1). The mean age was 55.4 years (range: 16–79 years) and the patients were nonsmokers or ex smokers with a <5 pack-year history. Thirty-three patients (66%) were atopic and the cohort consisted of 12 mild, 21 moderate, and 17 severe persistent asthmatic subjects based on symptoms and treatment intensity (13). All the subjects were treated with regular ICS.

TABLE 1.—Subject characteristics.

Characteristics	Data
Patients	50
Sex (male/female)	18/32
Mean age (y.o.)	55.4 (50.4–60.5)
Height (cm)	157.6 (154.8–160.4)
Weight (kg)	61.1 (56.8–65.4)
Atopic status	33 (66%)
Severity of asthma	Mild persistent: 12
	Moderate persistent: 21
	Severe persistent: 17
FEV_1 %predicted (%)	87.8 (81.8–93.9)
FEV_1/FVC (%)	72.4 (69.3–75.5)
FeNO level (ppb)	84.9 (69.6–100.1)
ACT score (point)	19.0 (18–20.1)
ICS dose (μg) BDP equivalent	1106 (957–1255)

Note: Data was expressed as mean (95% CI) or number of patients.
BDP; Beclomethasone dipropionate.

The Effect of Intensive Asthma Educational Program

Asthma treatment remained unchanged during the first 3 months. Following the educational program, a significant decrease in FeNO levels and increase in ACT scores were seen in the stable asthma group ($n = 42$) compared with the unstable asthma group ($n = 8$; $p < .001$; Figure 1A and B). There was no significant difference in FEV_1 %predicted (Figure 1C).

The Changes of FeNO Levels, ACT Scores, and FEV_1 %predicted over 12 Months

In 8 of 50 asthmatic subjects (16%), the ICS dose was increased or other antiasthmatic drugs were added due to poor asthma control. Asthma medications were decreased in 14 of 42 patients (33%) reflecting improved asthma control. Significant decreases in FeNO levels and increases in ACT score following asthma educational program remained consistent in the stable asthmatic group over the course of 12 months (Figure 1A and B).

Correlations between Absolute Levels of FeNO, ACT Scores, and FEV_1 %predicted at Each Visit

There were significant negative correlations between absolute levels of FeNO and ACT scores at the beginning of the study and at 3 months following asthma educational program ($r = -0.47$, $p = .001$; $r = -0.49$, $p = .002$, respectively) (Table 2). Negative weak correlations were found between absolute levels of FeNO and FEV_1 %predicted over the same period ($r = -0.26$, $p = .07$; $r = -0.39$, $p = .02$, respectively). However, these correlations were not present at 6 months (Table 2).

Correlations between Changes (Δ) in FeNO, ACT, and FEV_1 at Each Visit

Highly significant correlations were observed between the ΔFeNO, ΔACT, and ΔFEV_1 which were maintained over the course of 12 months ($p < .05$; Table 3).

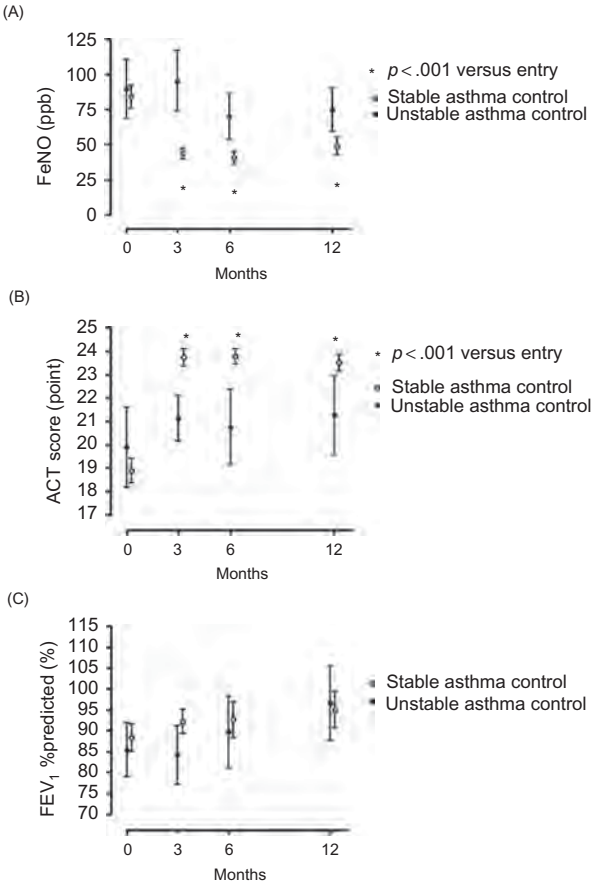

FIGURE 1.—Levels at time points indicated for FeNO levels (A), ACT score (B), and FEV_1 %predicted (C) between the subjects with or without achieving asthma control after the intensive educational interventions. Forty-two asthmatic subjects achieved good control whereas eight asthmatic subjects still had poor control.

