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Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures

Koji Sakamoto [a,b], Hiroyuki Taniguchi [b,*], Yasuhiro Kondoh [b], Kenji Wakai [c], Tomoki Kimura [b], Kensuke Kataoka [b], Naozumi Hashimoto [a], Osamu Nishiyama [d], Yoshinori Hasegawa [a]

[a] *Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Japan*
[b] *Department of Respiratory Medicine and Allergy, Tosei General Hospital, Nishioiwake-cho, Seto-shi, Aichi 489-8642, Japan*
[c] *Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Japan*
[d] *Department of Pulmonary Medicine and Allergology, Kinki University School of Medicine, Japan*

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KEYWORDS
Acute exacerbation;
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Summary
Backgrounds: Bronchoalveolar lavage (BAL) is generally regarded as a safe diagnostic procedure. However, acute exacerbation after BAL is increasingly recognized as a specific complication for patients with idiopathic pulmonary fibrosis (IPF). So far little is known about the correlation between BAL and acute exacerbation of IPF (AE-IPF).
Methods: A cohort of 112 IPF patients at a single institution was analyzed retrospectively. We defined BAL-related AE-IPF as development of AE-IPF within 30 days after the procedure. The incidence rate of AE-IPF per person-month during the post-BAL period was compared with that after the post-BAL period. The relative risk was estimated as the former rate divided by the latter. We also reviewed the previous literature.
Results: Four AE-IPF cases occurred during the 201 person-month post-BAL period. The risk of AE-IPF was significantly elevated within 30 days after BAL (rate ratio = 4.12; 95% CI = 1.03–12.2). None of the 111 initial BAL procedures were followed by AE-IPF within a month. In a post hoc analysis, the relative risk of developing AE after second or later BAL procedures was estimated to be considerably higher (rate ratio = 9.10; 95% CI = 2.27–26.98).
Twelve cases of BAL-induced AE-IPF were found in our study and in the literature review. Among them, nine showed moderate to severe functional impairment, and eight had either findings of leukocytosis, positive C-reactive protein, or neutrophilia in BAL.
Conclusions: These results suggest that IPF patients should be carefully monitored after BAL, especially those with functional impairment or active inflammation.

* Corresponding author. Tel.: +81 561 82 5101x7309; fax: +81 561 82 9139.
E-mail address: hiro-tosei-lung@kkd.biglobe.ne.jp (H. Taniguchi).

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Introduction

Bronchoalveolar lavage (BAL) has been used in diagnostic and prognostic evaluation in diffuse parenchymal lung disease, and has a central role in the diagnosis of a number of rare disorders and in excluding opportunistic infection in treated patients.[1] In diagnosing idiopathic pulmonary fibrosis (IPF), the pattern of inflammatory cells identified in BAL may be helpful in narrowing the differential diagnosis of fibrosing interstitial pneumonias, but it is not in itself diagnostic.[2] Therefore, recent guidelines do not recommend its routine use in diagnosing IPF.[3,4] Nevertheless, a recent study demonstrated that the addition of BAL to diagnostic procedures is useful in patients suspected of having IPF with a confident CT diagnosis.[5] Moreover, BAL cell differentials were reported to have prognostic value in patients with IPF.[6,7] BAL also remains an invaluable research tool, providing information regarding immune effector cells that accumulate in the alveolus and their non-cellular products. This approach will continue to be helpful in exploring the pathogenesis of the disease and is widely used in the clinical setting.

BAL is generally regarded as a very safe procedure.[8] Lethal complications are very rare and while minor complications such as vasovagal reactions, fever, cardiac arrhythmias, hemorrhage and pneumothorax have been reported, most are considered self-limiting. In terms of IPF, however, several cases in which there was progressive degeneration of IPF after BAL have been reported.[9–11] Therefore, along with surgical lung biopsy,[12] some experts suspect that BAL may be one of the precipitating factors for developing acute exacerbation of IPF (AE-IPF).[13]

To date the correlation between BAL and AE-IPF remains largely unknown. We conducted a retrospective cohort study to investigate the temporal relationship between BAL procedures and onset of AE-IPF. We further reviewed the relevant literature to explore possible denominators of BAL-induced AE-IPF patients.

