



SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

XXXV

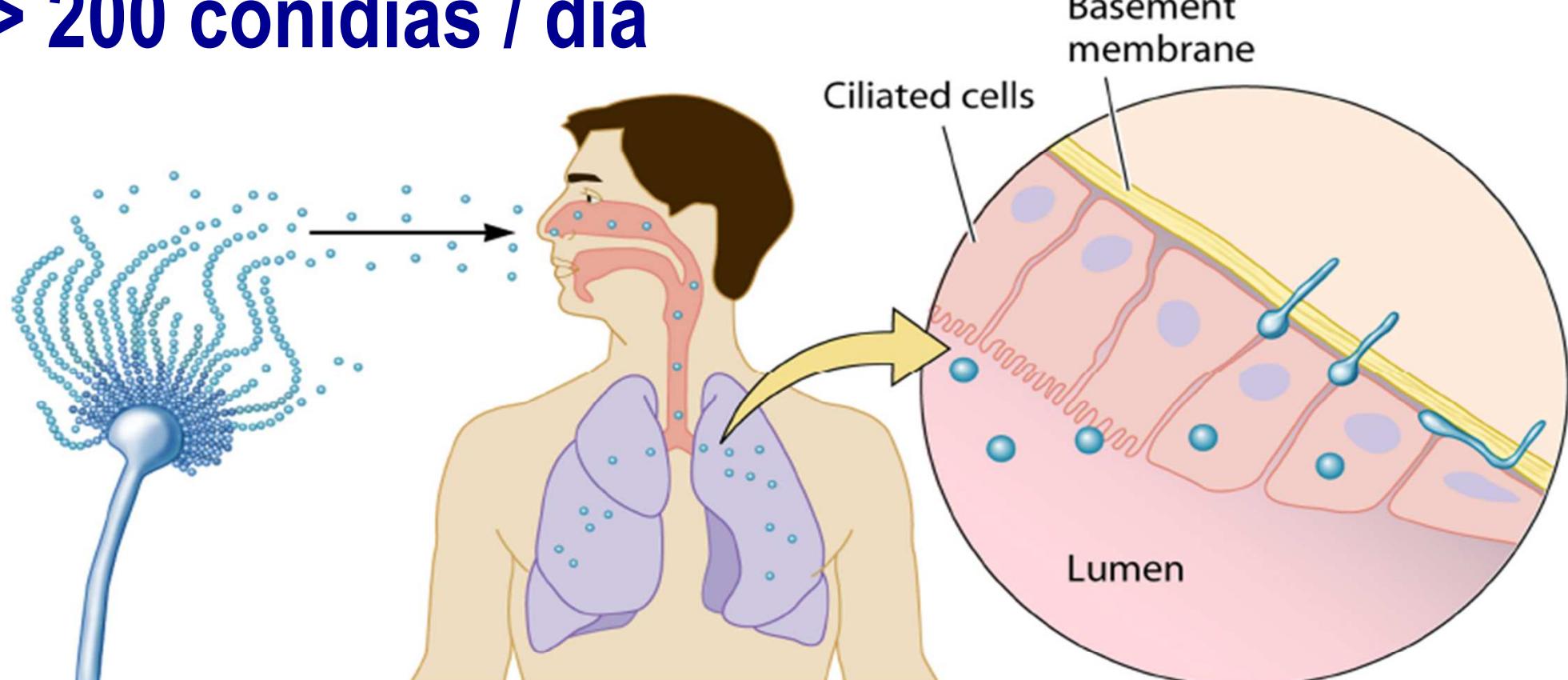
Congreso Nacional de la
Sociedad Española de
Medicina Interna (SEMI)

Aspergilosis pulmonar en pacientes con enfermedad pulmonar estructural

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API - Patogenia

> 200 conidias / día



Sporulation

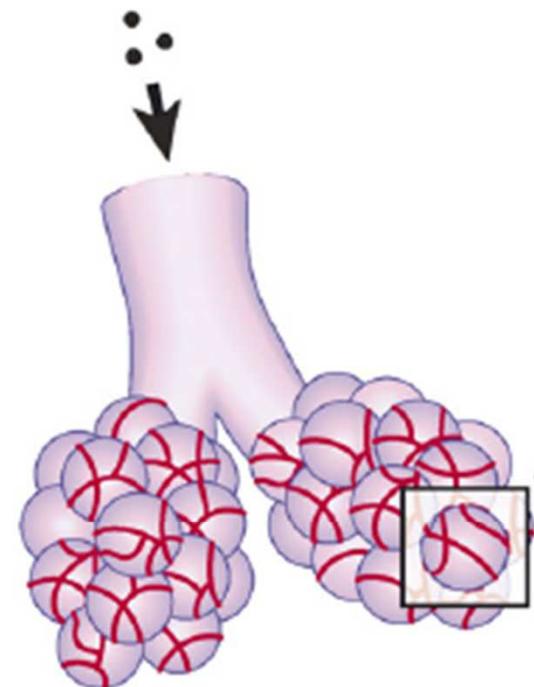
Inhalation of airborne conidia

Conidial germination in
absence of sufficient
pulmonary defenses

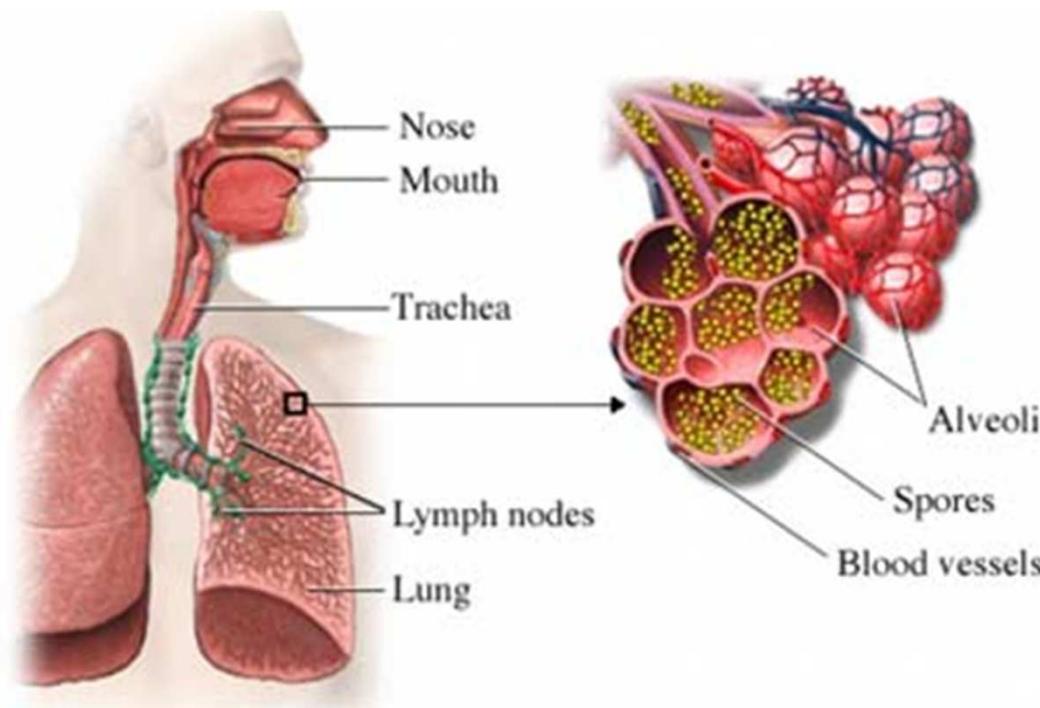
Dagenais TRT et al. Clin Microbiol Rev 2009