Predictive Value of Each Parameter as a Marker to Achieve Stable Asthma Control

ROC curves were constructed to determine the cutoff levels for obtaining stable asthma control using absolute levels or changes in FeNO, ACT, and FEV_1. There were no useful parameters to discriminate subjects with stable asthma from those with unstable asthma using absolute levels (Figure 2A). However, an 18.6% decrease in ΔFeNO [AUC = 0.85, sensitivity of 80.0%, specificity of 83.3%, (LR) (+) of 4.8, LR(−) of 4.17, PPV of 92.3%, and NPV of 40%; $p = .007$] and a 3-point increase in ΔACT (AUC = 0.794, sensitivity of 73.3%, specificity of 87.5%, LR(+) of 5.86, LR(−) of 3.28, PPV of 95.7%, and NPV of 46.7%; $p = .012$) were noted.

DISCUSSION

This is a prospective, observational study to estimate the association of asthma educational program with asthma control. We have compared the absolute levels and changes in FeNO, ACT, and FEV_1 with asthma control. Our results indicate that intensive asthma educational program may be associated with improved asthma control.

TABLE 2.—Correlations between absolute levels of FeNO, ACT scores, and FEV_1 %predicted.

FeNO	Entry	*p*	3 months	*p*	6 months	*p*	12 months	*p*
ACT	−0.47*	.001	−0.49*	.002	−0.20	.249	−0.06	.742
FEV_1 % predicted	−0.26	.07	−0.39*	.019	−0.28	.110	−0.08	.649

Note: Spearman rank correlation coefficients were calculated and the data were expressed as *r* values.
*$p < .05$.

TABLE 3.—Correlations between changes of FeNO levels, ACT scores, and FEV_1.

ΔFeNO	3-entry	*p*	6-entry	*p*	12-entry	*p*
ΔACT	−0.76*	<.001	−0.61*	<.001	−0.53*	.005
ΔFEV_1	−0.53*	.001	−0.54*	.003	−0.42*	.03

Note: Spearman rank correlation coefficients were calculated and the data were expressed as *r* values.
*$p < .05$.

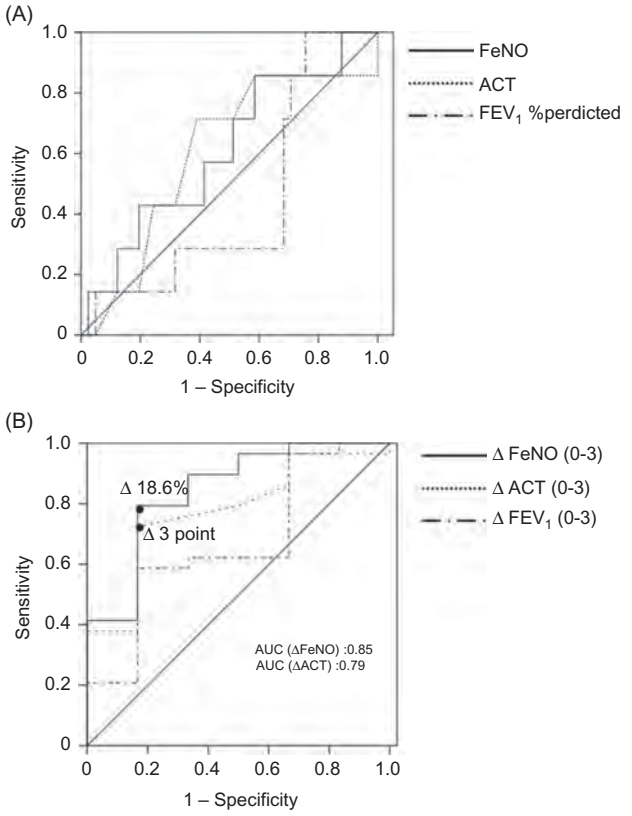

FIGURE 2.—ROC curves of absolute levels (A) and changes (B) of three parameters to determine good asthma control.

FeNO levels and ACT scores, but not FEV_1 %predicted, in the stable asthmatic group indicate improved asthma control over the course of 12 months. Changes (Δ) in FeNO levels, ACT scores, and FEV_1 had a stronger correlation, suggesting that multiple measurements and monitoring these changes may be a better way of predicting future asthma control.

Asthmatic subjects without self-management plans are often less adherent to prescribed medications and are more likely to be poorly controlled (4, 14). Many asthmatic patients do not use their inhaler devices correctly and asthmatic patients who are more adherent to therapy are less likely to suffer exacerbations (15, 16). Therefore, asthma education plays a vital role in improving and obtaining asthma control. The GINA guidelines emphasize the importance of asthma education, highlighting that educational intervention should be an integral part of interactions between patients and physicians (5). This interaction plays an important role by increasing motivation, skills, and confidence with subsequent benefits in asthma control. This results in improved asthma symptoms and lung function, and a decreased economic burden in terms of medical expenses (17).

