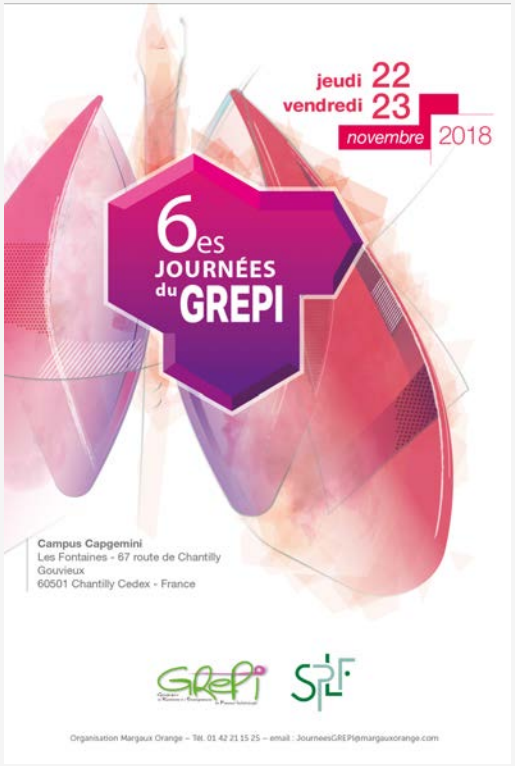


# Diagnostic indirect d'une infection fongique invasive

Fanny Lanternier
Service de maladies infectieuses
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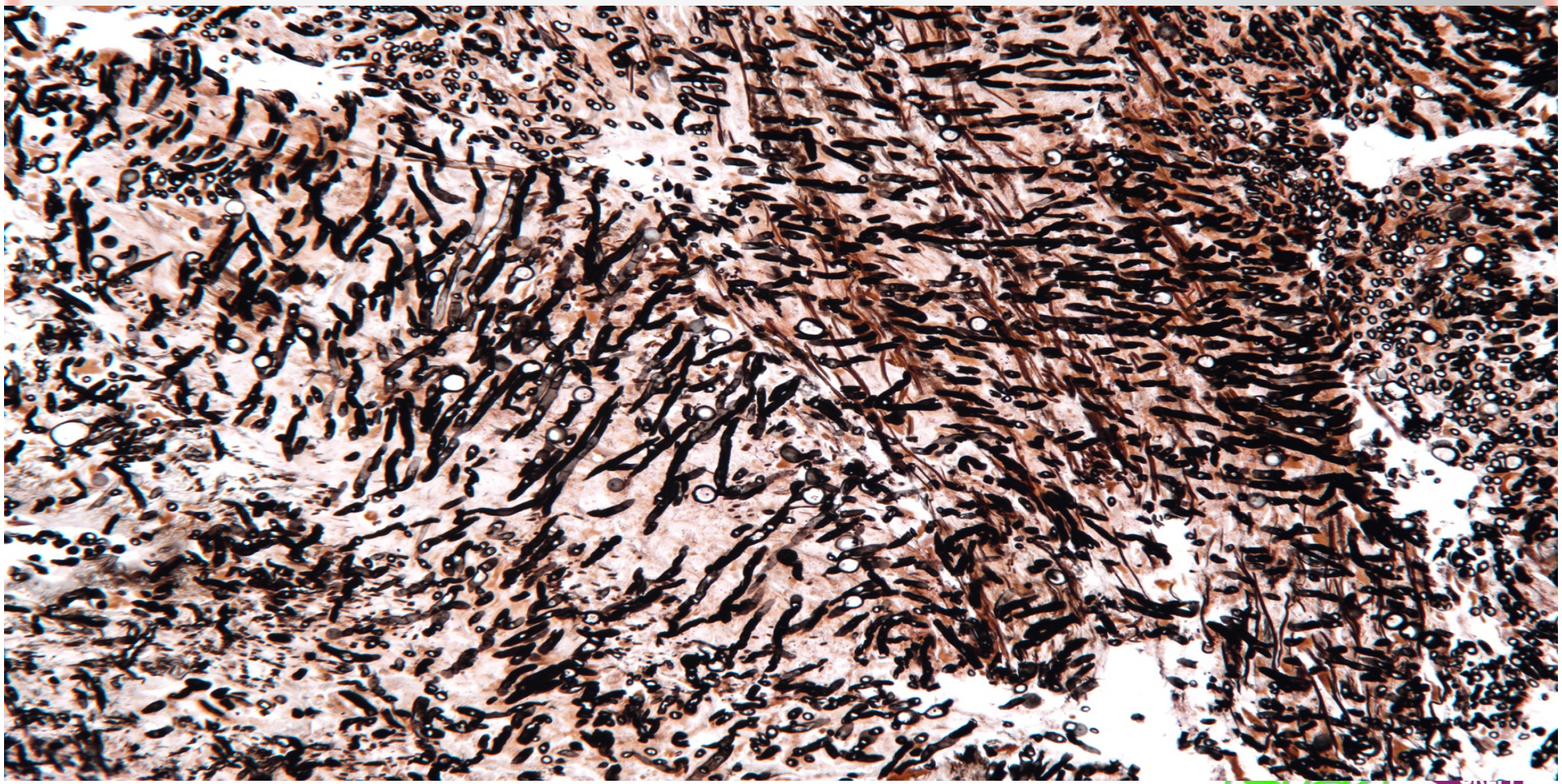
Université Paris Descartes
CNR Mycoses invasives et antifongiques
Institut Pasteur

# Cas

- Garçon 18 ans
- Lymphome lymphoblastique T
- Aplasie profonde fébrile le 17/09

- Biopsie: masse 24/10 envoyée en anatomopathologie: filaments.

