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1 **Factors associated with coinfections in invasive aspergillosis: a retrospective cohort study**

2

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44 † Prof. Ermanno Candolfi is deceased (in 2019).

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49

50 **Running head:** Coinfections in invasive aspergillosis

51

52 Preliminary results have been presented as an oral communication at ECCMID 2019.

53

54 **Keywords:** Invasive Fungal Infections; Coinfections; Fungal; Leukaemia; Mortality; Risk Factors

55

56

57

58 **Abstract**

59 **Objectives:** To describe the coinfections in invasive aspergillosis, to identify factors associated with
60 coinfections and to evaluate the impact of coinfection on mortality.

61 **Patients and methods:** We conducted a monocentric retrospective study of consecutive putative,
62 probable, or proven invasive aspergillosis that occurred from 1997 to 2017. All coinfections, with
63 an onset within 7 days before or after the first sign of aspergillosis, were identified. Factors
64 associated with coinfections and mortality were analysed by multivariable analysis.

65 **Results:** Among the 690 patients with IA included in the study, median age was 57 years (range: 7
66 days-90 years). A coinfection was diagnosed in 272/690 (39.4%, 95%CI [35.8-43.2]) patients. The
67 location of this coinfection was pulmonary only in 131/272 patients (48%), bloodstream only in
68 66/272 patients (24%) and other/multiple sites in 75/272 patients (28%). Coinfections were
69 bacterial (n=110/272 patients, 40%), viral (n=58/272, 21%), fungal (n=57/272, 21%), parasitic
70 (n=5/272, 2%) or due to multiple types of pathogens (n=42/272, 15%). Factors associated with a
71 coinfection in adjusted analysis were: allogeneic haematopoietic stem cell transplantation (OR=2.3
72 [1.2-4.4]), other haematological malignancies (OR=2.1 [1.2-3.8]), other underlying diseases
73 (OR=4.3 [1.4-13.6]); lymphopenia (OR=1.7 [1.1-2.5]); C-reactive protein >180 mg/l (OR=1.9 [1.2-
74 3.0]); fever (OR=2.4 [1.5-4.1]); tracheal intubation (OR=2.6 [1.5-4.7]); isolation of ≥ 2 different
75 *Aspergillus* species (OR=2.7 [1.1-6.3]); and presence of non-nodular lesions on chest computed
76 tomography (OR=2.2 [1.3-3.7] and OR=2.2 [1.2-4.0]). Coinfections were independently associated
77 with a higher mortality at week 12 (adjusted HR 1.5 [1.1-1.9], $p < 0.01$).

78 **Conclusions:** Coinfections were frequent in IA patients and were associated with higher mortality.

79

80 **Introduction**

81 Invasive aspergillosis (IA) affects mostly severely immunocompromised patients. Despite
82 improvements in diagnosis and treatment, 12-week mortality exceeds 30% [1-6]. High rates of
83 coinfections have been described in patients with IA in a few studies. Georgiadou *et al.* showed
84 49% of documented pulmonary coinfections in 126 patients with haematological malignancy (HM)
85 and IA [7]. In another monocentric study in Israel, 21% of the HM patients had a polymicrobial
86 pneumonia diagnosed on bronchoalveolar lavage fluid (BALF) [8]. *Aspergillus* was the most
87 common pathogen identified (87%) and in-hospital mortality was higher in the coinfecting group.
88 Recently, IA occurring after influenza virus infections was shown to have a 50% mortality rate [9,
89 10]. Despite their high frequency, the risk factors for coinfections in IA and the impact on mortality
90 have not yet been well studied. Our aim was to describe the coinfections associated with IA in a
91 large cohort of patients with putative, probable or proven aspergillosis, to identify the factors
92 associated with coinfections and to analyse the mortality.

93
94 **Methods**

95 We conducted a retrospective study of consecutive IA cases that occurred in the University
96 Hospital of Strasbourg from 1997 to 2017. The study is part of a retrospective, non-interventional
97 study on opportunistic infections in immunosuppressed and frail patients. Institutional ethical
98 committee has approved the study. According to French regulations, the database has been
99 declared to the *Commission Nationale de l'Informatique et des Libertés*. The study has been
100 registered in ClinicalTrials.gov (NCT03920735). All patients alive were asked to give their consent
101 after receiving an information letter. In agreement with ethical committee recommendations,
102 informed consent was not requested from the relatives of patients who had died. Patients who

103 had been enrolled in a prospective epidemiologic, diagnostic, or therapeutic clinical trial at time of
104 their infection had all signed the appropriate informed consent form.