This study found a significant increase in ACT scores and decrease in FeNO levels at 3 months following asthma educational program in the stable asthmatic group. No significant difference was seen in the unstable asthmatic group. Several previous studies have noted similar findings, reporting that asthma education is associated with improvements in symptoms (4, 18–21), lung function (18–21), and quality of life (QOL) (19, 21). However, while some of these studies noted an association between all three factors (19,21), others found that only symptoms correlated with an educational program (4, 18, 20). This difference may be explained by the content of educational program, study designs, and characteristics of the subjects. In our study, a significant reduction in FeNO levels could be seen in the stable asthma group. There is a paucity of information regarding the relationship between asthma education and FeNO. Dressel et al. noted a significant decrease in FeNO levels and improved asthma symptoms following an educational program in occupational asthmatic patients. In addition, they found that these improvements were not correlated with lung function (22). These findings and results from our study support the view that an intensive asthma educational program may be a valuable adjunct to achieve stable asthma control.

In this study, significant decreases in FeNO levels and increases in ACT scores remained consistent over the course of 12 months in stable asthmatic subjects. Symptom questionnaires and lung function tests are recommended in the GINA guidelines as markers of asthma control (5). Although they are easy to perform on almost all subjects, they are sometimes discordant with airway inflammation (23). Furthermore, symptoms are subjective and results may be influenced by patient's perception (24). Other markers such as sputum eosinophils and AHR have shown good correlations with asthma control (25, 26). However, these tests are time consuming,

invasive, require technical skill to process, and are, therefore, difficult to incorporate into standard clinical practice. Our results suggest that a combination of ACT and FeNO may be a quick and easy way to differentiate between stable and unstable asthmatic subjects.

In this study, we found a significant relationship between ΔFeNO, ΔACT, and ΔFEV_1 over the course of 12 months, whereas significant correlations between absolute levels were only observed at 3 months. FeNO reflects airway inflammation directly and correlates with conventional markers such as FEV_1, AHR, and sputum eosinophil counts (6–9). Several randomized control trials comparing the single or add-on effects of FeNO, with established parameters of asthma control, have only noted a limited benefit (27–30). These findings may reflect differences in study designs, the small number of subjects enrolled, variation in significance levels, and differences in asthma severity. Furthermore, individual patients may have their own personal best and range of FeNO levels, as seen with PEF measurements (31). FeNO levels in some asthmatic patients remain predominantly high regardless of an improvement in lung function and symptoms (29). Therefore, an individual cutoff level or proportional change, from baseline rather than an absolute cutoff level may be more useful.

The results of this study indicate that a 20% ΔFeNO decrease and a 3-point ΔACT increase may predict stable asthma control. To date, few studies have examined the relationship between ΔFeNO and other conventional parameters of asthma control. Jones et al. reported that change in FeNO level from baseline had a higher PPV compared with an absolute cutoff level in terms of asthma control (32). Michils et al. suggested that a single measurement of FeNO was not a good reflection of asthma control, particularly in patients on medium-to-high doses of ICS (33). A study looking at ΔACT found that a minimally important difference (MID) of three points is a significant predictor of asthma control (34). These studies support our observations that using changes in the levels of parameters may be better than using absolute levels for the evaluation of asthma control. We suggest that monitoring changes in FeNO levels and ACT scores in individual patients over time could be used as markers for achieving stable asthma control.

There are several limitations to this study. This is a prospective, observational study with a relatively small number of subjects tested. In addition, the educational intervention may be confounded by the Hawthorne effect, whereby subjects can subconsciously alter their behavior in a specific manner simply because of awareness of being educated and observed. Finally, subjects in this study may not represent the general asthmatic population. Only asthmatic subjects with poor adherence were recruited, and this may generate a positive selection bias. However, this is a group that we believe requires greater asthma education than their well-controlled counterparts.

In conclusion, this study suggests that comprehensive asthma educational program should be viewed as an important treatment option and considered prior to instigating changes in treatment. In addition, the changes (Δ) in FeNO and ACT levels could become useful surrogate markers for long-term asthma management. Further, large randomized studies are warranted to determine the influence of asthma education on disease control and the utility of changes (Δ) of FeNO and ACT.

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DECLARATION OF INTEREST

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REVIEW ARTICLE

Review Series: Non-Invasive Monitoring of Airway Inflammation in Asthma

Exhaled Nitric Oxide (FeNO) as a Non-Invasive Marker of Airway Inflammation

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ABSTRACT
Nitric oxide (NO), previously very famous for being an environmental pollutant in the field of pulmonary medicine, is now known as the smallest, lightest, and most famed molecule to act as a biological messenger. Furthermore, recent basic researches have revealed the production mechanisms and physiological functions of nitric oxide in the lung, and clinical researches have been clarifying its tight relation to airway inflammation in asthma. On the bases of this knowledge, fractional nitric oxide (FeNO) has now been introduced as one of the most practical tools for the diagnosis and management of bronchial asthma.