API – Patogenia

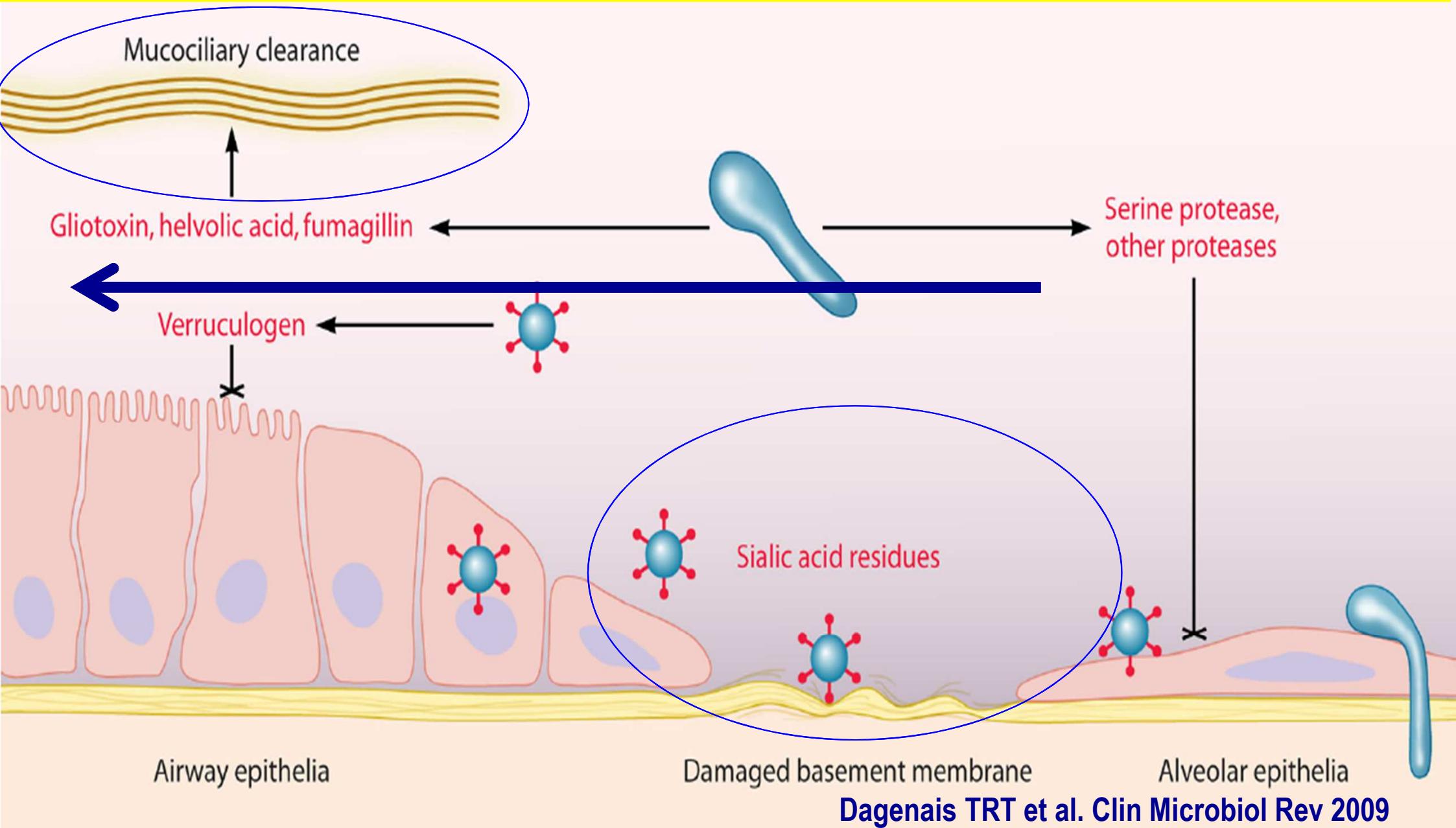
A. fumigatus conidia
(2–3 mm diameter)