Methods

This was a retrospective cohort study. Patients with IPF diagnosed from April 1995 to December 2007 and subsequently followed at Tosei General Hospital (Seto, Aichi, Japan) were eligible. The diagnosis of IPF was made according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus Classification.[14] Demographic data at the time of diagnosis (including sex, age, smoking history), onset and outcome of acute exacerbation, and number of times and timing of BAL procedures were investigated from medical records. AE-IPF was defined using the revised Japanese criteria for AE-IPF which states that all of the following three conditions must be satisfied during the course of IPF within a single month: (1) dyspnea increases, (2) new ground-glass opacities appear on HRCT in addition to previous honeycomb lesions, (3) oxygen partial pressure in resting arterial blood (PaO_2) is lower by more than 10 mmHg than previous measurements. Obvious causes of these changes, such as infection, pneumothorax, cancer, pulmonary embolism or congestive heart failure, were excluded.[15–17] Particularly in terms of excluding possible infection, following evaluation was routinely performed in our institution; cultures of blood and sputum for mycobacteria, fungi, and bacteria, assessment of serum titers against *Mycoplasma pneumoniae*, *Chlamydophila psittaci*, *Chlamydophila pneumoniae*, *Legionella pneumophila,* and various viruses. In addition, excluding the possibility of infection was made with additional BAL unless contraindicated.

The occurrence of AE-IPF within 30 days after BAL was considered to be "BAL-induced AE-IPF." BAL performed after the onset of acute deterioration of respiratory status was not included in this analysis. To test the hypothesis that development of AE-IPF was more frequent after BAL procedure, we set 30 days following the day of BAL as the period of risk. To describe the risk from BAL of developing AE-IPF, the person-month incidence rate for AE-IPF was calculated and the incident rate ratio was determined as follows[18]: person-month incidence rate of AE at risk (events per person-month) is divided by person-month incidence rate of AE not at risk (events per person-month). An incident rate ratio above 1 means AE is more likely to occur during the period at risk, namely, during 30 days after BAL. The statistical significance of an increased risk ratio was tested with two-sided Fisher's exact test. The follow-up time spanned the time from diagnosis of IPF until the onset of AE-IPF, death, or last contact, whichever was earliest. The study protocol was approved by the Ethics Committee of Tosei General Hospital.

In addition, published cases of AE-IPF that developed after a BAL procedure were identified using computer databases. We searched for similar reports published from 1985 through December 2009, using PubMed for reports in English and Ichushi Web (http://www.jamas.or.jp) for Japanese reports. Only published cases with detailed clinical summaries were included in this review. Pertinent clinical, laboratory and histological data were abstracted.

Result

Retrospective cohort study

Demographic and clinical data for the 112 patients enrolled are shown in Table 1. The diagnoses of 53 cases (47.3%) were pathologically confirmed with surgical lung biopsy. During the median follow-up of 34.0 months, a total of 231 BAL procedures were identified. As shown in Fig. 1, thirty BAL procedures were performed after the onset of acute deterioration in order to rule out the possible complication of infection.

During the follow-up, 60 patients (53.6%) died. Causes of death were terminal respiratory failure in 25 cases, acute exacerbation in 24 cases, infection in 4 cases, lung cancer in 6 cases, and pneumothorax in 1 case. Among the 201 BAL procedures performed in patients with stable condition, four (2.0%) were followed by the onset of AE-IPF within a month (crude incident rate: 19.9 per 1000 person-months). The remaining 21 episodes of AE-IPF occurred in patients not at risk (crude incident rate: 4.8 per 1000 person-months). The risk ratio was calculated to be 4.12 (95%CI = 1.03–12.2, $p = 0.046$) (Table 2).

All patients except one underwent BAL procedures at the beginning of observation. None of the 111 initial BAL procedures were followed by AE-IPF within a month.

Table 1 Characteristics of patients enrolled.

Total case	112
Sex, male/female	91/21
Surgically proven UIP, *n* (%)	53 (47.3%)
Age at baseline	64 (60—69)
Follow-up period, m	34.0 (21.7—53.8)
Death, n (%)	60 (53.6%)
Acute exacerbation, n (%)	25 (22.8%)
Number of BAL procedures, per patient	1 (1-2)

Data are expressed as median (IQR), unless otherwise specified.