- Appel pour décision thérapeutique



# Quels examens demandez-vous?

- Antigène GM serum
- Beta D glucane
- PCR Aspergillus
- PCR Mucorales
- Ag GM LBA

# Antigène galactomannane

- Polysaccharide cell wall
- Résultat de la croissance des filaments, non de sa lyse
- Présent dans:
  - *Aspergillus*
  - *Fusarium*
  - *Scedosporium*
  - *Alternaria*
  - *Histoplasma*
  - *Penicillium*
- Sérum, LBA, LCR

# Antigène galactomannane en hématologie

**Table 4. Laboratory evaluation of the 3 patient populations at the time of diagnosis of IPA**

| | Allogeneic HSCT (N = 23) | AL (N = 22) | Others* (N = 10) |
|---|---|---|---|
| **Serum GM antigen** | | | |
| Median (range) | 0.81 (0.02- > 10) | 0.36 (0.07-7.50) | 1.12 (0.06-8.85) |
| No./no. (%) tested ≥ 0.5 | 15/23 (65%) | 9/22 (41%) | 6/10 (60%) |
| **BAL GM antigen** | | | |
| Median (range) | 2.00 (0-9.80) | 1.00 (0.07-6.83) | 4.10 (0.13-6.12) |
| No./no. (%) tested ≥ 0.5 | 9/14 (64%) | 5/9 (56%) | 4/5 (80%) |
| **Positive samples, no./no. tested (%)†** | | | |
| None | 4/19 (21%) | 12/16 (75%) | 1/9 (11%) |
| BA | 12/17 (71%) | 2/11 (18%) | 6/7 (86%) |
| Direct examination only | 5 | 1 | 2 |
| Culture only | 0 | 0 | 0 |
| Direct + culture | 7 | 1 | 4 |
| BAL‡ | 9/17 (53%) | 2/13 (15%) | 5/6 (83%) |
| Direct only | 0 | 1 | 0 |
| Culture only | 3 | 0 | 2 |
| Direct + culture | 6 | 1 | 3 |
| Sputum | 9/12 (75%) | 2/4 (50%) | 4/4 (100%) |
| Direct only | 3 | 1 | 1 |
| Direct + culture | 6 | 1 | 3 |

Bergeron A, Blood 2012


# Beta D glucane

- Outil diagnostic:
  - Aspergillose
  - Candidoses invasives
  - Intérêt infections chroniques (candidoses hépatospléniques, endocardite, mycétome, otites malignes aspergillaires)
  - Pneumocystose

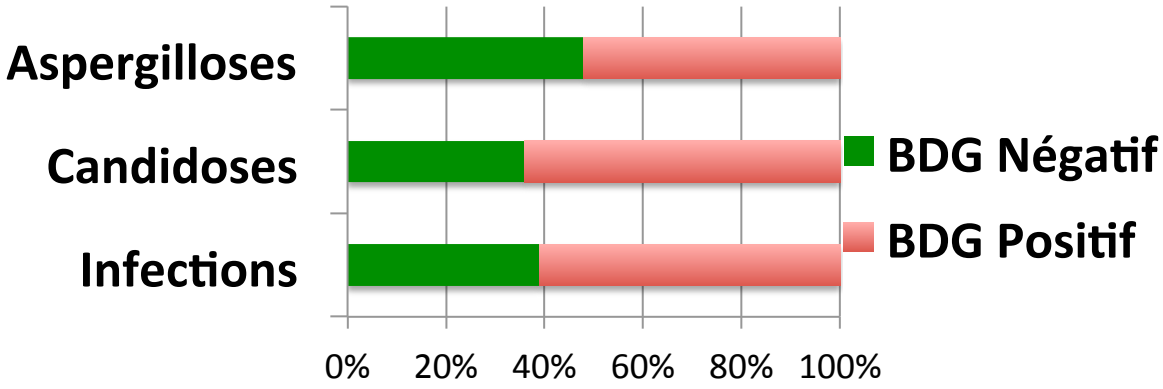
# Beta D glucane

Etude observationnelle monocentrique 2011-2015

143 patients
IFI prouvées/probables

45 pts AI

Pulmonaire
Cérébrale /Sinus
Osseuse




C. Angebault et coll. OFID 2016

# Beta D glucane et aspergillose hématologie

**TABLE 2** Performance of galactomannan and (1-3)-β diagnosis of invasive aspergillosis

| Variable | No. (%) | |
|---|---|---|
| | IA[a] ($n = 69$) | Control ($n = 147$) |
| Galactomannan test[b] | | |
| Negative | 35 (51) | 142 (97) |
| Positive | 34 (49) | 5 (3) |
| (1-3)-β-D-Glucan test[c] | | |
| Negative | 13 (19) | 120 (82) |
| Positive | 56 (81) | 27 (18) |

Sulahian, JCM 2014

# Biomarqueurs et IgIV

**Table 1.** Galactomannan (GM) and beta-D-glucan (BG) antigens detected in intraveinous immunoglobulins (IVIg) infusions and in sera sampled prior or after intraveinous immunolgobulins (IVIg) injection in a panel of 18 patients undergoing regular IVIg injections.