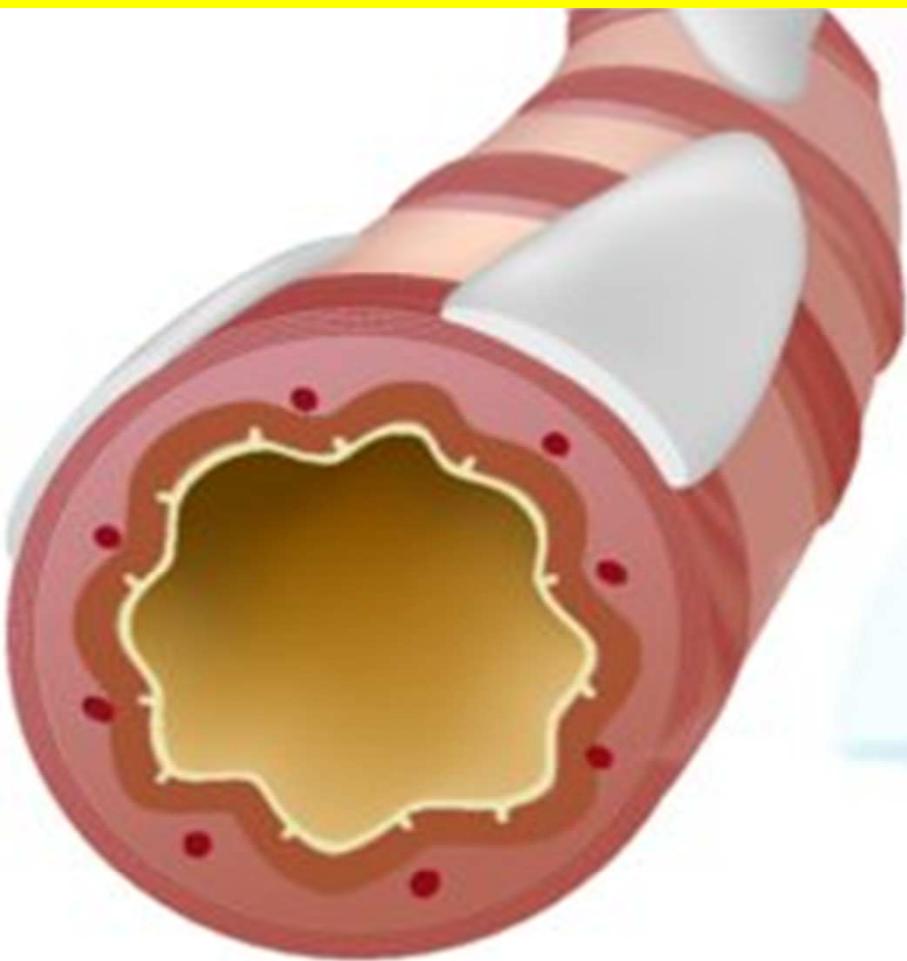
API - Patogenia



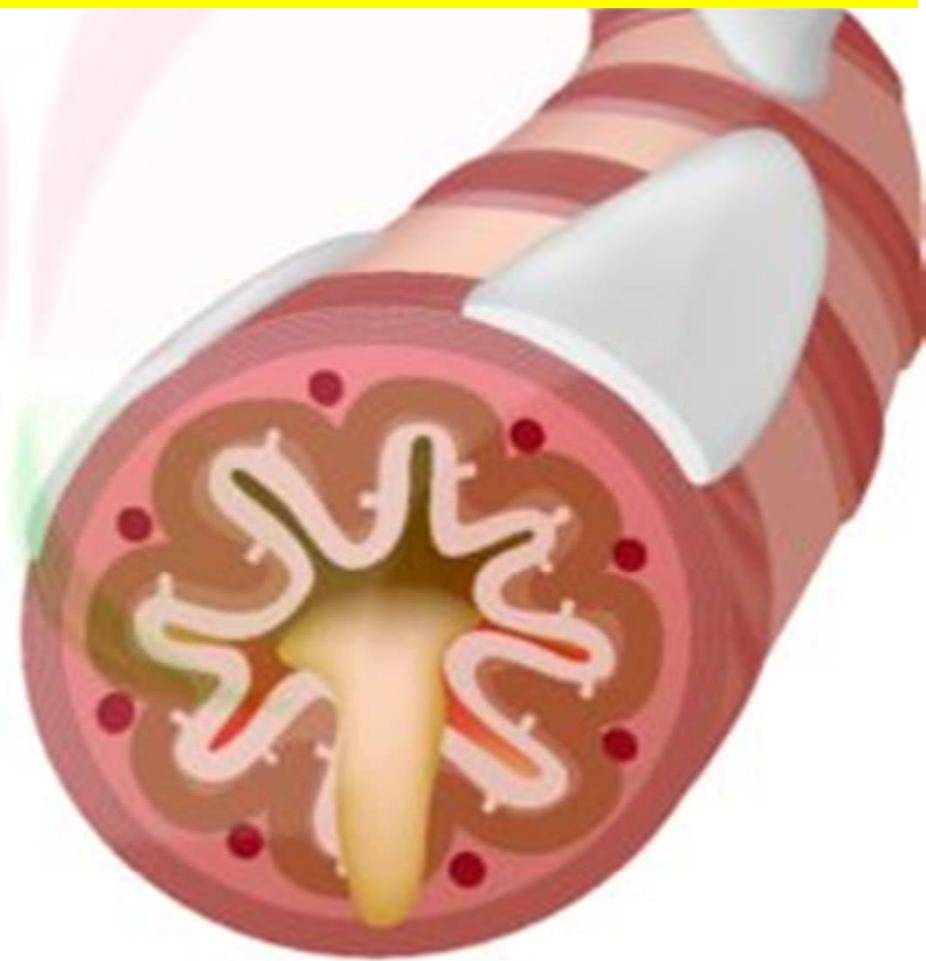
API - Patogenia



Bronquio normal



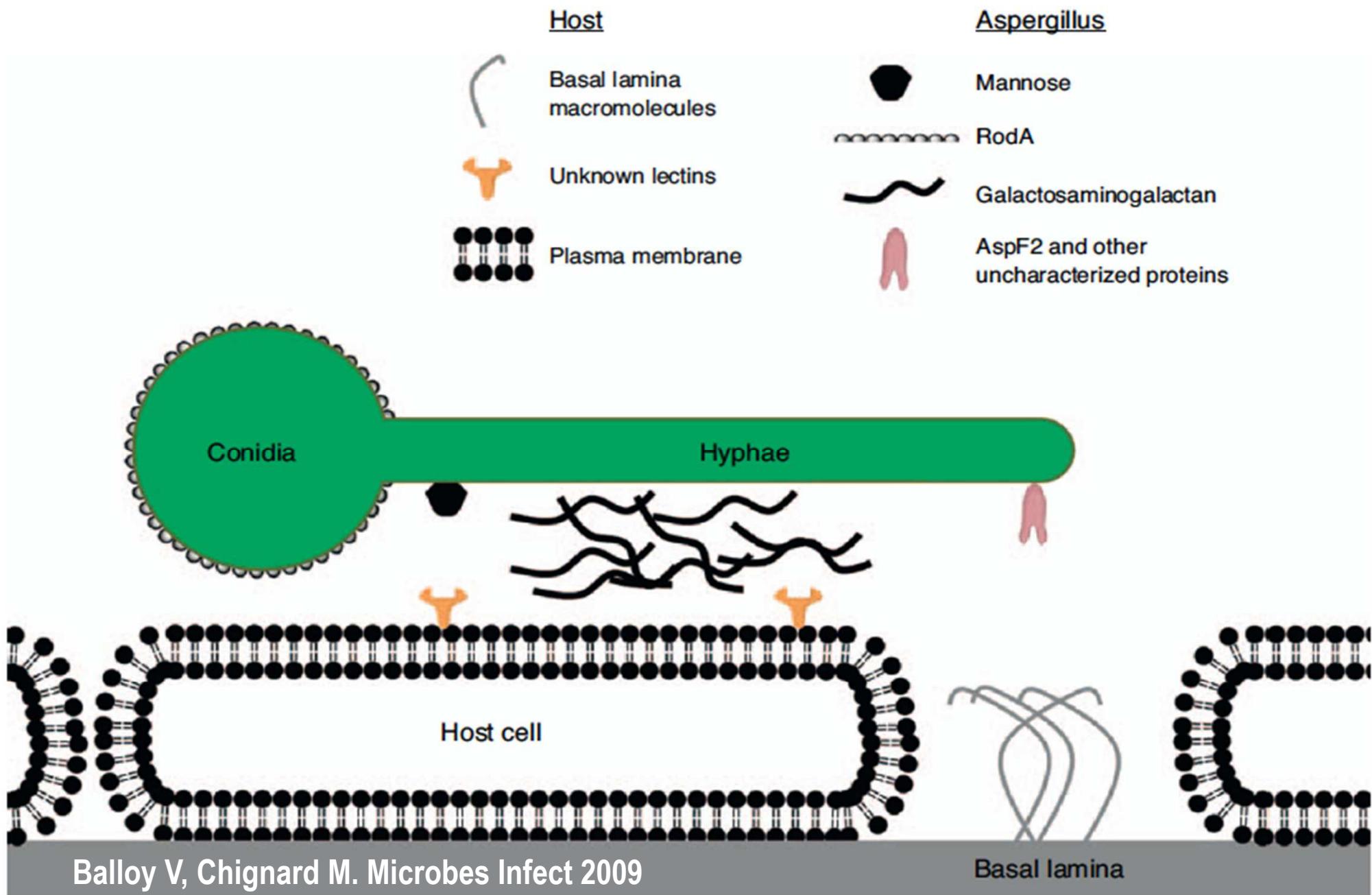
Bronquitis crónica



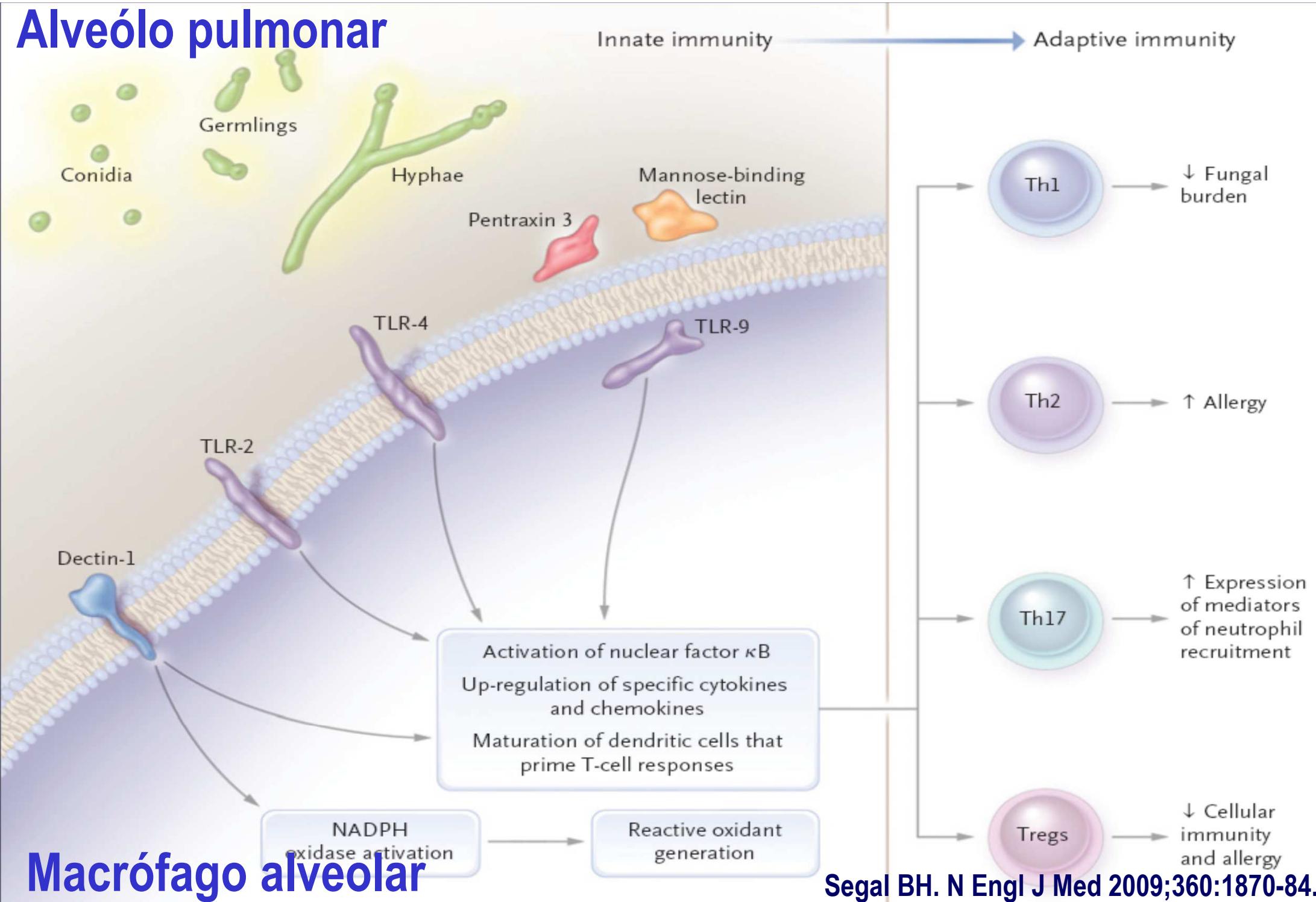
A. fumigatus – Fact. virulencia

Category	Role <i>in vivo</i>	Molecule
Adhesins	Adhesión	Complement receptor (54–58 kDa) Laminin receptor (72 kDa) Hydrophobins (14 and 16 kDa)
Pigments		Dihydroxynaphthalene-melanin
Toxic molecules	Alt. fagocitosis	RNase (18 kDa) Hemolysin (30 kDa) Secondary metabolites, e.g., gliotoxin
Enzymes	Inmunosupresión	Serine protease (33 kDa) Aspartic protease (38 kDa) Metalloprotease (40 kDa) Dipeptidylpeptidases (88 and 94 kDa) Catalases (350 kDa and unknown) Superoxide dismutases (27 and 67 kDa)
	Daño epitelial	Phospholipase(s) Latge JP. CMR 1999