KEY WORDS
asthma, cut-off, diagnosis, monitor, non-invasive

INTRODUCTION

Previously known as a toxic molecule listed as an environmental pollutant, nitric oxide (NO) is now known to be the smallest, lightest, and most famed molecule to act as a biological messenger in mammals. NO was first recognized as a physiologically important molecule in the manuscript written by Fruchgott and Zawadzki, entitled "The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine", published in Nature in 1980.[1] Initially, the factor released from vascular endothelial cells was named as endothelium derived relaxing factor (EDRF), and large number of scientists had been pursued the true feature of EDRF. In 1987, two groups led by Ignaro and by Moncada, independently discovered and reported that EDRF is a simple gaseous molecule called NO.[2,3] After the discovery, a large amount of studies in field of medicine revealed its many roles in a wide range of pathophysiological status including cardiovascular, immune, metabolic, and neurological diseases. For an ordinary person, it became a very famous physiological mediator of penile erection and opened the door for the treatment of impotence.[4] In 1992, NO was selected as Molecule of the Year for a startlingly simple molecule unites neuroscience, physiology and immunobiology and revised scientists' understanding of how cells communicate and defend themselves.[5] In 1998, the Nobel prize for Physiology or Medicine was awarded to Doctors, Furchgott R, Ignarro L, and Murad F.[6]

In the field of pulmonary medicine, physiological and pathological roles of NO in lung disease have also been investigated. Epithelium dependent inhibition of airway smooth muscle contraction and epithelium dependent relaxation of airway smooth muscle, similar effect of vascular endothelium to vascular smooth muscle, have been reported.[7,8] These phenomena also suggested the existence of epithelium derived relaxing factor (EpDRF).[9] Since NO is also confirmed to be a potent smooth muscle relaxing agent (Fig. 1),[10] several pharmacological studies verifying whether EpDRF is also NO were carried out and confirmed production of NO from airway epithelium.[11] In these processes, measurement systems for NO in exhaled air have been developed.[12] By applying such systems, exhaled NO have been measured in many pulmonary diseases and significant increase

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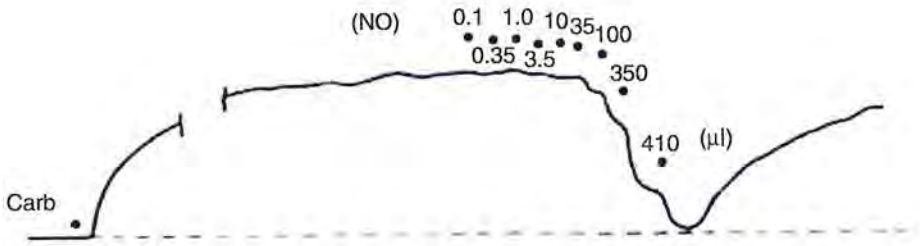

Fig. 1 Airway smooth muscle relaxation induced by nitric oxide (NO). Guinea pig tracheal strip was contracted by stimulated by Carbachol (Carb), then 0.1 to 410 ul of saturated solution of NO (estimated concentration 2 mM) was prepared, and was added to the tissue bath. Clear concentration-dependent relaxation was observed (Adapted from reference 10).

in exhaled NO of the patients with asthma became apparent.[13,14] Since the measurement is noninvasive and effort independent, exhaled NO has been much expected as a new tool for the diagnosis and management of asthma, and large efforts have been devoted on the clinical research.

PRODUCTION AND FUNCTION OF NO IN THE AIRWAYS

In the respiratory tract, NO is produced by a wide variety of cell types and is generated through conversion of L-arginine to L-citrulline by the action of nitric oxide synthase (NOS). Three isoforms of NOS are known: neuronal NOS (NOS I or nNOS), inducible NOS (NOS II or iNOS), and endothelial NOS (NOS III or eNOS).[15] Two isoforms, nNOS and eNOS, are expressed constitutively, but iNOS is not normally expressed in most tissues but is induced in several types of cells by pro-inflammatory cytokines.[16-18] All three types of NOS isoforms are known to be expressed in the lung. Endothelial NOS (eNOS) immunoreactivity is found in endothelial cells of pulmonary vessels. In addition, it is constitutively expressed in human bronchial epithelium and in type II pneumocytes.[19,20] NO produced by eNOS and released from endothelial cells in the pulmonary circulation is speculated to regulate vascular basal tone and counteract hypoxic vasoconstriction.[21] Neuronal NOS (nNOS) is expressed in human airway nerves, including those present in the airway smooth muscle,[22,23] and is estimated to be a major mediator of the inhibitory non-adrenergic non-cholinergic nervous (iNANC) system.[24] Co-localization with vasoactive intestinal polypeptide (VIP) is also observed.[25] Nerves distributed to submucosal glands also contain nNOS and NO regulates secretory function of the glands.[22,26] In the lung, iNOS (or NOS II) is known to be expressed in macrophages,[27] epithelial cells,[28-30] type II pneumocytes,[31,32] endothelial cells,[33] airway and vascular smooth muscle,[34] mast cells,[35] neutrophils,[36] chondrocytes,[23] and fibroblast.[37] Usually, iNOS in these cells is expressed when stimulated by endogenous mediators such as chemokines and cytokines, and by exogenous stimulant such as bacterial toxins, viruses, allergens, etc. Constitutive expression of iNOS in airway epithelial cells and rapid loss of its expression after removal of the epithelial cells from the in vivo airway environment were reported only in humans and suggest that the expression is dependent upon conditions and/or factors present in the airway.[38] iNOS derived NO is also speculated to regulate both airway smooth muscle tone and inflammatory responses.