| Id | Gender | Age (years) | Underlying pathology | IVIg | Dose | Set of serum | GM (Index) | | | BG (pg/ml) | | | *Aspergillus fumigatus* DNA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Pre-IVIg serum | Post-IVIg serum | IVIg sample | Pre-IVIg serum | Post-IVIg serum | IVIg sample | Post-IVIg serum |
| 1 | M | 29 | XLA | Clairyg | 15g/2wks | 1 | 1.00 | 1.30 | 1.09 | 198 | >523 | >523 | negative |
| | | | | Tegeline | 25g/3wks | 2 | 0.42 | 1.05 | 3.27 | - | >523 | >523 | negative |
| 2 | F | 56 | CVID | Clairyg | 25g/3wks | 3 | 0.32 | 0.70 | 1.10 | <80 | >523 | >523 | negative |
| | | | | Tegeline | 20g/3wks | 4 | 0.69 | 0.94 | 3.21 | 215 | >523 | >523 | negative |
| 3 | M | 53 | Hypogammaglobulinemia (IgG2) | Clairyg | 25g/4wks | 5 | 0.11 | 0.43 | 0.95 | <80 | >523 | >523 | negative |
| | | | | Tegeline | 25g/4wks | 6 | 0.14 | 0.29 | 3.88 | 146 | >523 | >523 | negative |
| 4 | M | 21 | HIES (STAT3) | Clairyg | 25g/3wks | 7 | 0.12 | 0.64 | 1.12 | 129 | >523 | >523 | negative |
| 5 | M | 41 | Secondary ID disease | Clairyg | 50g/4wks | 8 | 0.29 | 0.57 | 1.06 | 243 | >523 | >523 | negative |
| 6 | F | 54 | SCID | Clairyg | 25g/3wks | 9 | 0.17 | 0.44 | 0.91 | 227 | >523 | >523 | negative |
| 7 | M | 25 | XLA | Clairyg | 40g/3wks | 10 | 0.36 | 0.80 | 1.50 | 102 | >523 | >523 | negative |
| 8 | M | 68 | Secondary ID disease | Clairyg | 50g/3wks | 11 | 0.11 | 0.22 | 1.33 | 135 | >523 | >523 | negative |
| 9 | F | 69 | CVID | Clairyg | 30g/4wks | 12 | 0.12 | 0.50 | 0.99 | <80 | >523 | >523 | negative |
| 10 | F | 75 | Secondary ID disease | Privigen | 30g/4wks | 13 | 0.11 | 0.09 | 0.12 | <80 | >523 | >523 | negative |
| 11 | M | 47 | Secondary ID disease | Privigen | 40g/3wks | 14 | 0.15 | 0.15 | 0.23 | <80 | >523 | >523 | negative |
| 12 | M | 28 | HIES | Privigen | 30g/4wks | 15 | 0.18 | 0.18 | 0.15 | 89 | >523 | >523 | negative |
| 13 | M | 50 | CVID | Privigen | 35g/3wks | 16 | 0.45 | 0.43 | 0.12 | 109 | >523 | >523 | negative |
| 14 | M | 84 | Secondary ID disease | Privigen | 25g/4wks | 18 | 0.12 | 0.18 | 0.13 | 210 | >523 | >523 | negative |
| 15 | F | 41 | HIES (STAT3) | Privigen | 30g/4wks | 19 | 0.13 | 0.15 | 0.26 | <80 | >523 | >523 | negative |
| 16 | M | 52 | CVID | Kiovig | 50g/4wks | 17 | 0.29 | 0.20 | 0.15 | 180 | >523 | >523 | negative |
| 17 | M | 28 | *SCID* | Octagam | 40g/4wks | 20 | 0.12 | 0.40 | 0.41 | 134 | >523 | >523 | negative |
| 18 | M | 45 | CVID | Octagam | 50g/4wks | 21 | 0.35 | 0.44 | 0.31 | 108 | >523 | >523 | negative |

Footnote:

Bougnoux et al, ESCMID 2010

# PCR *Aspergillus fumigatus* sérique

- Prospective, Hématologie
- 125 patients inclus (137 épisodes évalués)
  - 17 cas AI (1 prouvé, 14 probables et 2 possibles) →8 patients allogreffés
  - Incidence AI : 11,3%
- Screening : GM : 2/ sem
- q-PCR *A. fumigatus* (28S): 1/sem /Sérum (1mL et 100 µL)

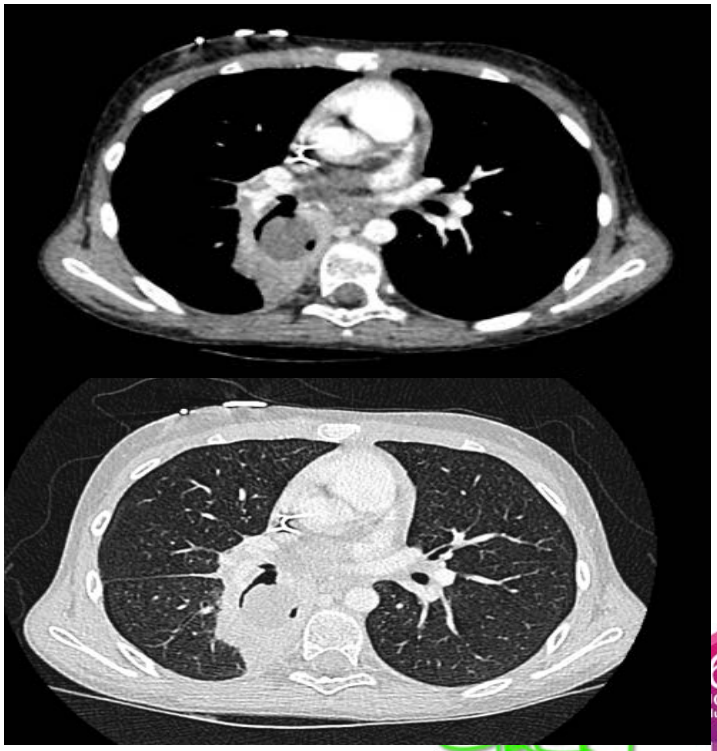
| AI | qPCR | | GM |
|---|---|---|---|
| | faible volume | large volume | |
| Sensitivité | 100% | 76,5 | 88,2 |
| Spécificité | 96,7 | 96,7 | 95,8 |
| VPP | 81 | 81,3 | 75 |
| VPN | 100 | 95,6 | 98,3 |