Therefore, we hypothesize that BAL performed as a second round or later procedure might be strongly linked to development of AE. We calculated the relative risk of developing AE-IPF after second or later BALs which were done in the course of IPF. The rate ratio was as high as 9.10 (95% CI = 2.27—26.98, $p = 0.0032$) (Fisher's exact test) (Supplemental Table1).

Summary of four cases of possible BAL-induced AE-IPF

Four patients in our cohort developed AE-IPF during the 30 days following BAL. All four patients were men with

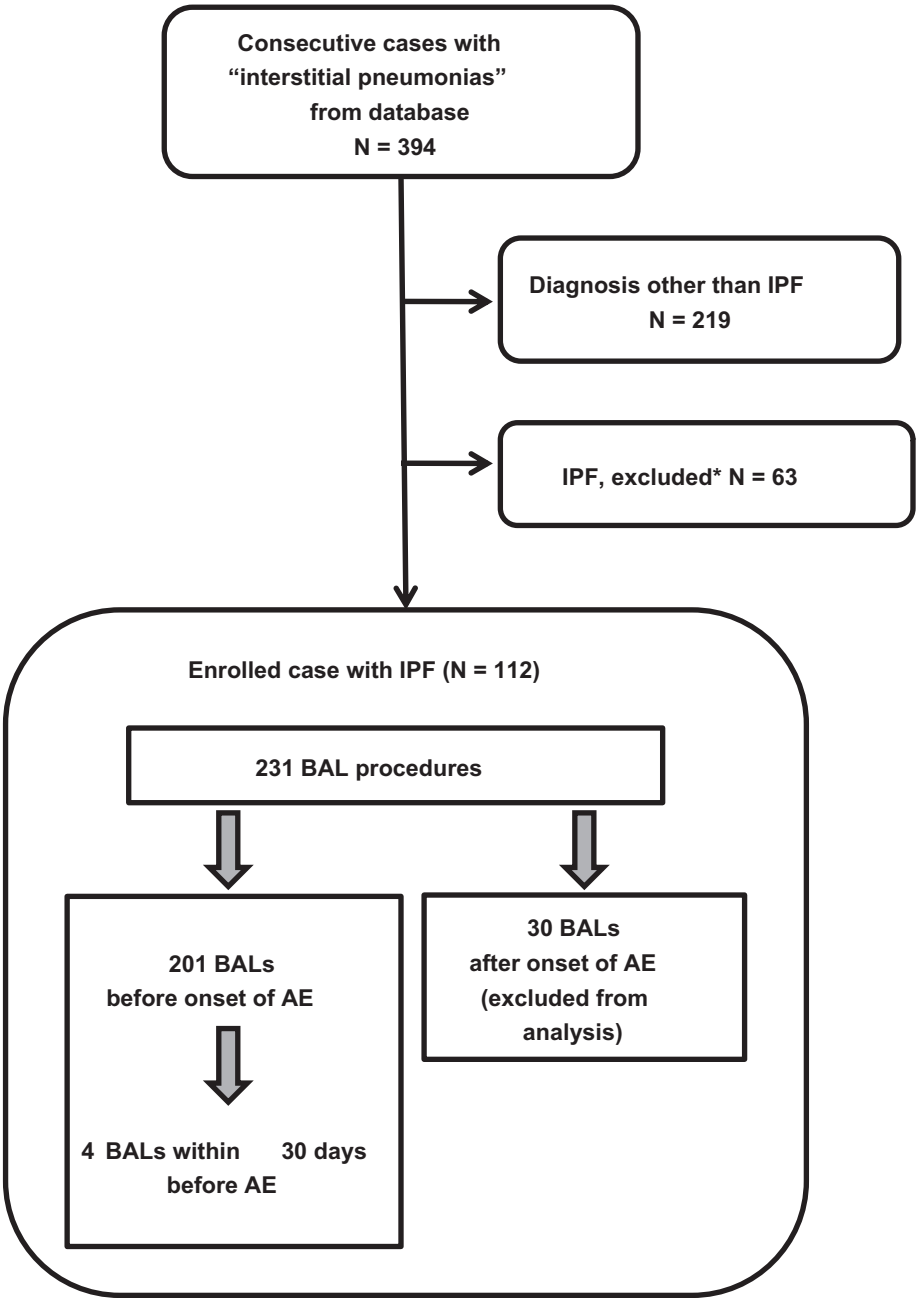

Figure 1 Analysis profile * reasons for exclusion were as follows: did not completely fulfill the predefined diagnostic criteria of IPF by retrospective reconfirmation in this study, follow-up periods were shorter than 6 months because of patient drop-out, and patient enrolled in investigational treatment with agents with unpublished risk of development of AE.