105 Suspected cases of IA were identified from the mycology laboratory database and from the
106 hospital diagnosis database. Selection process is detailed in supplementary material. Patients
107 included in a previous study on prognosis factors in IA are also part of this study [11]. Patients
108 were included if they had been diagnosed with IA meeting the updated European Organization for
109 Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria for proven or
110 probable IA in cancer and severely immunosuppressed patients [12] or the clinical algorithm for
111 putative IA in critically ill patients [13]. These criteria were modified by using a cut-off for
112 galactomannan index of ≥ 0.5 in serum or BAL, based on manufacturer's recommendations (Bio-
113 Rad, Marne-La-Coquette, France). Pulmonary IA were not included if no chest computed
114 tomography (CT) was available.

115

116 Date of first clinical, radiological or mycological sign attributed to IA was defined as Day 0 (D0). We
117 collected all variables available on D0 or at earliest time point around D0 with the exception of
118 mycological data that were collected over the full course of the IA to allow a definite diagnosis of
119 this infection. Two groups were considered and compared: IA without coinfection and IA with a
120 coinfection. A coinfection was defined by the presence of clinical and/or radiological signs of
121 infection and the identification of a relevant pathogen in significant amount, within 7 days before
122 or after D0 of IA [7]. Details and definitions appear in supplementary material [6, 7, 12, 14-16].

123

124 Categorical variables are described with numbers and percentages. For the study of factors
125 associated with coinfections, and as a patient could suffer several episodes of IA, comparisons
126 between groups were made using a mixed logistic regression model including a random patient

127 effect. All variables with a p-value <0.2 in univariate analysis (Table 1) were included in a
128 multivariable model. Continuous variables were dichotomized using clinically relevant thresholds.
129 Results are presented as odds ratios (OR) with their 95% confidence intervals (95%CI) calculated
130 using the Wald method. Multicollinearity was assessed using the variance inflation factor (VIF)
131 ensuring that no factor had a VIF greater than 2. The number of events per variable was greater
132 than 10. Goodness of fit of the multivariable logistic model was assessed using the Hosmer-
133 Lemeshow test. The rate of missing data was low (6.5% for multivariable model) and no
134 imputation method was used. The effect of coinfection on mortality was assessed using a
135 multivariable Cox regression model including a random patient effect. The adjustment variables
136 included in the multivariable model were those with a p-value <0.2 in univariate analysis.
137 Proportional hazards assumption was assessed using Schoenfeld residuals. Results are presented
138 as hazards ratios (HR). Confidence intervals were computed using a robust variance. A p-value
139 <0.05 was considered statistically significant. All analyses were performed using R software
140 version 3.6.0 (2019) (R Foundation for Statistical Computing, Vienna, Austria. URL [https://www.R-](https://www.R-project.org/)
141 [project.org/](https://www.R-project.org/)).

142

143 **Results**

144 **1) Global population characteristics**

145 Among 1075 suspicions of IA, we have identified 690 IA [549/690 (80%) probable, 29/690 (4%)
146 putative, and 112/690 (16%) proven] in 661 patients (Figure 1). Median age was 57 years (range 7
147 days - 90 years) and 65% (n=451/690) of patients were men (Table 1). Primary underlying diseases
148 and other predisposing factors are listed in Table 1.

149

150 Microscopy, culture, or histopathology was positive in 404/690 (59%) patients. Galactomannan
151 detection test was performed in serum in 678/690 (98%) episodes and was positive in 395/678
152 (58%). BAL was performed in 449 (69%) of the 651 lower respiratory tract IA. Galactomannan
153 detection test was performed in BALF in 396 episodes and was positive in 266/396 (67%) of them.
154 Overall BALF analysis (positive culture or galactomannan test) was the only mycological
155 documentation of IA in 121 (19%) of the 651 lower respiratory tract IA.

156

157 Site of IA was lower respiratory tract only, another single organ and disseminated in respectively
158 586/690 (85%), 28/690 (4%) and 76/690 (11%) cases. Among the 651 lower respiratory tract IA,
159 chest CT findings were nodule(s) only in 138/651 (21%) episodes, nodule(s) with other lesions in
160 329/651(51%) and other lesions without nodule in 174/651 (27%). Ten patients with endoscopy-
161 confirmed bronchial or tracheal lesions without lung involvement had a normal CT.