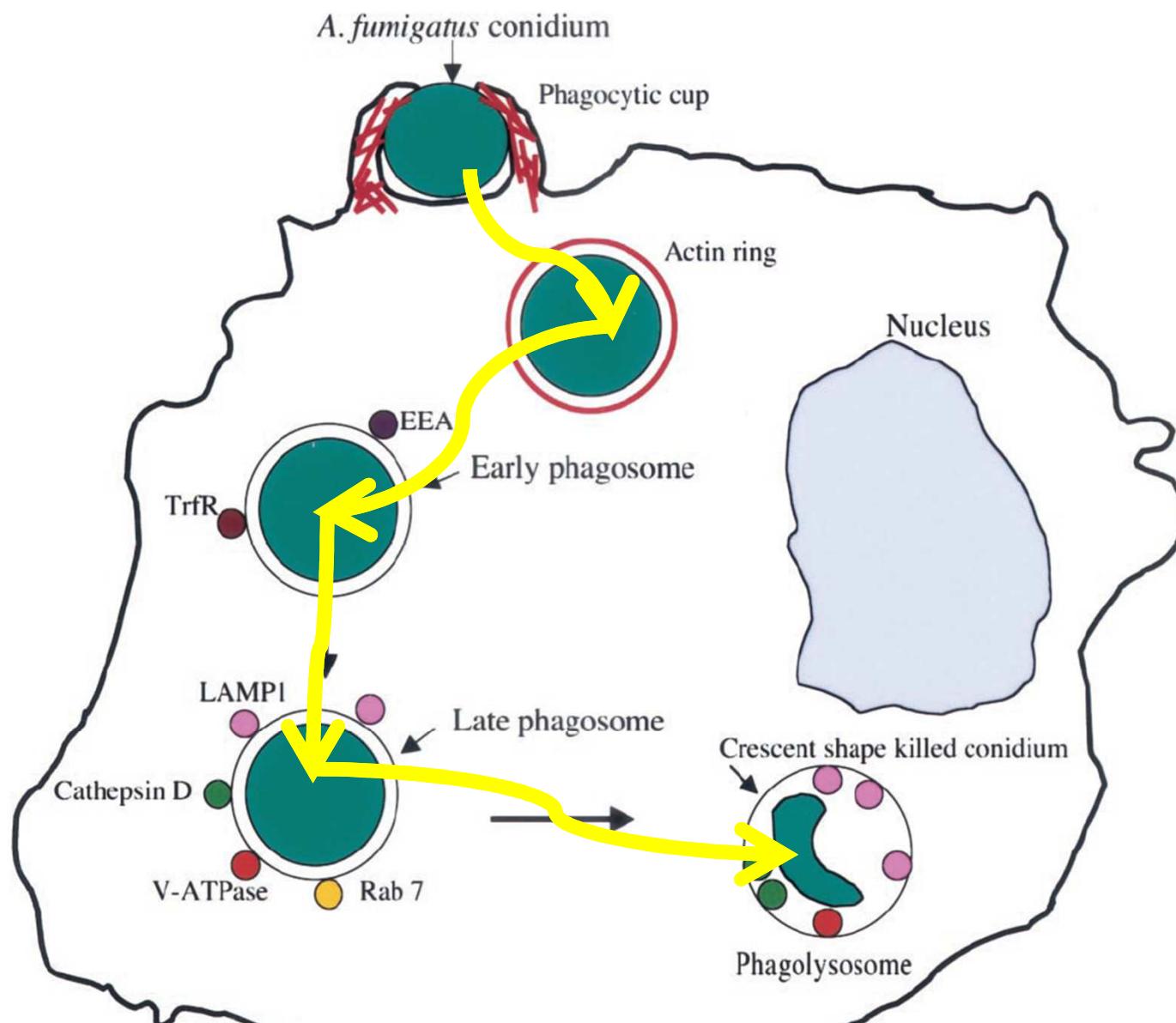
A. fumigatus - Adherence to host cells



Alveólo pulmonar

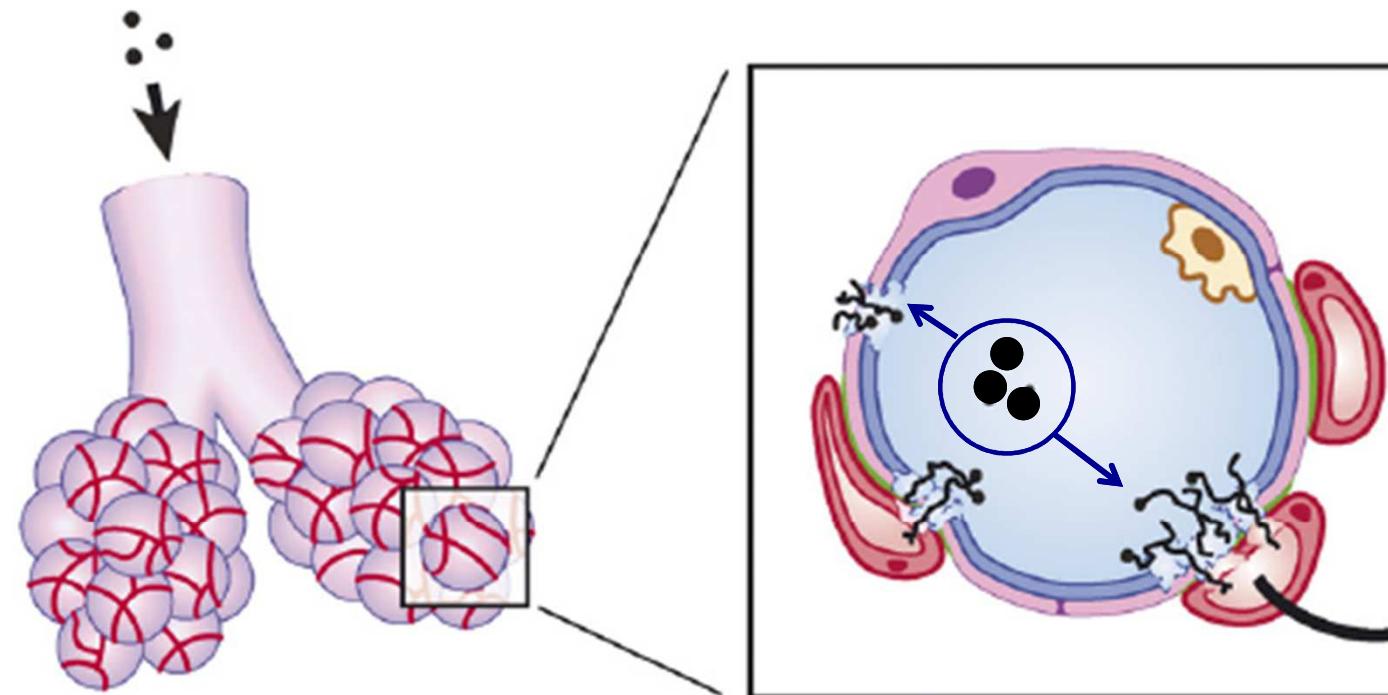


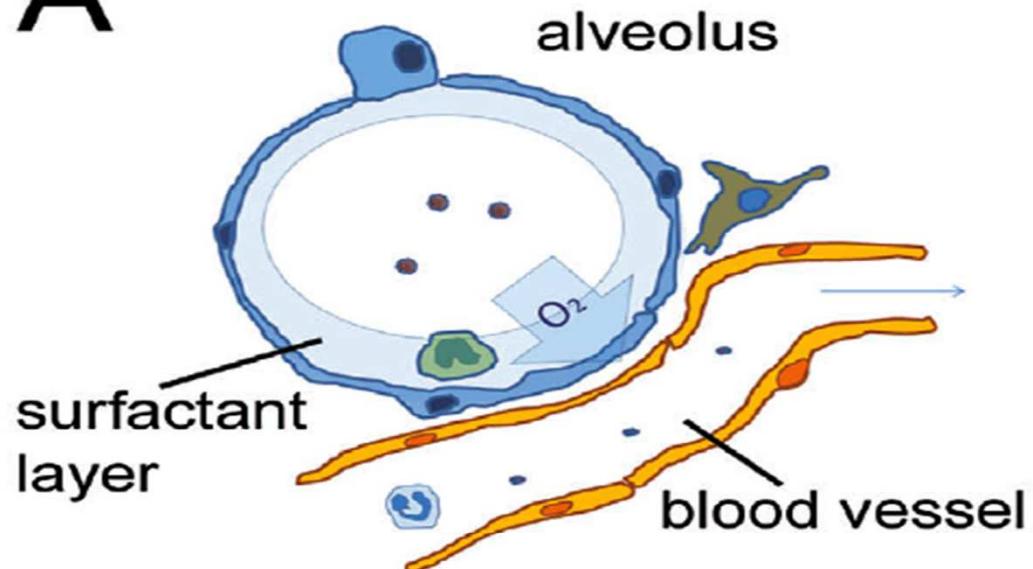
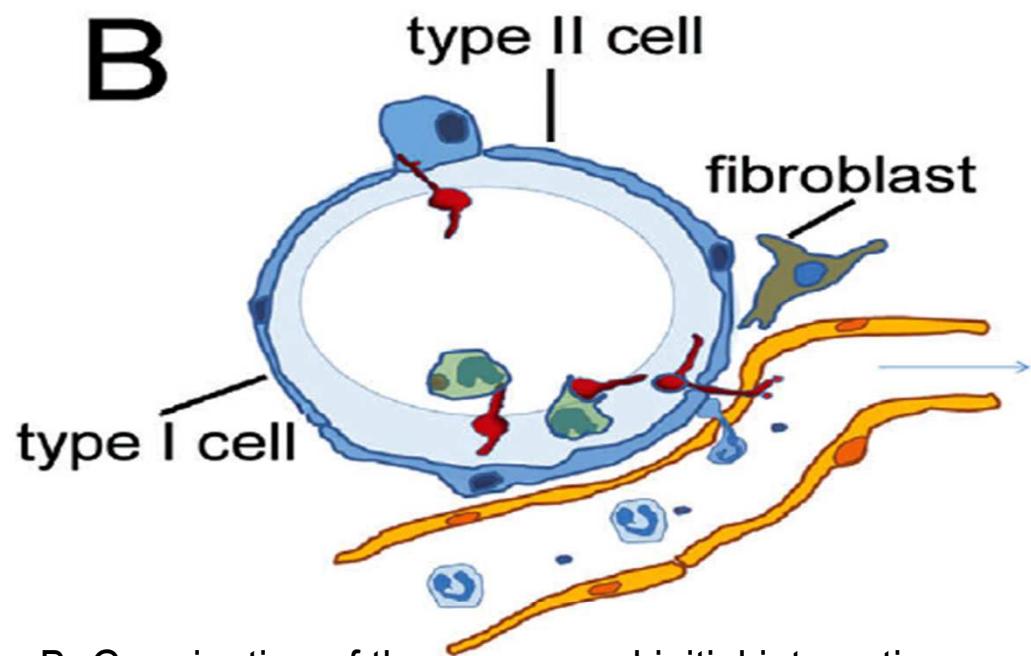
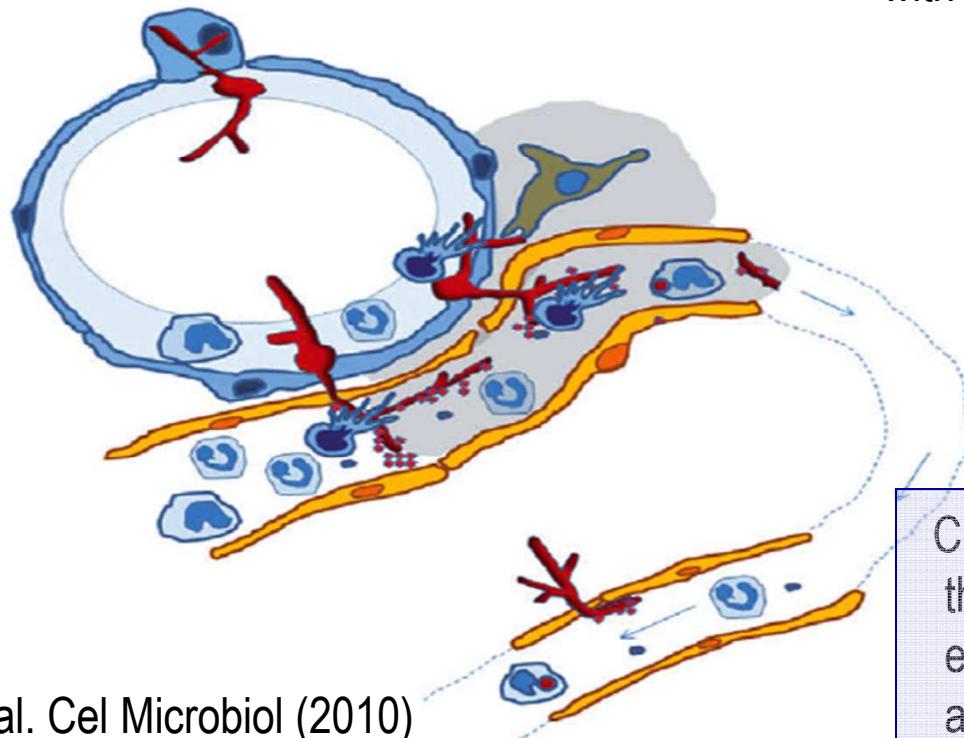
Aspergillus – Fagocytosis



API – Patogenia

A. fumigatus conidia
(2–3 mm in diameter)



A**B****C**

A. Resting conidia arrive in the alveolus.

