Which algorithm diagnoses invasive pulmonary aspergillosis best in ICU patients with COPD?

To the Editor:

Invasive pulmonary aspergillosis (IPA) is a potentially lethal opportunistic infection, mainly affecting immunocompromised patients, particularly those with prolonged neutropenia [1]. Several reports have shown that *Aspergillus* spp. can also cause IPA in patients with *a priori* less severe immune dysfunction, such as those in intensive care units (ICUs) [2–5] or with chronic obstructive pulmonary disease (COPD) [5–8]. In these patients, diagnosis of IPA remains a challenge, because the reference diagnostic criteria (defined by the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG)) were developed for research in high-risk patients and not specifically for patients in the ICU or patients with COPD [9]. Two alternative algorithms have been proposed for this setting: the COPD algorithm for patients with COPD [6] and the Clinical algorithm for patients in the ICU [10].

We compared the three algorithms to evaluate which of them is the most accurate for classifying critically ill patients with COPD and *Aspergillus*-positive cultures.

This study was part of the *Asp*ICU project [11], focusing on patients with COPD and *Aspergillus*-positive lower airway cultures. Collected data included demographics, clinical features, cultures, radiological findings (suggestive of IPA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [12].

Using the COPD [6], Clinical [10] and EORTC/MSG [9] algorithms, patients were classified as having proven IPA, putative/probable IPA or colonisation. None of the patients could be classified as having "possible" IPA (as defined by the COPD and EORTC/MSG algorithms) because this requires negative cultures and all the patients in *Asp*ICU had at least one positive culture.

The validity of the algorithms was assessed against histological results when available. Algorithm sensitivities and specificities were compared using McNemar's Chi-squared test with continuity correction. The validity of diagnostic signs from the Clinical algorithm was also assessed; both putative and proven diagnoses were considered as IPA for this analysis. The Chi-squared test was used to rule out the hypothesis that diagnostic signs and Clinical algorithm results were independent. Statistical analyses were performed using R software (version 3.1.2; R Core Team, Vienna, Austria), and $p<0.05$ was considered significant.

The *Asp*ICU study included 563 patients in the ICU [11], of whom 174 (31%) had COPD. To obtain a more homogenous cohort, 32 patients were not included in this analysis (no lung involvement (n=5); insufficiently documented COPD diagnosis (n=6); neutrophil count <500 per μL (n=2); solid organ transplantation (n=12); immunosuppressive medication (n=9); chemotherapy (n=3); leukaemia (n=3) and myelodysplastic syndrome (n=3)), leaving a total of 142 patients. The patient classifications according to the three algorithms are shown in table 1.

Using the COPD, Clinical and EORTC/MSG algorithms, mechanical ventilation was found to be required in, respectively, 26 out of 50, 39 out of 71 and 17 out of 25 patients with proven or probable/putative IPA compared with 1 out of 53, 6 out of 71 and 28 out of 117 patients, respectively, with colonisation.

Histological results were available for 23 patients: 13 had IPA and 10 had colonisation. In eight patients, IPA was diagnosed only after death. Before the autopsy results, four patients were classified as having

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In ICU COPD patients, the Clinical algorithm seems to be more useful to diagnose IPA than the COPD or EORTC/MSG ones http://ow.ly/N2TN30e6Zur

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TABLE 1 Final diagnosis and validity values using the three algorithms

Diagnosis	GOLD stage					All COPD cases			
	I (3)	II (38)	III (23)	IV (47)	Unknown (31)	Sensitivity	Specificity	PPV	NPV
COPD algorithm						54%	70%	70%	54%
Proven (13)	1	3	2	6	1				
Probable (37)	0	0	11	26	0				
Colonisation (53)	2	15	7	10	19				
Inconclusive (39)	0	20	3	5	11				
Clinical algorithm						85%	70%	79%	78%
Proven (13)	1	3	2	6	1				
Putative (58)	0	15	8	26	9				
Colonisation (71)	2	20	13	15	21				
EORTC/MSG algorithm						23%	80%	60%	44%
Proven (13)	1	3	2	6	1				
Probable (12)	0	2	0	10	0				
Colonisation (117)	2	33	21	31	30				

The numbers in parentheses are the total number of patients in each category. COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; EORTC/MSG algorithm: European Organization for the Research and Treatment of Cancer/Mycosis Study Group; PPV: positive predictive value; NPV: negative predictive value.