162

163 **2) Coinfections characteristics**

164 A coinfection was diagnosed in 272/690 (39%) episodes (Table 2). The site of coinfection was
165 pulmonary only in 131/272 patients (48%), bloodstream infection in 66/272 patients (24%) and
166 other or multiple sites in 75/272 patients (28%). Coinfection with bacteria only was identified in
167 110/272 patients (40%), viruses in 58/272 (21%), fungi in 57/272 (21%) and parasites in 5/272
168 (2%). In 42/272 cases (15%), ≥ 2 different types of copathogens were involved. The descriptions of
169 the pathogens involved in coinfections are presented in Table 2 and supplementary Table 2. The
170 proportion of BAL performed in lower respiratory tract IA with or without coinfection was similar
171 (72% (n=184/257) and 67% (n=265/394) respectively; p=0.26).

172 We stratified our data in two periods (<2009 and ≥ 2009), corresponding to the implementation of
173 multiplex respiratory virus PCR. After 2009, 158 coinfections in 347 (46%) IA patients were

174 documented compared to 114 in 343 (33%) IA before 2009 ($p < 0.01$) (Supplementary Table 1). Viral
175 coinfections were more frequently diagnosed after 2009 ($n = 66/347$; 19%) compared to before
176 ($n = 22/343$; 6%) ($p < 0.01$) whereas no differences were observed for other type of pathogens. Due
177 to these differences, the diagnosis period (< 2009 versus ≥ 2009) was entered in the multivariable
178 analysis.

179

180 **3) Factors associated with a coinfection**

181 Univariable analysis results appear in Table 1. In multivariable analysis, factors associated with
182 more coinfections were alloHSCT, other HM, the group of other underlying diseases, presence of
183 non-nodular lesions on CT, low lymphocyte count, high C-reactive protein levels, fever, tracheal
184 intubation and isolation of ≥ 2 different species of *Aspergillus*. (Table 3). Age > 65 years was
185 associated with a lower rate of coinfection.

186

187 **4) Impact of coinfections on survival**

188 Survival in the global population was 56% ($n = 306/690$ deaths) at week 12 and 35% ($n = 446/690$
189 deaths) at 1 year (Figure 1). Twelve-week survival rate was 46% ($n = 146/272$ deaths) in patients
190 with a coinfection compared to 62% ($n = 160/418$ deaths) in patients without coinfection (Figure 2).
191 In univariable analysis, coinfection with bacteria (HR 1.4, 95% CI [1.02–1.9], fungi (HR 1.8 [1.2–2.6],
192 parasites (HR 5.8 [2.8–12.1]) or ≥ 2 types of copathogens (HR 2.9 [2.0–4.2]), but not viral
193 coinfection (HR 1.0 [0.7–1.6]), had higher risk of death compared to the absence of coinfection.
194 Pulmonary (HR 1.4 [1.03–1.8]), bloodstream (HR 1.6 [1.1–2.3]) and other/multiple sites (HR 2.2
195 [1.6–3.0]) were also associated with an increased risk of death compared to no coinfection. In
196 multivariable analysis, coinfection was independently associated with a higher twelve-week

197 mortality (adjusted HR 1.5 [1.1–1.9], $p < 0.01$). Other factors associated with mortality are in
198 Supplementary Table 3.

199

200 **Discussion**

201 We described a large case series of putative, probable, or proven IA over 21 years in a tertiary care
202 centre. We documented a high rate (39%) of coinfections with a broad spectrum of copathogens.
203 Coinfections were associated with increased mortality at week 12. We identified factors
204 associated with coinfections.

205

206 This study describes one of the largest monocentric cohort of IA ever published [17-19]. Our
207 analysis provides real-life data in non-selected patients with mycological documentation of IA.
208 Underlying conditions predisposing to IA cover a large spectrum of diseases, broader than usually
209 reported in randomised clinical trials which focus more on specific subpopulations [1, 20-22]. As
210 expected, HM and HSCT or SOT are predominant conditions predisposing to IA. However, we also
211 identified cases in patients with non-classical risk factors such as systemic autoimmune or
212 inflammatory diseases, liver failure, trauma, surgery, chronic pulmonary disease, aspiration
213 pneumonitis, near-drowning, and prematurity. More than half of these latter patients have
214 received steroids or other immunosuppressive drugs or were neutropenic. Distribution of
215 underlying conditions are in accordance with the multicentre surveillance study conducted
216 between 2005 and 2007 in France with, however, a higher proportion of SOT in our cohort due to
217 the large SOT activity in Strasbourg [23].