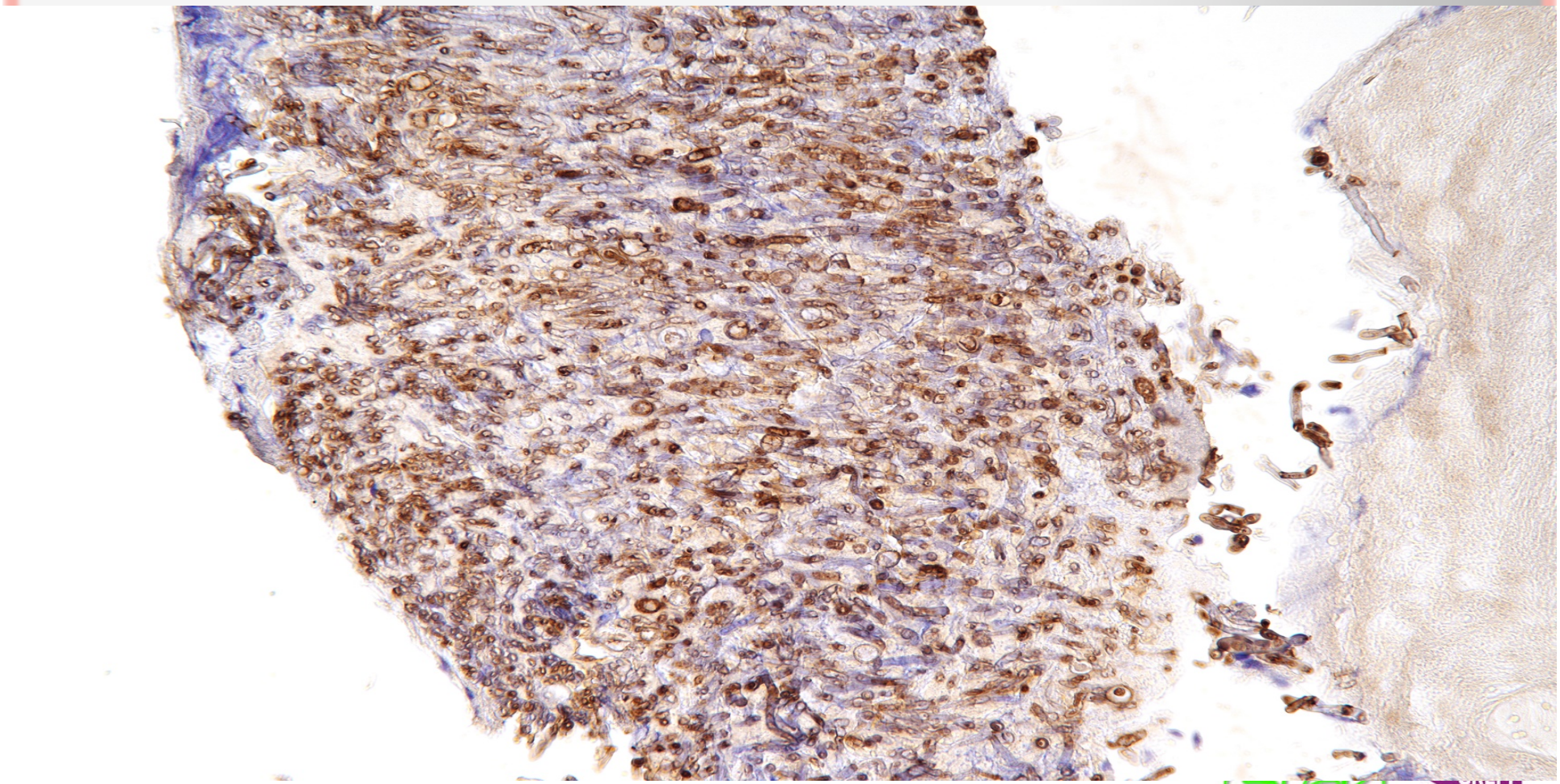
Suarez F et coll. JCM 2008

# Cas

- Beta D glucanes = 103
- Antigène galactommanane = 0,65
- PCR Aspergillus et Mucorales sang négatives

- Appel pour décision thérapeutique





IHC *Aspergillus* spp.

**Vos patients reçoivent une prophylaxie par posaconazole dans les périodes à risque**

- Vous monitorez GM 2X/sem
- Vous n'utilisez plus le GM
- Vous réalisez un GM en cas de fièvre
- Vous réalisez un GM en cas de pneumopathie

# Faut il continuer à surveiller l'Ag GM chez les patients risque sous prophylaxie par posaconazole?

- 262 épisodes à risque
- Prophylaxie posaconazole
- AgGM 2X/sem
- 1.9% IA (tous GM +)
- 30 faux GM+
- VPP=12%
- GM et suspicion IFD: VPP=89.6%

Duarte R, CID 2014

- Arrêt surveillance GM chez patients sous prophylaxie
- Utilisation GM en cas de symptômes
- 100 épisodes à risque
- 6,9% de GM

Duarte R, BMT, 2017

**Table 1.** Patient demographics, episode characteristics and fungal infection outcomes according to a pre-emptive surveillance versus diagnostic-driven strategy of GM use

| | *Pre-emptive (n = 262)* | *Diagnostic driven (n = 100)* |
|---|---|---|
| *A. Patient demographics* | | |
| Number of High-Risk Episodes | 262 | 100 |
| Number patients | 121 | 52 |
| *B. Episode characteristics* | | |
| AML chemotherapy | 161 (61%) | 62 (62%) |
| Induction/salvage | 101 (63%) | 35 (56.5%) |
| Allogeneic HCT | 79 (30%) | 26 (26%) |
| Myeloablative | 30 (38%) | 15 (58%) |
| T-cell Depleted | 34 (43%) | 14 (54%) |
| Unrelated donor/Cord Blood | 34 (43%) | 14 (54%) |
| GvHD | 22 (8%) | 12 (12%) |
| Acute | 18 (81%) | 9 (75%) |
| *C. Fungal infection outcomes* | | |
| Breakthrough IFI | 10 (3.8%) | 2 (2%) |
| *Aspergillus spp* | 5 (1.9%) | 0 |
| *Candida spp* | 5 (1.9%) | 1 (1%) |
| Other molds | 0 | 1[b] (1%) |
| Fungal-related death | 4 (1.5%) | 2 (2%) |
| Overall mortality | 17, 6.5% | 6, 6% |
| Antifungal IV treatment | 44 (16.7%) | 15 (15%) |

# En dehors de l'hématologie: Comparaisons tests

221 patients
Pathologie respiratoire sous-jacente
Monocentrique Autriche
LBA
Comparaison
B D glucane
Ag GM

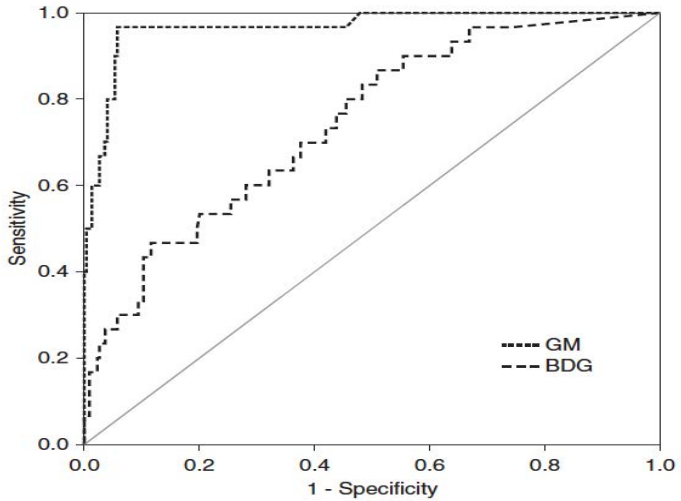
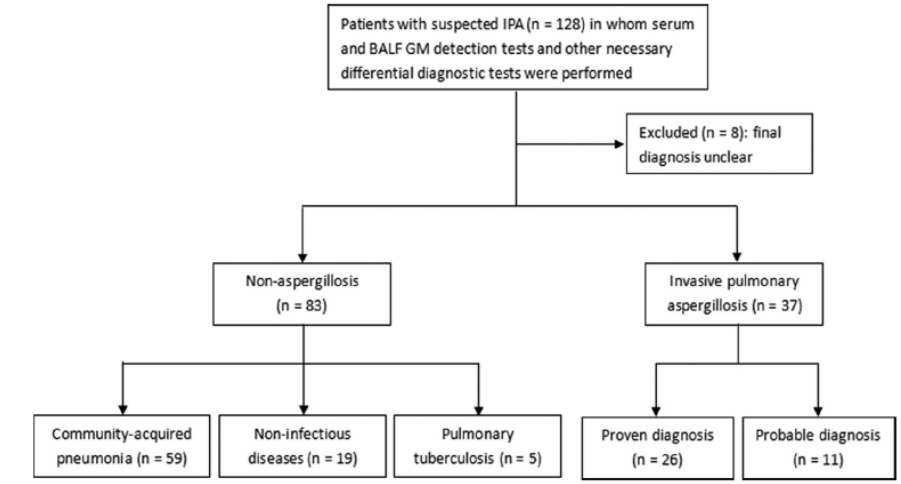