MEASUREMENT OF EXHALED NO

The presence of NO in the exhaled air of humans was demonstrated by chemiluminescence, diazotization and mass spectrometry in 1991.[12] Thereafter, several measurement systems have been developed. The most commonly used system is chemiluminescence, and in Japan, two types are available; NOA280i (Severs, GE Analytical Instruments, Boulder, USA) and NA623N (Chest MI, Tokyo, Japan). These can be applied for both online and offline measurement of fractional exhaled NO (FeNO) in ppb. With these two types, we can get almost the same FeNO values.[39-42] It is known that FeNO is strongly affected by expiratory flow rate, FeNO levels in dead space air are high, and those in nasal cavities are very high. Therefore, several cautions should be kept in mind to get reasonable FeNO values. These cautions are included in American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations for the measurement of FeNO,[43,44] and following these recommendations is very important when FeNO is measured with these analyzers.

Another NO measurement system is the electrochemical method. The merits of the system are its compact size and portability. In Japan, two types of analyzers, NIOX MINO (Aerocrine, Stockholm, Sweden) and NObreath (Bedfont Scientific, Kent, UK), are available. There are some differences in FeNO levels measured by these analyzers when compared to a chemiluminescence analyzer. Differences of FeNO levels measured by different analyzers have been examined and conversion equations are also

available.[39-42] Several attempts to separate alveolar NO from airway NO have been performed by measuring FeNO at multiple exhalation flow rates,[45-48] however, it seems very difficult to apply such methods to clinical medicine and they might be useful as research tools.

NO AND AIRWAY INFLAMMATION IN ASTHMA

Asthma is a syndrome characterized by the presence of two physiological characteristics, reversible airflow limitation and airway hyperresponsiveness with respiratory symptoms. However, a recent advance in asthma research revealed the importance of airway inflammation existing behind these physiological characteristics. According to such progress in the concept of asthma, diagnosis and treatment strategies have been changing dramatically. One of the most prominent examples is the introduction of anti-inflammatory therapy with ICS, resulting in the pronounced the improvement in control and quality of life of the patients, and a dramatic reduction in the number of emergency room visit and deaths of the patients in Japan.

The recognition of the important roles of airway inflammation in asthma also promoted the development of new technology to evaluate airway inflammation in asthma. In these processes, a FeNO measurement was recognized as the most anticipated candidate. In early 1990s, significant increase in FeNO of ICS naïve patients with asthma, and decreased FeNO after ICS treatment was revealed,[13,14] suggesting the relationship between airway inflammation and elevation of FeNO. Hamid *et al.* applied immune-histochemical methods for bronchial biopsy specimen to investigate the presence of NOS in asthma. Immunoreactivity to iNOS was observed in the epithelium and some inflammatory cells in 22 of 23 biopsies from asthmatics, but in only 2 of 20 controls.[49] Guo *et al.* also examined iNOS expression by mRNA and protein assay and revealed that human airway epithelium has abundant expression of iNOS due to continuous transcriptional activation of the gene in vivo, and that individuals with asthma have higher than normal NO concentrations and increased iNOS mRNA and protein due to transcriptional regulation through activation of STAT1.[50] In addition, they revealed decreased expression of iNOS mRNA in asthmatics receiving ICS.[50] Redington *et al.* also examined iNOS expression in the airway epithelium and revealed enhanced expression in asthmatic subjects and regulation by corticosteroid treatment.[51]

The regulation mechanisms of iNOS expression are far from full elucidation. Although abundant expression of iNOS is observed in human airway epithelium, it will instantly disappear when these cells are cultured ex vivo,[38] suggesting the existence of in vivo factors or stimuli in the airway. In other types of cells, iNOS expression is only observed after stimulation with cytokines such as IFN-γ, IL-1β, and/or TNF-α.[52] Guo *et al.* revealed that a combination of IFN-γ/IL-4, which occurs naturally in lung epithelial lining fluid, leads to maintenance of iNOS expression in human airway epithelium through production of soluble mediators and stabilization of mRNA.[53] Alving and Malinovschi suggested a possible model of iNOS regulation of human airway from the results of recent studies[54] (Fig. 2). In healthy subjects (Fig. 2a), continuous expression of iNOS is maintained by IFN-γ, which normally exists in the respiratory tract. In this process, induction of unidentified soluble mediators by IFN-γ and the subsequent activation of the JAK/STA pathway are considered to be important.[55] In asthmatic airways (Fig. 2b), different regulation mechanisms are estimated (Fig. 2b). Initially, Th2 cytokines such as IL-4 and IL-13 were recognized to down-regulate iNOS expression.[56] However, several recent studies revealed that IL-4 and IL-13 actually induce iNOS expression in human airway epithelial cells in reasonable medium conditions through the STAT-6 pathway.[50,53,57,58]