218

219 We identified that 39% of IA cases in this global population had concomitant coinfections. BAL was
220 performed in 69% of the patients with a lower respiratory tract involvement. This rate is high

221 compared to published data and facilitated the identification of pulmonary coinfections in our
222 cohort [24, 25]. These data confirm the critical role of BAL in the investigation of pulmonary CT
223 abnormalities in immunocompromised patients: it improved the accurate diagnosis rate of
224 pulmonary IA with one in five cases diagnosed by BALF analysis only and identified copathogens.

225

226 Our results on the prevalence of coinfections are in concordance with those found in specific
227 populations. Georgiadou *et al.* showed that 62 (49%) of the 126 patients with HM diseases had
228 documented pulmonary coinfections [7]. Bacteria and viruses were also the most frequent
229 copathogens in their cohort. Even higher rates of coinfections (65% and 70%) have been reported
230 in two paediatric series IA [26, 27]. Two autopsy series respectively over a 15-year period (1989-
231 2003) and 20-year period (1989-2008) have shown 42% and 46% of bacterial and fungal
232 coinfections [28, 29]. The impact of influenza virus infections on both the occurrence of IA and the
233 outcome has been recently highlighted [9, 10].

234

235 In our study, we have included all coinfections irrespective of their location. Although the type of
236 coinfections and the copathogens were therefore heterogeneous, it reflects real-life and
237 underlines the severity of immunosuppression in patients developing IA. The proportion of viruses
238 increased after the use of multiplex PCR in respiratory samples, notably in BALF.

239

240 Interestingly, we were able to identify factors that were associated with coinfections and that may
241 help practitioners to identify these coinfections. Among underlying diseases, alloHSCT, other HM
242 and other underlying diseases were associated with increased rates of coinfection compared to
243 acute leukaemia patients. The lower risk in acute leukaemia patients may be explained by the

244 environmental protective methods, antimicrobial prophylaxis and early empiric antibacterial
245 therapy in these patients.

246

247 Age ≥ 65 years was a protective factor, which may be linked to less aggressive chemotherapy and
248 lower rate of alloHSCT in elderly patients. BAL was performed at the same frequency in patients
249 younger or older than 65 years (66% and 65% respectively). Paediatric studies reported rates of
250 coinfection up to 70% also suggesting lower age is more frequently associated with multiple
251 infections [27].

252

253 Among the other factors, tracheal intubation may be a gateway for multiple lung infections but
254 also a marker of disease severity. Low lymphocyte count reflects immunosuppression and might
255 favour the coinfections. The coinfections were more symptomatic with more frequent fever and
256 higher C-reactive protein levels. Chest CT patterns were associated with coinfections and should
257 be used as a red flag to suspect coinfections. Indeed, presence of non-nodular lesions such as
258 consolidations, micronodules, alveolar or interstitial infiltrates were more often associated with
259 coinfection than presence of nodules only.

260

261 A study conducted in Israel in HM patients with 21% of polymicrobial pneumonia, identified
262 alloHSCT and graft versus host disease as risk factors for polymicrobial infections [8]. Polymicrobial
263 infections were also more symptomatic with more dyspnoea, haemoptysis and required more
264 respiratory support. Another study focusing on coinfections in HM patients did not find any
265 difference in terms of subpopulation and radiological characteristics between patients with or
266 without coinfections [7]. In IA patients with fever, high C-reactive protein and pulmonary CT

267 showing other lesions than nodule(s), we suggest to actively search for coinfections to avoid delay
268 in treatments. BAL is the cornerstone for an appropriate identification of multiple pathogens.

269

270 Coinfections were independently associated with increased mortality in our study. Hospital
271 mortality was also higher in the polymicrobial group (49 versus 19%, $p < 0,001$) in the study
272 conducted in Israel [8]. In 67 patients with HM admitted to an intensive care unit in France for
273 acute respiratory failure related to IA, concomitant bacterial infections were documented in 24
274 (36%) patients and were associated with higher mortality [30].