**Figure 1.** Receiver operating characteristics curve analysis for proven/probable invasive pulmonary aspergillosis (IPA) versus no IPA. BDG = 1,3-β-D-glucan; GM = galactomannan.

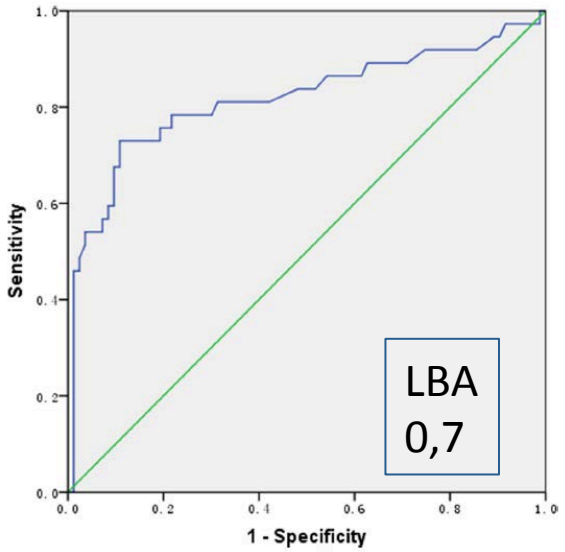
Prattes, AJRCCM, 2014

6es JOURNÉES du GREPI

# Valeur GM serum et LBA patient non neutropénique



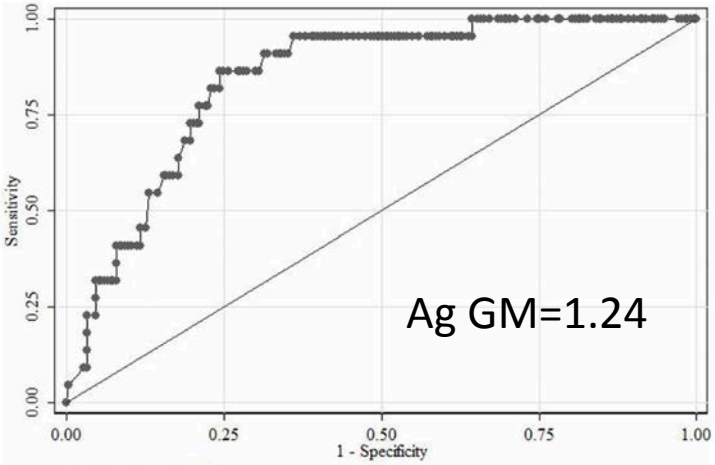

| Sample and ODI | False-positive rate (%) | False-negative rate (%) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| BALF GM | | | | | | |
| ≥0.5 | 19.28 | 24.32 | 75.68 | 80.72 | 63.64 | 88.16 |
| ≥1.0 | 9.64 | 35.14 | 64.86 | 90.36 | 75.00 | 85.23 |
| Serum GM | | | | | | |
| ≥0.5 | 12.86 | 62.16 | 37.84 | 87.14 | 60.87 | 72.62 |
| ≥1.0 | 4.29 | 75.68 | 24.32 | 95.71 | 75.00 | 70.53 |