There are several epidemiological evidences suggesting the relation between allergic airway inflammation and increased FeNO. Saito *et al.* examined FeNO levels, pulmonary function, and serum total and antigen specific IgE levels in 278 normal school children aged 10 to 12.[59] There are statistically significant positive correlations between FeNO and total IgE or mite specific IgE, and significant negative correlations between FeNO and FEV1/FVC. In addition, FeNO was determined by means of multiple logistic regression analysis to be the best predictor for recurrent wheeze, suggesting the relationship between allergic airway inflammation and FeNO levels. They also obtained the same results when they examined 280 normal adults aged 18 to 82 who received annual health check.[60] Moody *et al.* revealed that the increase in FeNO is associated with house dust mite sensitivity in asymptomatic subjects.[61] Additionally, some atopic subjects without symptoms and airway hyperresponsiveness have airway eosinophilc inflammation.[62] These findings support the tight relationship between increase of FeNO levels and allergic airway inflammation.

NO AS A DIAGNOSTIC TOOL OF ASTHMA

Traditionally, asthma has been characterized by respiratory symptoms such as cough, wheeze, and dyspnea, reversible airflow limitation, and non-specific airway hyperresponsiveness.[63,64] These are evaluated by pulmonary function tests before and after inhalation of bronchodilators such as β-adrenergic receptor agonists, and bronchial challenge test with bronchoconstrictors such as histamine and acetylcholine.[64] For the airway inflammation, trans-bronchial biopsy (TBB) and brochoalveolar lavage (BAL) under the fi-

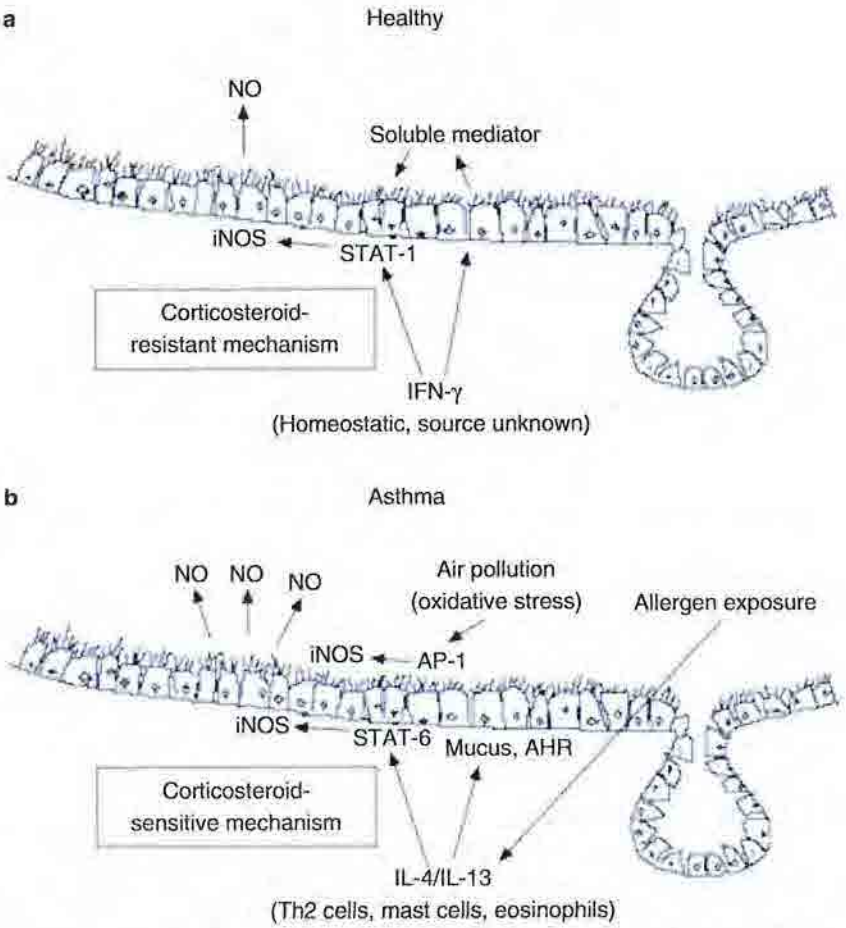

Fig. 2 A possible model of iNOS regulation of human airway. **a)** normal healthy airway, **b)** asthmatic airway (Adapted from reference 54).

beroptic bronchoscopic examination are applied. Recently, cell sorting of sputum induced by the inhalation of hypertonic saline has also been utilized. However, these methods are relatively invasive and sometimes induce asthma attacks. It is therefore difficult to apply widely in general clinical practice.