Table 2 Estimation of relative risk of AE-IPF during 30 days after BAL procedure.

	Event of AE	Person-months	Crude incident rate (event/person-month)
Post BAL (at risk)	4	201	0.0199
Not at risk	21	4344	0.0048
Relative risk 4.12 (95% CI = 1.03−12.2, $p = 0.046$) (Fisher's exact test)			

a smoking history. They had experienced bronchoscopy and BAL at least once prior to the causal BAL procedure. Development of AE-IPF was diagnosed 12−30 days after causal BAL. Diagnosis of AE-IPF was made with additional BAL in all four cases in order to exclude possible infection, and no viruses or microbes were detected. Treatment of AE was done with high-dose corticosteroids (pulse therapy), in some cases together with immunosuppressants and anti-coagulants. Only one patient successfully survived AE and was discharged from the hospital.

Review of the literature

We found 5 articles[9−11,19,20] reporting cases of BAL-induced acute exacerbation of IPF reported in the English or Japanese language literature. From a review of the details of cases with interstitial pneumonitis other than IPF, duplicate reports of the same case and cases with insufficient data were excluded. Finally, eight cases from four articles were identified. Combined with our 4 cases, the clinical details of the 12 detected cases of BAL-induced AE-IPF are summarized in Table 3. Among them, nine patients had decreased vital capacity (FVC $<$ 65% predicted value) and/or impaired gas diffusion capacity (DLco $<$50% predicted value) at the time of causal BAL. Seven patients had either elevated body temperature ($>$37° Celsius) or elevated serum C-reactive protein above the normal value. Six patients were treated with corticosteroids prior to causal BAL. The intervals between causal BAL and diagnosis of AE ranged from diagnosis immediately after the procedure to 41 days. Treatment for AE was done with high doses of corticosteroids in all cases except one, in which treatment was with antibiotics only and the patient recovered from AE. In the end, only four of 12 patients survived the AE that developed after a BAL procedure.

Discussion

In the present study, we demonstrated an increased risk of acute exacerbation of IPF after BAL procedures in our cohort. During the 30 days following a BAL procedure, the risk for AE-IPF was estimated to increase about 4-fold. It is also worth noting that no AE-IPF was experienced after BAL procedures done for an initial diagnosis, and therefore subsequent BAL procedures were estimated to be a higher risk. In addition, possible denominators of AE-IPF following BAL were indicated from analysis of pooled cases that included the four cases from our cohort and eight from the literature review. We should beware of the possibility that BAL may predispose IPF patients to the development of AE, and carefully consider its indication on the basis of individual cases.

To our knowledge, this was the first study to evaluate the risk from BAL for the onset of AE-IPF in terms of the temporal relationship. Several reports have described cases of acute deterioration of idiopathic interstitial pneumonias including IPF, as shown in Table 3. A recent systematic review[13] citing these reports, also mentioned the possibility that BAL may become a trigger of AE-IPF. However, previous studies could not quantify the relative risk of BAL in triggering acute exacerbation because of the lack of sufficient information on the population and/or period of observation.