Zhou W, JCM 2017

# Ag GM en réanimation

23 IA de réa
Inde
Prédicteur aspergillose: Ag GM sérum >1.24
Associée décès
Plus précoce que imagerie



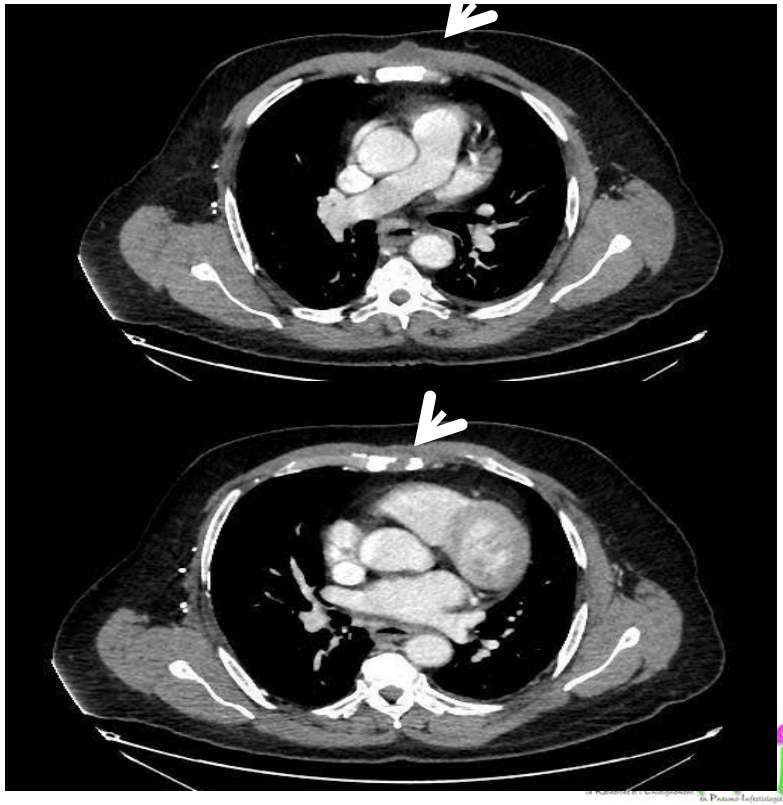

Dabas Y, Plos one 2017

# Recommandations ECMID 2017

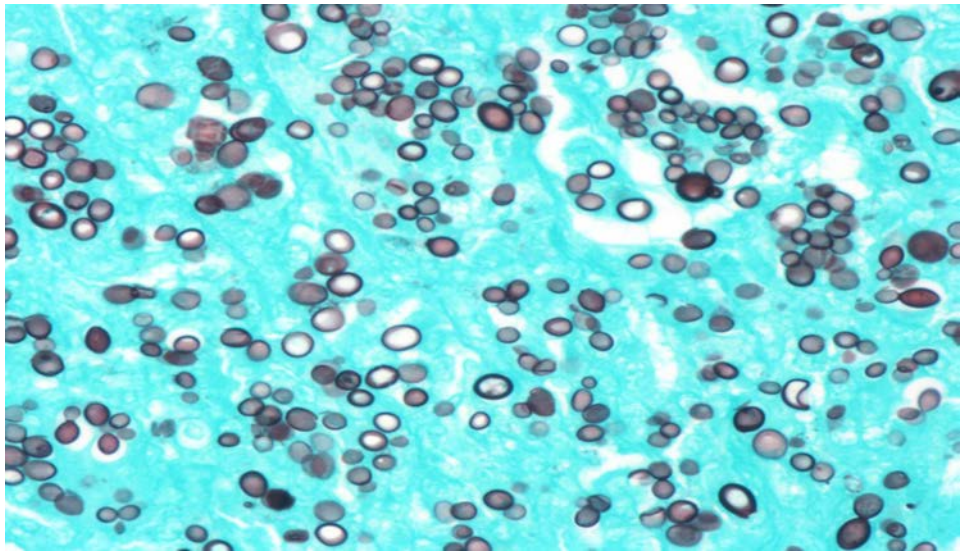
| Population | Intention | Intervention | SoR | QoE | Comment |
|---|---|---|---|---|---|
| Patients with prolonged neutropenia or allogeneic stem cell transplantation recipients **not on mould-active prophylaxis** | Prospective screening for IA | GM in blood[a]<br>Draw samples every 3–4 days | A<br>C | I<br>III | Highest test accuracy requiring two consecutive samples with an ODI ≥0.5 or retesting the same sample<br>Prospective monitoring should be combined with HRCT and clinical evaluation |
| Patients with prolonged neutropenic or allogeneic stem cell transplantation recipients **on mould active prophylaxis** | Prospective screening for IA | GM in blood[a] | D | II | Low prevalence of IA in this setting with consequently low PPV of blood GM test<br>Prophylaxis may have a negative impact on sensitivity of the test or the low yield may be due to decreased incidence of IA |
| Patients with a haematological malignancy | To diagnose IA | GM in blood[a] | | | Significantly lower sensitivity in non-neutropenic patients |
| • Neutropenic patients | | | A | II | |
| • Non-neutropenic patients | | | B | II | |
| ICU patients | To diagnose IA | GM in blood[a] | C | II | Better performance in neutropenic than in non-neutropenic patients |
| Solid organ recipients | To diagnose IA | GM in blood[a] | C | II | Low sensitivity, good specificity<br>Most data for lung SOT |
| Any other patient | To diagnose IA | GM in blood[a] | C | II | Piperacillin/tazobactam may no longer be responsible for false-positive results according to recent studies<br>Cross-reactivity in case of histoplasmosis, fusariosis, talaromycosis (formerly: penicilliosis)<br>False-positive results reported due to ingestion of ice-pops, |

# Cas numéro 2

- Patient, 72 ans
- Vit au Mali
- Aucun antécédent
- Abcès pré sternal
- Biopsie de l'abcès



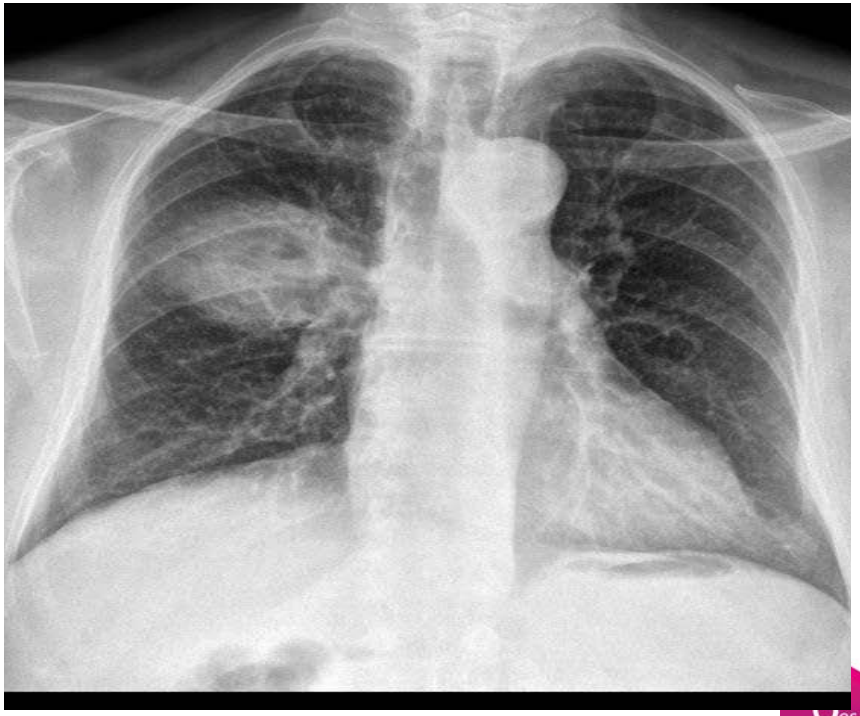
# Résultats de la biopsie



- Quels examens demandez vous?
  - Ag GM
  - Beta D glucane
  - Sérologie mannane-anti-mannane
  - PCR Mucorales
  - PCR *Histoplasma*