275

276 There are limitations in our study. The analysis is retrospective over 21 years, and despite our
277 efforts to identify the IA cases, it is likely we have missed a few of them. Clinical practices in
278 diagnosis, classification and treatment have changed over year. We added the period of diagnosis
279 of IA (< 2009 and ≥ 2009) in the multivariable analysis to limit this bias. The EORTC/MSG
280 classification has been updated in 2019. We have therefore retrospectively validated the cases
281 with current criteria, modified by the use of a galactomannan cut-off above 0.5 according to
282 manufacturer's recommendations. While classification of putative, probable, proven IA is based on
283 strict criteria, the discrimination between bacterial coinfection and colonization is not always easy.
284 To reduce this risk, we only accepted results from quantitative cultures of BALF and endotracheal
285 aspirate and applied a cut-off of 10^4 CFU/ml and 10^5 CFU/ml, respectively. These cut-offs provide a
286 high specificity for community acquired, hospital acquired and ventilator associated pneumonia
287 [14-16]. Higher mortality in patients with co-infection may be explained by multiple factors
288 including the treatment of this coinfection. Unfortunately, we did not collect data on therapy of
289 the coinfection to assess its appropriateness. Finally, the monocentric design of the study limits its

290 extrapolation as the incidence and the diagnostic procedures for IA and coinfection might change
291 across different sites.

292

293 In conclusion, this analysis in a large and global cohort of patients with IA confirmed the high rate
294 of coinfections and their poor outcome. We identified factors associated with coinfection that
295 should act as warning for the clinician about this potential risk, to avoid treatment delay.

296

297 **Collaborators:**

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304 Toussaint, Anne Zilliox.

305

306 **Author's contribution:**

307 François Danion, Céline Duval, Raoul Herbrecht: **conception and design of the work, acquisition,**
308 **analysis, and interpretation of data; drafting of the work; final approval; agreement to be**
309 **accountable**

310 François Séverac: **analysis and interpretation of data; drafting of the work; final approval;**
311 **agreement to be accountable**

312 Julie Denis, Valérie Letscher-Bru, Marcela Sabou: **acquisition and interpretation of data; critical**
313 **review of the work; final approval; agreement to be accountable**

314 Philippe Bachellier, Ermanno Candolfi, Vincent Castelain, Raphael Clere-Jehl, Laurence Dillenseger,
315 Eric Epailly, Justine Gantzer, Blandine Guffroy, Yves Hansmann, Jean-Etienne Herbrecht, Pierre
316 Leyendecker, Pauline Le Van Quyen, Pierre-Olivier Ludes, Guillaume Morel, Bruno Moulin,
317 Catherine Paillard, Benjamin Renaud-Picard, Francis Schneider, Morgane Solis, Charles Tacquard,
318 Emilie Talagrand-Reboul, Francis Veillon, Marie-Pierre Ledoux, and Célestine Simand: **acquisition**
319 **of data; critical review of the work; final approval; agreement to be accountable**

320

321 **Conflict of interest:**

322 François Danion reports personal fees from Gilead outside the submitted work.

323 Justine Gantzer reports personal fees from Chugai and Ipsen outside of the submitted work.

324 Blandine Guffroy reports personal fees from Shire, outside the submitted work.

325 Yves Hansmann reports personal fees from Pfizer, MSD, and Astellas, outside the submitted work.

326 Guillaume Morel reports personal fees from Pfizer, outside the submitted work.

327 Benjamin Renaud-Picard reports personal fees from Elivie outside of the submitted work.

328 Marcela Sabou reports personal fees from Pfizer outside the submitted work.

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336 Herbrecht, Valérie Letscher-Bru, Pierre Leyendecker, Pauline Le Van Quyen, Pierre-Olivier Ludes,
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343

344

345

346 **Figure legends**

347

348 **Figure 1.**

349 Patient flow diagram

350

351

352 **Figure 2.**

353 Twelve-week probability of survival: (a) all patients; (b) according to the presence or not of a
354 coinfection; (c) according to the type of copathogen; (d) according to the site of coinfection.