probable IPA and four as inconclusive using the COPD algorithm, while seven were classified as having putative IPA and one as having colonisation using the Clinical algorithm, and all eight were classified as having colonisation using the EORTC/MSG algorithm. Sensitivity, specificity and predictive values for the three algorithms are shown in table 1 (inconclusive diagnoses were classified as colonisation for these calculations). Overall, the diagnosis was correct (true positive or true negative) in 19, 12 and three cases using the Clinical, COPD and EORTC/MSG algorithms, respectively. The Clinical algorithm was more sensitive than the EORTC algorithm ($p=0.013$), while the sensitivity of the COPD algorithm was not significantly different from those of the other algorithms ($p=0.13$). The specificities of the three algorithms were not statistically different ($p=1$).

We also analysed the validity values of the clinical and radiological criteria from the Clinical algorithm to diagnose proven/putative IPA. Mechanical ventilation ($p=0.0001$) and nodules on chest radiograph ($p=0.0364$) were most predictive of IPA, while absence of abnormalities on chest radiograph essentially excluded a diagnosis of IPA ($p=0.0001$). IPA-suggestive abnormalities on chest computed tomography scan were not significantly predictive of a diagnosis of IPA.

Before the histological results, GOLD II patients who fulfilled the criteria for probable IPA could not be classified using the COPD algorithm; this was the case for seven patients, of whom two had IPA confirmed histologically. Using the Clinical and EORTC/MSG algorithms, these cases would have been classified as putative (six out of seven) or probable (two out of seven), respectively. 16 other GOLD II patients were classified as inconclusive because several criteria were missing and none was receiving steroids (autopsy-confirmed IPA in one patient). Using the Clinical algorithm, seven of these 16 cases would have been classified as having putative IPA, while all would have been classified as having colonisation using the EORTC/MSG algorithm.

Patients with COPD are at risk of developing IPA [5–8]. However, use of biopsy to confirm diagnosis remains challenging in patients who are mechanically ventilated [13, 14]. For patients in the ICU with COPD and *Aspergillus*-positive respiratory tract cultures, we compared three algorithms that have been proposed to discriminate colonisation from IPA. Comparisons in the 23 patients with histological data showed that a correct diagnosis was more often obtained using the Clinical algorithm, followed by the COPD algorithm and finally the EORTC/MSG algorithm. Interestingly, even GOLD II patients treated with steroids are at risk of developing IPA.

One of the algorithms is specific for patients with COPD [6] whereas the others [9, 10] are not. Moreover, the EORTC/MSG algorithm [9] has been validated only in immunocompromised patients, and patients in the ICU with COPD rarely meet the EORTC/MSG host factor criteria [9, 15]. Recently, Blot *et al.* [11] reported that more cases of IPA in patients in the ICU were diagnosed using the Clinical algorithm than using the EORTC/MSG criteria, primarily because host factors were often not present in these patients. Our data confirm that patients are more often classified as having proven/putative IPA by the Clinical

than by the EORTC/MSG algorithm. With both the COPD and EORTC/MSG algorithms, some patients could not be classified; for the former because colonisation criteria were not met or they were not GOLD III or IV (leading to 39 patients considered as inconclusive), and for the latter because COPD is not recognised as a host risk factor (leading to 116 patients being considered as having colonisation).

Among the 38 GOLD II patients, 15 were classified as having colonisation using the COPD algorithm, and 23 had inconclusive results. Among these patients, seven had the same features, clinical signs, mortality rate and radiological findings as the proven/probable IPA group; interestingly, two of these patients were shown histologically to have IPA.

Our study limitations include the absence of a strict procedure to diagnose IPA and the limited number of histological specimens. However, the patients were carefully reviewed, the study was performed in 30 centres from eight countries, and the Clinical algorithm has been validated recently [11]. Moreover, inclusion of histopathology-controlled cases allowed comparisons before and after histopathological results; for example, concordance was 89% using the COPD algorithm (data not shown). Another limitation is that our conclusions are only valid for patients with *Aspergillus*-positive cultures.

For patients in the ICU with COPD and *Aspergillus*-positive culture, the Clinical algorithm is more appropriate than the EORTC/MSG algorithm to discriminate IPA from colonisation. The COPD algorithm is less useful because of the numbers of inconclusive cases. IPA should be considered in patients with COPD, especially in those receiving systemic steroid therapy and who have a positive *Aspergillus* culture, respiratory failure and an abnormal chest radiograph, regardless of GOLD stage.

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