Because of the tight relation between FeNO and allergic airway inflammation and its non-invasiveness, attempts to use FeNO as a non-invasive tool for asthma diagnosis have been carried out in various clinical settings. Sato *et al.* examined 71 consecutive patients who visited out-patient clinics by complaining chronic cough continuing more than 3 weeks.[65] They examined FeNO, pulmonary function, serum IgE, methacholine airway responsiveness and induced sputum. FeNO is significantly higher in patients with asthma and cough variant asthma compared to other diseases including COPD and eosinophilic pneumonia without asthma, suggesting the usefulness of FeNO measurement in the diagnosis of asthma in patients with chronic cough. Cut-off value for FeNO for the diagnosis of asthma was 38.8 ppb with sensitivity of 79.2% and specificity of 91.3%. Similar results were also reported in patients with chronic cough by Chatkin *et al.*, Fujimura *et al.*, and Kowal *et al.*.[66-68]

For the patients with non-specific respiratory symptoms and suspected to having asthma, Smith *et al.* examined FeNO and sputum eosinophils in addition to conventional peak expiratory flow and spirometric parameters before and after bronchodilator treatment.[69] They observed the overall superiority of FeNO measurements and induced sputum analysis in the diagnosis of asthma compared with conventional tests. Dupont *et al.* also reported the usefulness of FeNO in 160 asthmatic patients diagnosed by the presence of reversible airflow obstruction (delta FEV1 > 12%) and histamine airway hyperresponsiveness (PC20 < 8.0 mg/ml).[70] Their cut-off level of FeNO at expiratory flow rate of 200 ml/s (FeNO200) was 16.0 ppb with the sensitivity of 69.4% and specificity of 90.0%. Fortuna *et al.* also reported that the diagnostic accuracy of FeNO measurement was superior to that of the standard diagnostic spirometry in patients with symptoms suggestive of asthma.[71] Fukuhara *et al.* recently reported the results of their prospective validation

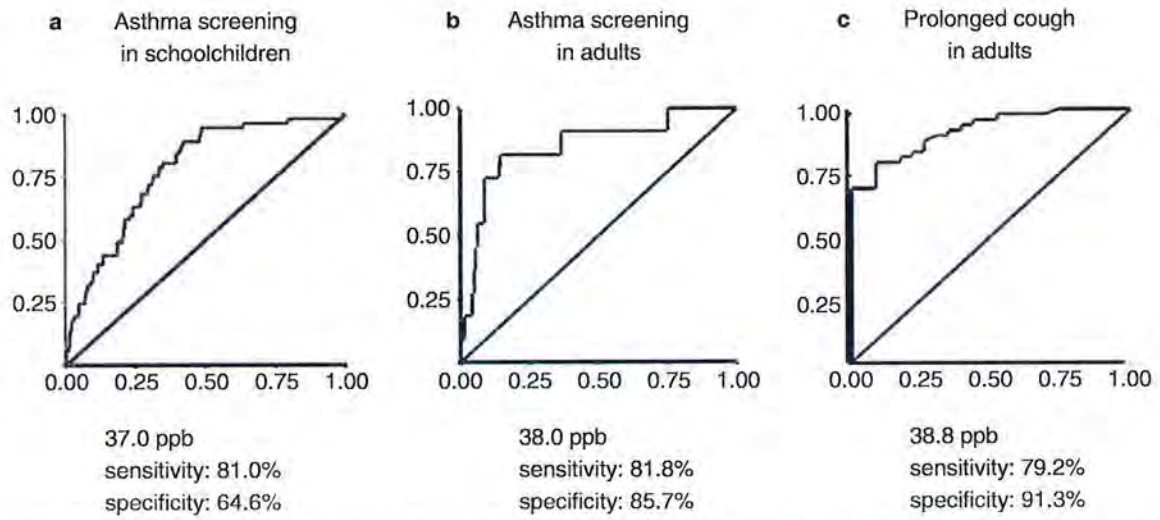

Fig. 3 The cut-off levels of fractional exhaled nitric oxide (FeNO) for diagnosing asthma obtained from 3 independent studies. **a)** for 277 school children, **b)** for 280 adult volunteers, **c)** for 71 patients with chronic cough (Adapted from reference 42).

study of asthma screening criteria based on subjective symptoms and FeNO at expiratory flow rate of 50 ml/sec ($FeNO_{50}$); i) recurrent cough, wheezeing, or dyspnea; ii) $FeNO_{50} > 40$ ppb, iii) exclusion of other lung diseases.[42] A cut-off value of 40 ppb was determined by the results of their 3 previous independent studies on school children, normal adults, and patients with prolonged cough (Fig. 3).[59,60,65] When compared to conventional asthma diagnostic criteria based on GINA and JGL guidelines,[63,64] FeNO based criteria showed good sensitivity, specificity, and a concordance rate (k) (78.6%, 89.5%, and 0.62, respectively). However, 9 of 42 patients were misdiagnosed as not having asthma by FeNO based criteria, and 7 of these 9 patients were non-atopic according to their IgE levels. From these results, they suggested that FeNO could be used as a tool for the non-invasive accurate diagnosis of asthma, particularly in atopic patients in daily clinical practice.