355

356

Table 1. Characteristics of patients with and without a coinfection and factors associated with the presence of a coinfection in univariate analysis

	Coinfection		p value
	No (n=418)	Yes (n=272)	
Age, years, n (%)			0.05
≤40	66 (16%)	46 (17%)	
41-64	223 (53%)	165 (61%)	
≥65	129 (31%)	61 (22%)	
Sex, male, n (%)	271 (65%)	180 (66%)	0.72
Active or history of smoking, n (%)	206 (49%)	130 (48%)	0.58
Prior respiratory disease, n (%)	125 (30%)	79 (29%)	0.81
Primary underlying disease, n (%)			<0.01
Acute leukaemia	135 (32%)	50 (18%)	
Allogeneic HSCT	52 (12%)	46 (17%)	
Autologous HSCT	24 (6%)	9 (3%)	
Other haematological malignancy ^a	87 (21%)	69 (25%)	
Immunologic or benign haematological disease ^b	23 (6%)	16 (6%)	
Solid organ transplantation	67 (16%)	49 (18%)	
Solid tumour	20 (5%)	16 (6%)	
Other ^c	10 (2%)	17 (6%)	
Diabetes mellitus, n (%)	84 (20%)	67 (25%)	0.16
T-cell immunosuppressant, n (%)	142 (34%)	96 (35%)	0.72
Systemic steroids, n (%)	207 (50%)	151 (56%)	0.13
Previous invasive aspergillosis episode, n (%)	26 (6%)	21 (8%)	0.44
Antifungal prophylaxis, n (%)	211 (50%)	108 (39%)	<0.01
Antibiotics, n (%)	277 (66%)	182 (67%)	0.86
Fever ≥38.5, n (%)	305 (76%)	215 (83%)	0.02
Tracheal intubation, n (%)	38 (9%)	64 (24%)	<0.01
Neutrophils <500/μl, n (%)	225 (54%)	122 (45%)	0.02
Lymphocytes (/μl), n (%)			0.18
<500	216 (52%)	158 (58%)	
500-4000	182 (44%)	99 (36%)	
>4000	20 (5%)	15 (6%)	
Monocytes <100/μl, n (%)	206 (49%)	123 (45%)	0.30
C-reactive protein >180 (mg/l), n (%)	77 (19%)	76 (29%)	<0.01
Fibrinogen ≥5 (g/l), n (%)	242 (59%)	133 (50)	0.03
Creatinine clearance <50 (ml/min), n (%)	79 (19%)	69 (26%)	0.05
Chest CT, n (%)			<0.01
Nodule(s) only	105 (25%)	33 (12%)	
Nodule(s) with other lesion(s) ^d	188 (45%)	141 (52%)	
Other lesion(s) ^d without nodule	92 (22%)	82 (30%)	
Extra-pulmonary invasive aspergillosis ^e	33 (8%)	16 (6%)	
Pleural effusion	166 (40%)	139 (51%)	<0.01
Isolation of <i>Aspergillus species</i> , n (%)			<0.01
None	207 (50%)	105 (39%)	
<i>Aspergillus fumigatus</i> complex	170 (41%)	127 (47%)	
Other <i>Aspergillus</i> sp.	28 (7%)	19 (7%)	
≥2 different <i>Aspergillus</i> sp.	13 (3%)	21 (8%)	
Galactomannan in serum			0.67
Positive	245 (59%)	150 (55%)	
Negative	166 (40%)	117 (43%)	
Not done	7 (2%)	5 (2%)	

Table 1 (continued)

Galactomannan in BALF			0.70
Positive	156 (37%)	110 (40%)	
Negative	81 (19%)	49 (18%)	
Not done	181 (43%)	113 (42%)	
Proven invasive aspergillosis, n (%)	69 (17%)	43 (16%)	0.81
Site of invasive aspergillosis, n (%)			0.23
Lower respiratory tract only ^e	360 (86%)	226 (83%)	
Other single sites	17 (4%)	11 (4%)	
Disseminated	41 (10%)	35 (13%)	
Diagnosis after the year 2009, (%)	189 (45%)	158 (58%)	<0.01

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Abbreviations: BALF: bronchoalveolar lavage fluid; CT: computed tomography; HSCT: haematopoietic stem cell transplantation.

^a Lymphoma, chronic lymphocytic leukaemia, multiple myeloma, chronic myeloproliferative neoplasm, non-transformed myelodysplastic syndrome.

^b Systemic auto-immune or inflammatory diseases (13), aplastic anaemia (6), other auto-immune or toxic cytopenia (7), inherited immune deficiency (5), HIV infection (4), other acquired immune deficiency (2), macrophage activation syndrome (2).