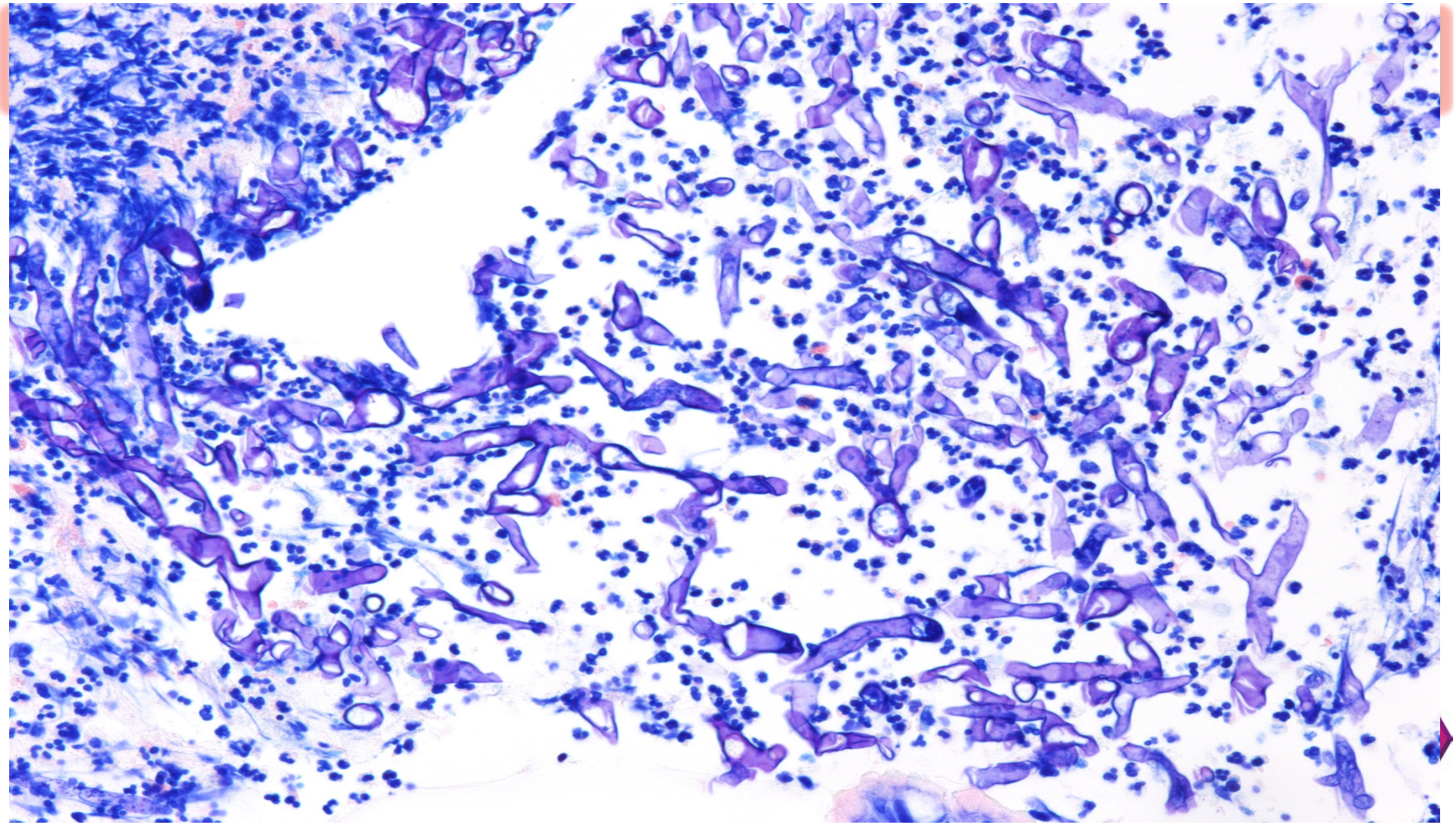
# Cas clinique

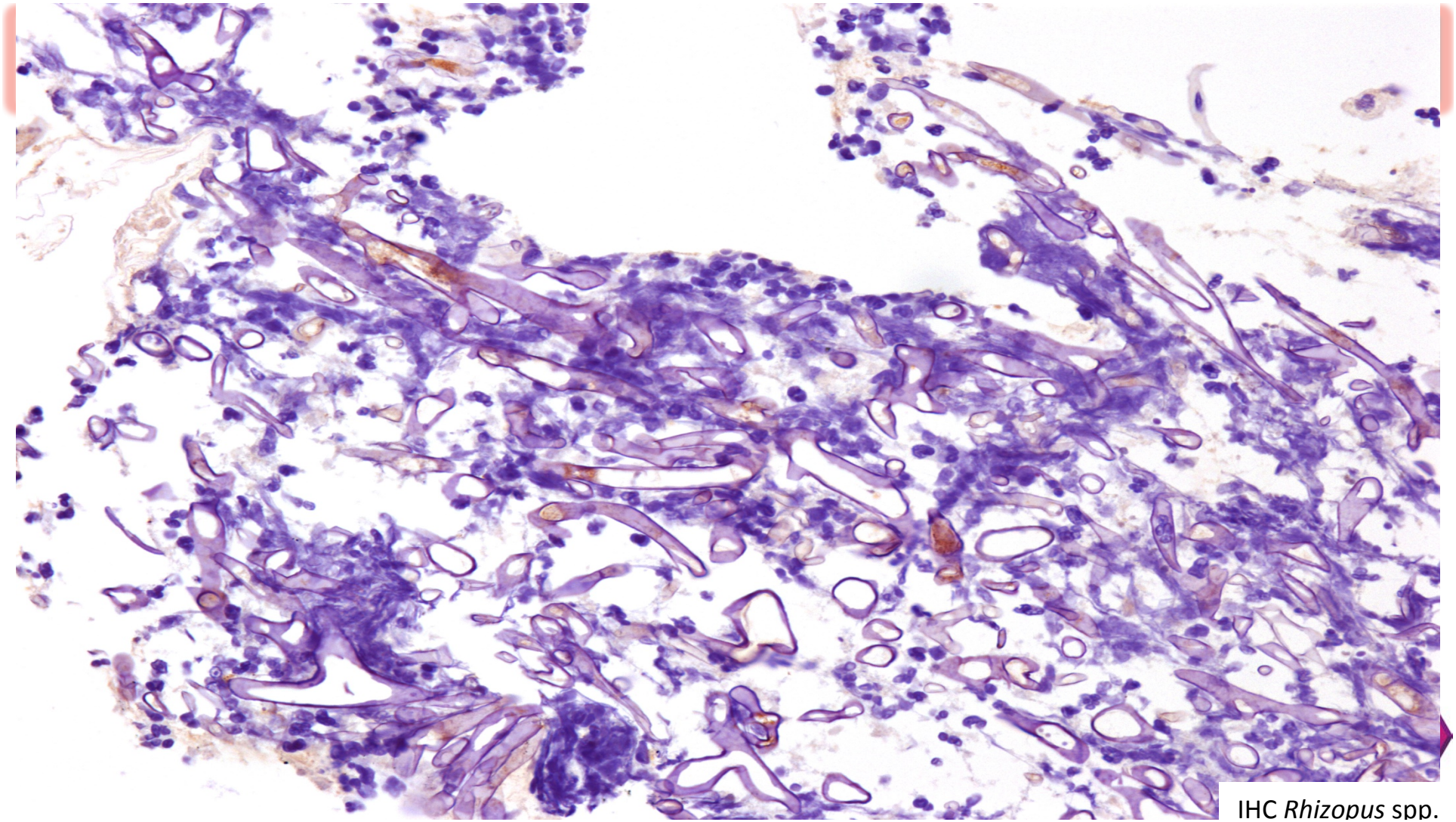
- 69 ans
- M2 post TR
- Depuis 1 semaine: fièvre, syndrome inflammatoire, toux
- Examen: 39°, hémoptysies
- Tazo