NO AS A CONTROL TOOL OF ASTHMA

Understanding that the most basic event in asthma is airway inflammation and the tight correlation between FeNO and airway inflammation has motivated the application of FeNO as a monitoring tool for asthma control. In 2005, Smith *et al.* did a single-blind, placebo-controlled trial of adult asthmatics to examine the usefulness of FeNO measurements for the adjustment of ICS doses. With the FeNO based strategy, the maintenance doses of ICS were significantly reduced without compromising asthma control compared to those with an algorithm based on conventional guidelines.[72] In the same year, Pijnenburg *et al.* did a randomized controlled trial to examine the usefulness of FeNO for the titration of ICS in atopic children with asthma. They also found that FeNO improved airway hyperresponsiveness and inflammation without elevating the ICS doses.[73] Following these studies, several consecutive studies were conducted and controversial results were reported. For the adult asthmatics, Shaw *et al.* reported that a treatment strategy based on FeNO measurement did not result in a large reduction in asthma exacerbation or in the total amount of ICS therapy used over 12 months, compared with the current asthma guideline.[74] But when the results were pored over precisely, in the initial several months, the required dose of ICS was higher in the FeNO based group compared to the control group, the dose gradually declined and the final daily dose of ICS was significantly lower in the FeNO based group compared to the control group (average; 557 ug/day and 895 ug/day, respectively, $p < 0.028$). More recently, Powel *et al.* carried out a double-blinded, randomized controlled trial to examined the usefulness of asthma management in pregnancy guided by FeNO. They revealed that asthma exacerbations during pregnancy can be significantly reduce with a validated FeNO-based treatment algorithm.[75] For adolescents and young adults, Szefler *et al.* did the largest randomized controlled trial to date with 780 patients with asthma to examine the usefulness of FeNO-based asthma management in addition to guideline-based treatment. They concluded that the addition of FeNO as an indicator of asthma control resulted in higher doses of ICS, without clinically important improvements in symptomatic asthma control.[76] But the subgroup analyses of the patients with a higher number of positive skin tests or those with serum nonspecific IgE higher than 460 kU/L revealed that the FeNO monitoring group had significantly fewer maximum days with symptoms in 2 weeks than that of the control group (0.84 and 0.51, p

< 0.024 and $p < 0.007$, respectively). As shown in the previous section, FeNO is suggested to be a very useful tool to monitor airway inflammation in atopic subjects. From these facts, it is suggested that application of FeNO as a tool for asthma control might be limited to the patients with atopic asthma.

Another point that should be borne in mind is the fact that the period of previously introduced studies were only up to 12 months. Sont *et al.* compared the difference in histopathologic outcome of asthma when using airway hyperesponsiveness as an additional guide to long-term treatment. They demonstrated that the examined strategy group showed a greater reduction in thickness of the subepithelial reticular layer compared to the reference strategy group, suggesting a role for the monitoring of airway hyperresponsiveness or other surrogate makers of inflammation in preventing airway remodeling.[77] Long-term usefulness of FeNO as a monitoring tool for asthma control, whether it could be helpful in prevention of airway remodeling or in decreasing annual decline in FEV1, needs to be examined.

FUTURE DIRECTIONS

As noted above, FeNO is a very useful diagnostic tool and control monitoring maker of asthma. Usefulness of FeNO in asthma management is probably better than spirogram, induced sputum, and AHR test, because of its non-invasiveness, effort independency, measurement simplicity, and reproducibility. Although the FeNO analyzer has not been approved as a medical device, it will be widely used as a convenient clinical tool for asthma management in the near future in Japan.

The FeNO analyzer has been used as a clinical research tools and wide application of FeNO in the clinical setting revealed the issues that should be solved before its clinical application. Now, many researchers recognize that there is a minor population of subjects with very high levels of FeNO without respiratory symptoms, and that there are asthmatics with all asthmatic symptoms but with normal FeNO levels. The mechanisms behind these phenomena are unclear, meaning that the production mechanisms of NO in the airway and lung parenchyma have not been thoroughly clarified. Additional point is that, although the ATS/ERS guideline was established to standardize the FeNO measurements,[43] there are variations in FeNO values measured by different analyzers.[41,42] It also affects the determination FeNO cut-off levels for the diagnosis and control of asthma. In addition, to be used widely in the clinical practice, the development of handier, more accurate, less expensive measurement systems is required. Furthermore, not only more practical studies but also more basic studies will be warranted.

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