B. Germination of the spores and initial interactions with alveolar macrophages and alveolar epithelial cells.

neutrophil

NET

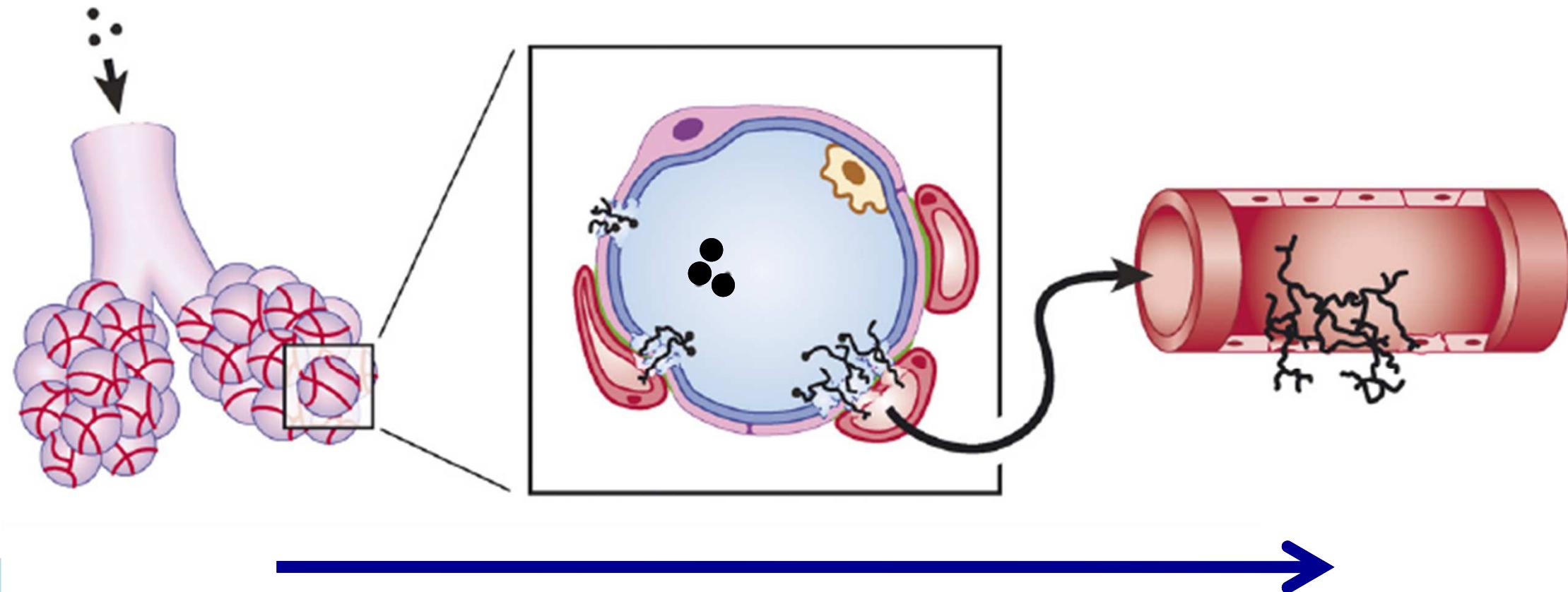
macrophage

activated platelet

C. Later stage of infection characterized by hyphae that infiltrate blood vessels, activation of platelets, establishment of hypoxic conditions(indicated in grey) and vascular spread of infection.