^c Trauma or post-surgery (7), liver failure (6), chronic pulmonary disease (5), aspiration pneumonitis (3), near-drowning (2), prematurity (2), diabetes (1), steroid therapy for chronic sinusitis (1).

^d Other lesions included consolidations, ground-glass opacities or micronodules.

^e Ten patients had only endoscopy-confirmed bronchial or tracheal lesions with normal chest CT.

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Table 2. Copathogens and sites of the coinfections in 272 episodes of invasive aspergillosis

Characteristics	Number (%)
Sites of coinfections ^a	272 (100%)
Pulmonary only	131 (48%)
Bloodstream only	66 (24%)
Other or multiple sites	75 (28%)
Types of coinfections ^a	272 (100%)
Bacterial coinfection only	110 (40%)
Viral coinfection only	58 (21%)
Fungal coinfection only	57 (21%)
Parasitic coinfection only	5 (2%)
≥2 types of coinfection	42 (15%)
Pathogens involved in coinfections ^a	378 (100%)
Bacteria	178 (47%)
<i>Staphylococcus aureus</i>	17 (4%)
Coagulase-negative staphylococci	26 (7%)
<i>Streptococcus</i> and <i>Enterococcus</i>	28 (7%)
<i>Escherichia coli</i>	27 (7%)
<i>Klebsiella pneumoniae</i>	11 (3%)
Other enterobacteria	18 (5%)
<i>Pseudomonas aeruginosa</i>	23 (6%)
Other non-fermenting Gram-negative bacilli	9 (2%)
Other bacteria	13 (3%)
Mycobacteria	6 (2%)
Viruses	101 (27%)
Influenza virus	24 (6%)
Other respiratory viruses	33 (9%)
Cytomegalovirus	12 (3%)
Herpes simplex virus	21 (6%)
Other	11 (3%)
Fungi	89 (23%)
<i>Candida</i> spp.	26 (7%)
<i>Cryptococcus</i> spp.	4 (1%)
Other yeasts	2 (1%)
Mucorales	25 (7%)
<i>Fusarium</i> spp.	5 (1%)
<i>Scedosporium</i> spp.	4 (1%)
Other filamentous fungi	8 (2%)
<i>Pneumocystis jirovecii</i>	15 (4%)
Parasites	10 (3%)
<i>Toxoplasma gondii</i>	8 (2%)
<i>Plasmodium falciparum</i>	2 (1%)

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^a A patient could have more than one copathogen, more than one site of coinfection and more than one species of bacteria, virus or fungus.

378 **Table 3. Multivariable analysis of factors associated with coinfection**

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	OR	IC95	p value
Age (years)			
≤40	ref		
41-64	0.99	0.59–1.67	0.984
≥65	0.47	0.25–0.90	0.022
Underlying disease			
Acute leukaemia	ref		
Allogeneic HSCT	2.30	1.21–4.37	0.011
Autologous HSCT	1.10	0.44–2.78	0.836
Other haematological malignancy	2.12	1.17–3.84	0.013
Immunologic or benign haematological disease	1.95	0.78–4.84	0.153
Solid organ transplantation	1.04	0.45–2.37	0.929
Solid tumour	1.03	0.42–2.54	0.949
Other	4.28	1.35–13.55	0.013
Diabetes mellitus	1.05	0.67–1.66	0.823
Systemic steroids	0.98	0.64–1.49	0.918
Antifungal prophylaxis	0.77	0.50–1.17	0.217
Fever ≥38.5	2.45	1.45–4.12	<0.001
Tracheal intubation	2.64	1.47–4.72	0.001
Neutrophils <500/μl	0.82	0.51–1.34	0.434
Lymphocytes (/μl)			
500-4000	ref		
<500	1.67	1.11–2.50	0.014
>4000	1.74	0.73–4.17	0.210
C-reactive protein >180 mg/l	1.90	1.21–2.97	0.005
Fibrinogen ≥5 g/l	0.77	0.52–1.13	0.182
Creatinine clearance <50 ml/min	1.16	0.72–1.87	0.548
Chest CT-scan			
Nodule(s) only	ref		
Nodule(s) with other lesion(s)	2.23	1.34–3.71	0.002
Other lesion(s) without nodule	2.22	1.25–3.96	0.007
Extra-pulmonary invasive aspergillosis	1.60	0.65–3.99	0.309
Pleural effusion	1.19	0.81–1.74	0.388
Isolation of <i>Aspergillus species</i>			
None	ref		
<i>Aspergillus fumigatus complex</i>	1.08	0.71–1.65	0.720
Other <i>Aspergillus sp.</i>	1.33	0.62–2.83	0.465
≥2 different <i>Aspergillus sp.</i>	2.67	1.12–6.35	0.026
Diagnosis after the year 2009	1.88	1.26–2.80	0.002