# Quels examens demandez vous?

Expecto: *Aspergillus fumigatus*
Fibro LBA: Culture neg
Traitement par Voriconazole
Aggravation clinique et hémoptysies





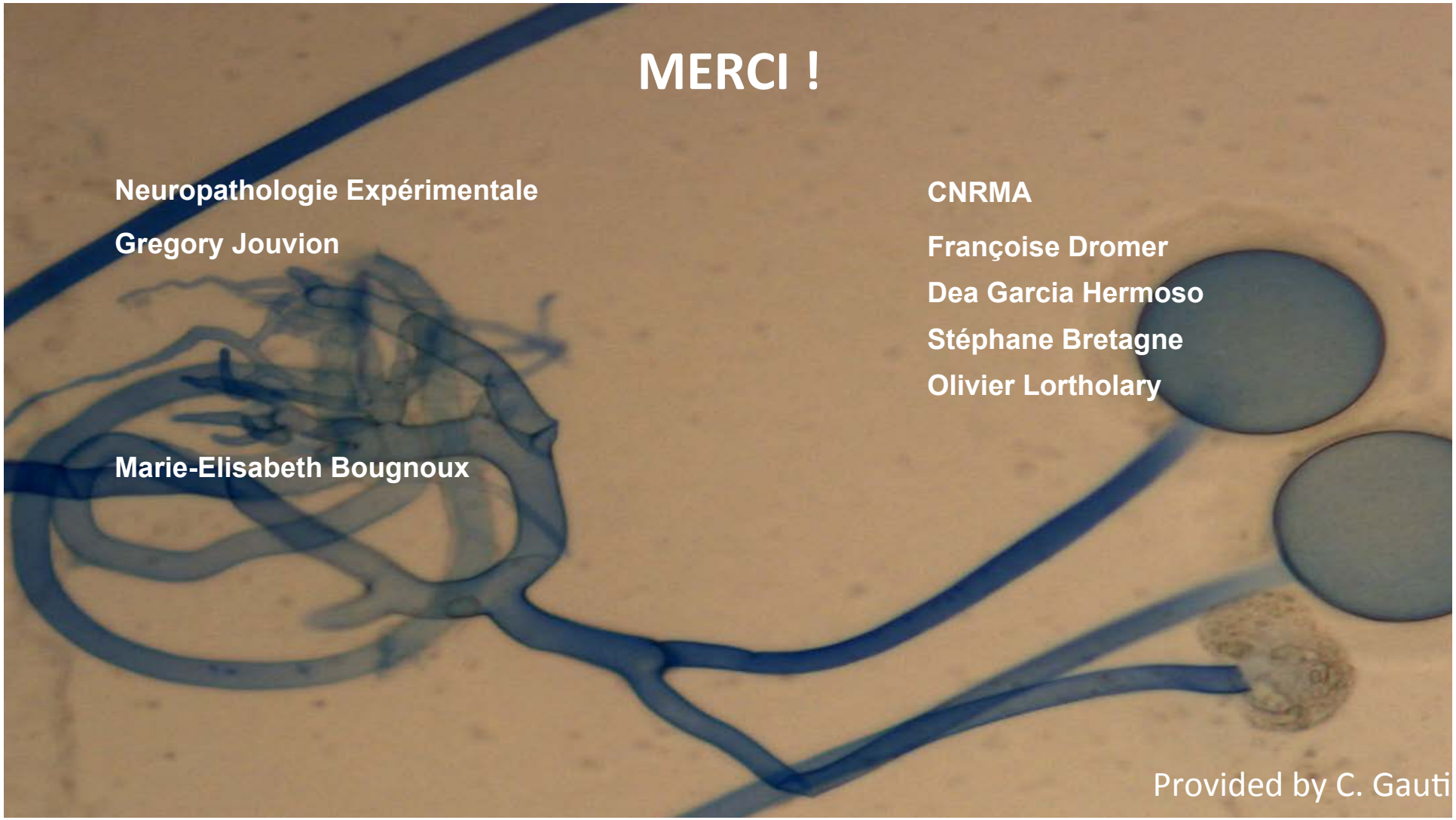
IHC *Rhizopus* spp.

# qPCR Mucorale sur sérum: diagnostic et suivi

- Etude nationale rétrospective
- 44 patients avec mucormycose, 34 avec hémopathie
- Combinaison de 3 qPCR sur sérum: *Mucor, Rhizopus, Lichteimia*
- 81% qPCR positive
  - 92% quand technique correcte
- qPCR positive 9 jours avant diagnostic mycologique et 2 jours avant diagnostic radiologique
- Survie à J84 plus élevée chez les patients avec qPCR négative (48% vs 4%)
- qPCR pour le diagnostic et le suivi de mucormycose

PHRC Modimucor

Million L, CMI, 2015


MERCI !
Neuropathologie Expérimentale
Gregory Jouvion
Marie-Elisabeth Bougnoux
CNRMA
Françoise Dromer
Dea Garcia Hermoso
Stéphane Bretagne
Olivier Lortholary
Provided by C. Gauti