API – Patogenia

A. fumigatus conidia
(2–3 mmin diameter)



API – Patogenia

Histopathologic Pattern in Neutropenic and Nonneutropenic Patients and HSCT Recipients With Invasive Pulmonary Aspergillosis*

Group	Angioinvasion	Hemorrhagic Infarction	Intra-alveolar Hemorrhage	Coagulative Necrosis	Granulomas	Inflammatory Necrosis
Nonneutropenic (n = 20)	4 (20)	3 (15)	10 (50)	8 (40)	2 (10)	10 (50)
Neutropenic (n = 10)	6 (60)†	4 (40)	9 (90)†	3 (30)	0 (0)	1 (10)†
HSCT (n = 10)	8 (80)†	5 (50)	10 (100)†	7 (70)	0 (0)	2 (20)

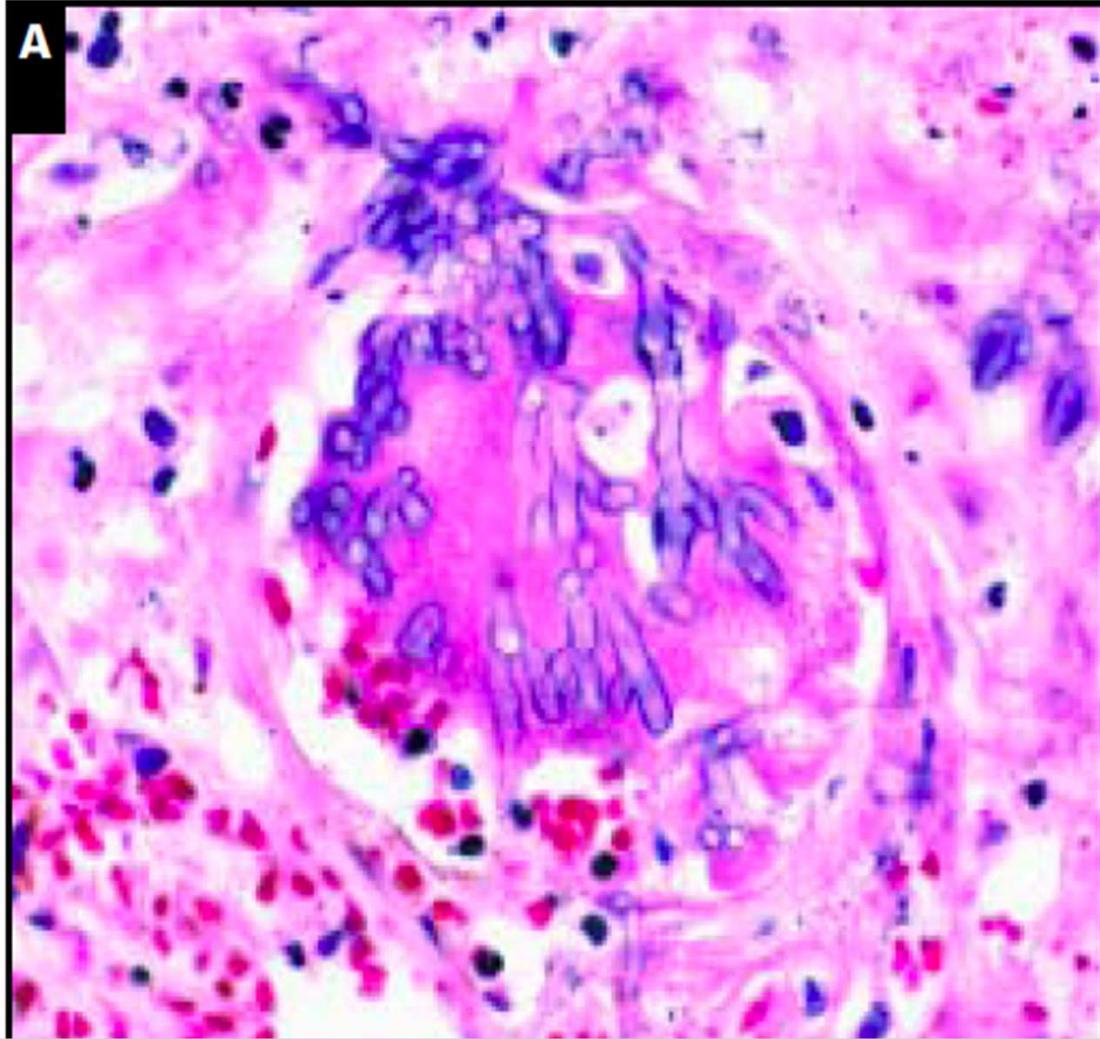
HSCT, hematopoietic stem cell transplant.

* Data are given as number (percentage).

† $P < .05$ (Fisher exact test) was considered statistically significant in comparison with the nonneutropenic group.