380 Abbreviations: Abbreviations: BAL: bronchoalveolar lavage; CT: computed tomography; HSCT:

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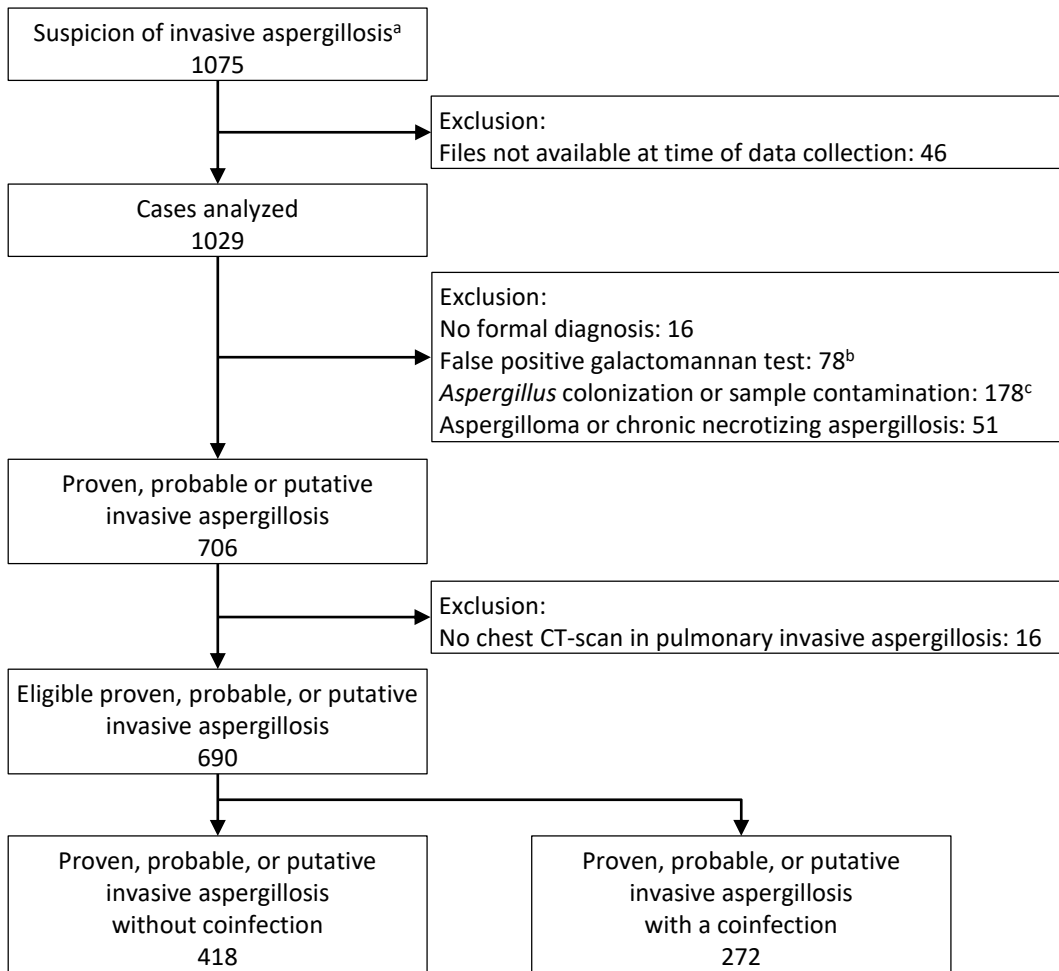
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^a based on a positive culture, galactomannan in serum, bronchoalveolar lavage fluid or cerebrospinal fluid, or PCR in serum, bronchoalveolar lavage fluid or tissue and at least one of the following condition : proven aspergillosis, presence of an host factor as defined by the EORTC /MSG criteria or hospitalized in an intensive care unit.

^b False positive galactomannan in serum (n=71) or in bronchoalveolar lavage fluid (n=7).

^c 185 species in 178 patients.