In our cohort the diagnosis of IPF was made in accordance with ATS/ERS classification.[14] Patients were carefully examined if they met criteria for other disease entities. Furthermore, diagnosis of AE-IPF was made with certainty according to the criteria described above. In our cohort the 1-year frequency of AE was estimated to be 6.3%, which was consistent with previous reports that demonstrated the 1-year frequency is around 5−10%.[11,16]

Focusing on the condition at the time when AE-IPF after BAL occurred, it is worth noting that none of the patients developed AE after the BAL procedures done for initial evaluation. To determine whether there are any common factors, we examined the clinical characteristics of 12 pooled cases with AE-IPF following BAL from our cohort and the previous literature. A previous study[21] gave the following three features as evidence of objective impairment for classifying the severity of disease: (1) FVC $<$ 65%, (2) desaturation with exertion, (3) DLco $\leq$ 50%. By adopting these criteria, we tried to classify the severity of functional impairment of eleven cases whose pulmonary function data just before BAL were available. Although we could not retrieve the data on exertional desaturation, 9 out of 11 cases were classified as having at least "moderate" or "severe" impairment. Similarly, marginal hypoxemia (less than 70 torr in PaO_2) was observed in 7 out of 12 cases. The patients who developed AE after BAL tended to have certain functional impairment before BAL procedures. This is compatible with recent studies evaluating risk factors for AE-IPF that reported low FVC is a significant predictor of AE-IPF.[17,22] Another noteworthy aspect is the "unstableness" of the disease. Elevated CRP level ($>$1 mg/dL) and/or increased WBC count ($>$9000/mm^3), which is unusual with stable IPF, were observed in six cases. Increased neutrophils in BALF ($>$10%) were identified in 2 other cases. Moreover, 6 out of 12 patients had received corticosteroid treatment before AE, which was possibly aimed at halting the accelerated progression of the disease. These results suggest the possibility that, in at least some of the cases, insidious infection or deterioration of the disease may exist before BAL, rather than that BAL itself causes AE. A recent report that demonstrated disease progression, defined by at least a 10% decline in FVC, was a risk factor for AE-IPF

Table 3 Cases in which acute exacerbation of IPF developed after BAL: Summary of our cohort and literature review.

Reference	At the time of BAL							Concomitant medication	BAL to AE (day)	BAL findings				Tx post AE	Prognosis	Pathologic Dx
	Sex/ Age	Smoking	%VC/ %DLco	Pa02	BT	CRP	WBC			TCC	Ne	Ly	Eo			
				Torr	C	mg/dL	/mm^3			10^6/ml	%	%	%			
Our institution	51/M	+	44/57	65.7	36.5	1.6	2800	CS	18	1.4	4	1.7	0.3	Pulse	Died 47d after BAL	UIP/DAH
	68/M	+	46/38	75.8	36.3	0.4	6800	CS	15	9.9	0.3	3	0.2	Pulse, CyA, LMH	Died 26d after BAL	UIP
	64/M	+	75/20	51.0[†]	38.5	4.6	15100	Abs	12	16	0.8	0.2	0.2	Pulse, CyA	Survived AE	−
	70/M	+	63/40	68.5	afebrile	0.1	5600	CS	30	1.3	0.2	0.3	0.3	Pulse, LMH	Died 80d after BAL	UIP
Yoshitomi	54/F	−	43/n.a.	77.3	37.4	0.6	6100	Abs	0	1.3	6.5	5.4	1.5	Pulse, CPA	Died 34d after BAL	UIP+DAD
et al.(16)	75/M	+	n.a. / n.a.	63.5[‡]	38	(3+)	9800	none	0	2.7	35	8.8	2.8	Only Abs	Survived AE	−
Suga et al.(10)	67/M	+	60/31	65	36.7	0.1	8700	CS	41	10	11	46	0	Pulse	Died 17d after BAL	DAD
	57/M	+	53/16	61.3	35.9	6.7	13800	CS	3	10	4.8	2.6	0	Pulse	Died 6d after BAL	−
Hiwatari	74/M	−	60/n.a.	82	afebrile	(−)	n.a.	CS	n.a.	1.5	4	10	0	Pulse, PSL	Died 18d after BAL	UIP?
et al.(9)	66/M	+	65/41	65	afebrile	(+)	n.a.	none	n.a.	0.8	30	2	1	Pulse, PSL	Died 104d after BAL	UIP+DAD
	79/F	−	99/58	80	afebrile	1	n.a.	none	n.a.	5.6	2	3	3	Pulse, PSL	Died 56d after BAL	UIP?
Ohtsuka et al.(17)	74/M	+	97/52	84.1	afebrile	0	6600	none	7	n.a	14	31	2	Pulse, Abs	Survived AE	−

BT: body temperature, WBC: white blood cell count, previous BAL: number of BAL procedures done before, TCC: total cell counts, Ne: neutrophils; Ly: lymphocytes, Eo: eosinophils, CS: corticosteroids, Pulse: corticosteroid pulse therapy, d: day, CyA: cyclosporine A; LMH: low molecular weight heparin, CPA: cyclophosphamide, Abs: antibiotics, UIP: usual interstitial pneumonia pattern, DAH: diffuse alveolar hemorrhage, DAD: diffuse alveolar damage pattern, n.a.: not available.

[†] Assessed under 3 L/min of supplemental oxygen via nasal prongs.

[‡] Assessed under FiO_2 at 0.25.

supports this speculation.[17] Considering that the relative risk of developing AE after second or later BAL procedures was estimated to be considerably higher (although in a *post hoc* analysis), patients should be more carefully monitored after BAL performed during the course of IPF than after BAL performed in initial evaluation.

There is some speculation on the possible mechanism responsible for the development of AE-IPF after BAL. The first is that BAL might spread subclinical infection in the lower respiratory tract. In cases of IPF, especially with administration of corticosteroids and/or immunosuppressants for its management, it is possible that certain pathogens colonize the lower respiratory tract of the patients and that many of these immunosuppressed patients fail to develop typical clinical signs. Contamination by pathogens or endotoxins through working channels of bronchoscopes is also possible.[22,23] In our series, however, no pathogen or endotoxin was detected from BAL fluid obtained at the diagnosis of AE-IPF.

Another speculation is that saline lavage itself may cause lung injury. Repeated bronchoalveolar lavage with saline has been utilized in making an animal model of acute lung injury.[24,25] Lavage with saline reduces the surfactant lipid concentration in alveolar lining fluids, altering alveolar surface tension. Decreased alveolar tension may facilitate alveolar collapse and increase the likelihood of mechanical injury to the alveolar walls during ventilation. Impaired alveolar host defenses caused by decreased surfactant proteins also may predispose patients to lung injury. In patients with pulmonary fibrosis or even in healthy subjects, there is evidence that proinflammatory cytokines such as IL-1-β and TNF-α increase in serum or BAL fluid after BAL procedure.[26,27]

This study has some limitations. It was based on a retrospective cohort from a single institution which includes only Asian patients. Ethnic differences in the incidence of pulmonary disease have been observed and ethnic difference in the susceptibility to AE-IPF is also suggested.[28] It is unclear whether the present results can be adapted to other populations, especially to other ethnic groups. Multicenter- multiregional- prospective studies are warranted to eliminate ethnic bias and other possible bias. Moreover, whether there was causal association between BAL and onset of AE-IPF could not be determined because the current study evaluated the temporal relationship only.

Although we acknowledge that other confounding factors exist (e.g. unrevealed infections, change in medications, patients' baseline characteristics), other risk factors for the development of AE-IPF remain largely unknown. In the context that confounders were assumed to be impossible to eliminate, we believe it is still of value to specify the relative risk within 30 days after BAL procedures.

In this study we adopted revised Japanese criteria in diagnosing AE-IPF. The AE/IPF criteria are different in the other studies, though they are largely similar. One of the reasons is the current official ATS/ERS/JRS/ALAT guideline of IPF did not define the criteria of AE.[29] Because development of acute exacerbation is being recognized as one of the most important outcomes in patients with IPF, further investigation is warranted to unify the AE-IPF criteria internationally in order to clarify the epidemiology of AE-IPF.

In summary, we investigated the temporal relationship between bronchoalveolar lavage and development of acute exacerbation in idiopathic pulmonary fibrosis. About a 4-fold increased risk of AE within 30 days after BAL was observed during the follow-up of 112 IPF patients and risk was estimated to be greater with BAL procedures done in second or later rounds in the course of the disease. Since many confounding factors may be present in the clinical setting, it remains uncertain whether BAL predisposes patients to the development of AE-IPF. Although further large-scale prospective studies are warranted for firm conclusions, our current results suggest that IPF patients should be carefully monitored after a diagnostic BAL procedure.

Conflicts of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript. All authors deny any other forms of conflict of interest to be declared regarding the current manuscript.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.11.006.

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