API en neutropénico – Patogenia

A



Angioinvasión

Hemorragia alveolar

API – Patogenia

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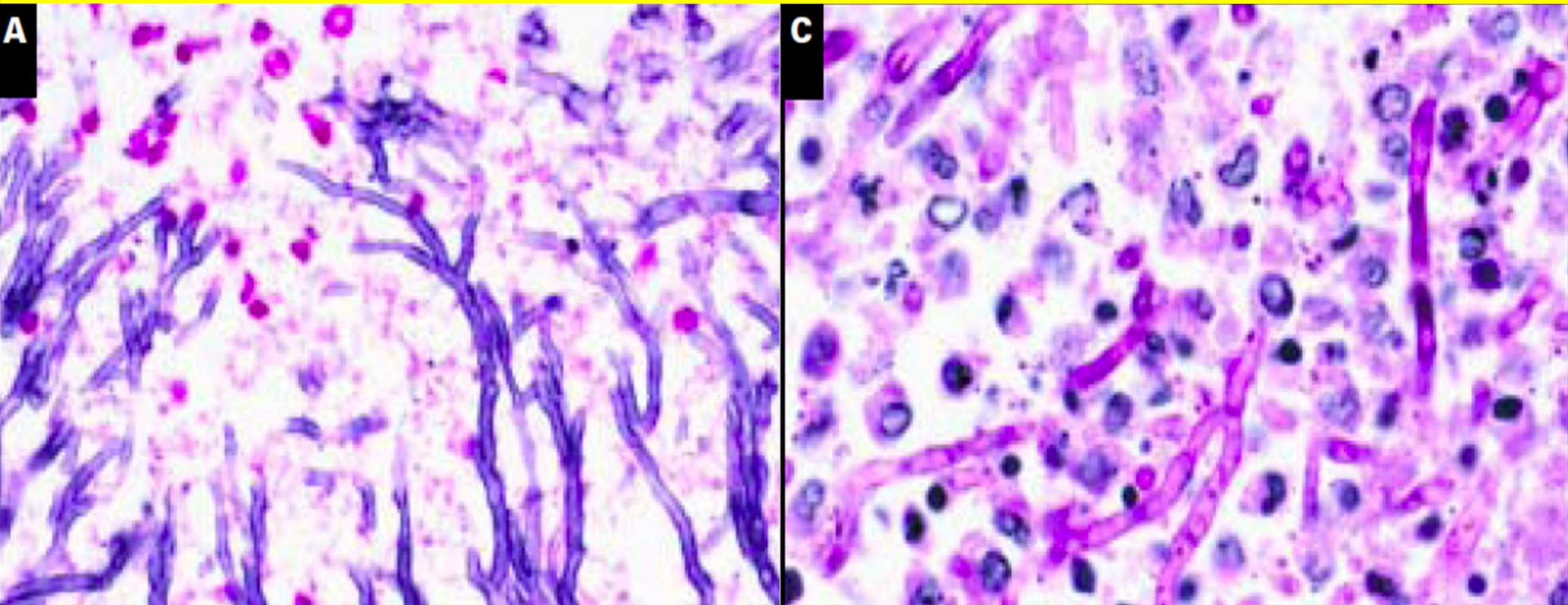
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API – Patogenia



Neutropenic patient:

Septate hyphae of *Aspergillus* with a paucity
of surrounding cellular inflammatory infiltrate

Nonneutropenic patient:

Inflammatory necrosis

Aspergillus en pulmón – Formas clínicas

Immune
Response
&
Pulmonary
disease

Diseases caused by *Aspergillus*

Aspergillosis – Pacientes no trasplantados

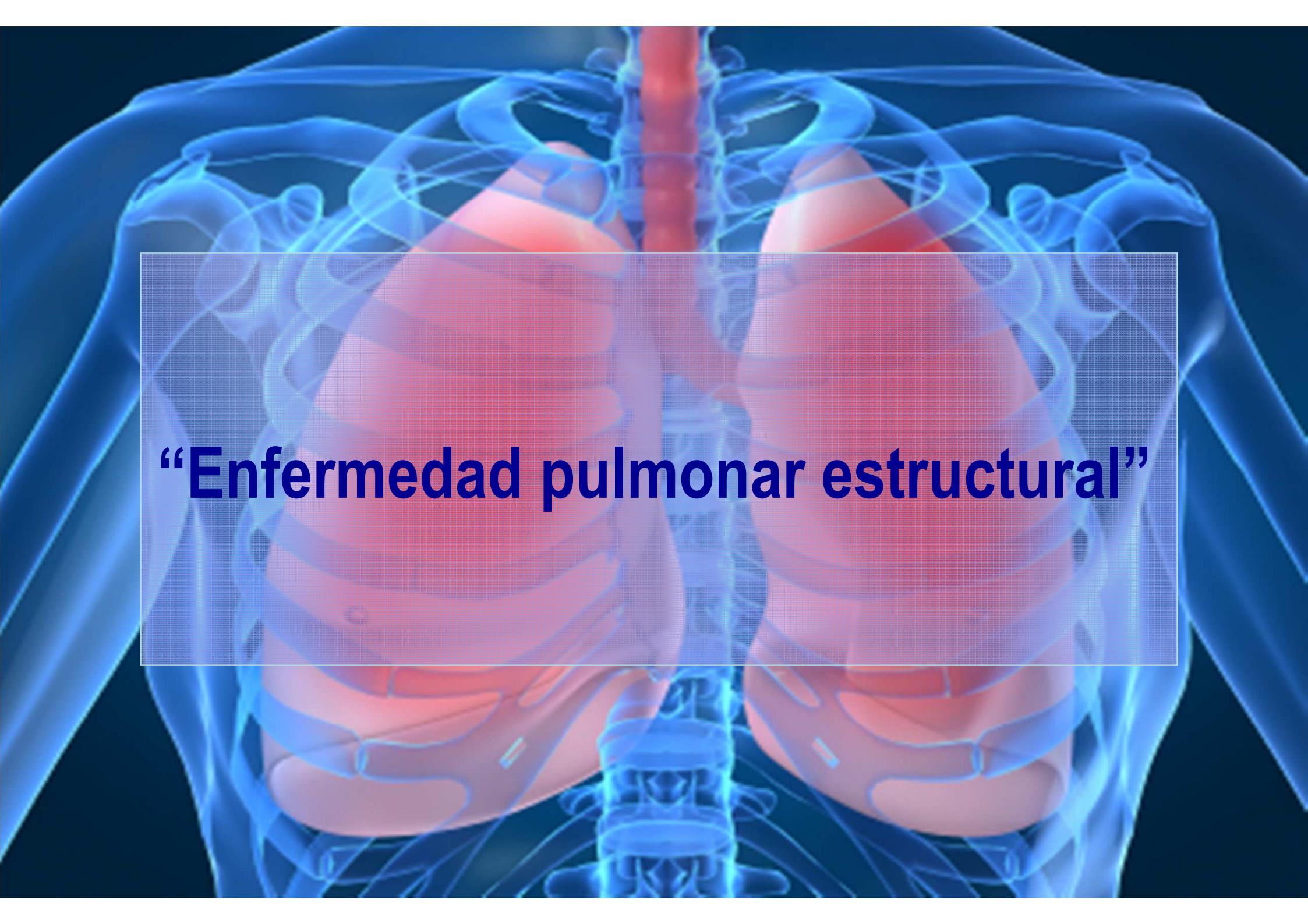
	Colonized N= 45	Possible (n=4)	Probable (n=15)	Definitive (n=5)	Aspergillosis N= 45
Age (mean ± SD)	71.9 ± 11.9	64.5 ± 7.6	64.3 ± 9.6	68.2 ± 10.3	65.1 ± 9.2 ^a
Males (%)	71.1	100	73.3	80.0	79.2
Charlson (median (IQ))	5.0 (5.0 - 6.0)	4.0 (3.0 - 5.7)	4.0 (2.0 - 5.0)	4.0 (2.0 - 5.0)	4.0 (2.2 - 5.0) ^b
COPD (% patients)	75.6	100	80.0	60.0	79.2
Previous stay in ICU (%)	22.2	25.0	53.8	20.0	41.7
Previous mechanical ventilation (%)	20.0	25.0	40.0	20.0	33.3
Previous antibiotic treatment (%)	93.3	100	93.3	100	95.8
Previous antifungal treatment (%)	20.0	25.0	53.0	20.0	41.7
Treatment with corticosteroids ^c (%)	62.2	75.0	81.0	60.0	75.0

^a p= 0.018 vs. colonized

^b p=0.034 vs. colonized

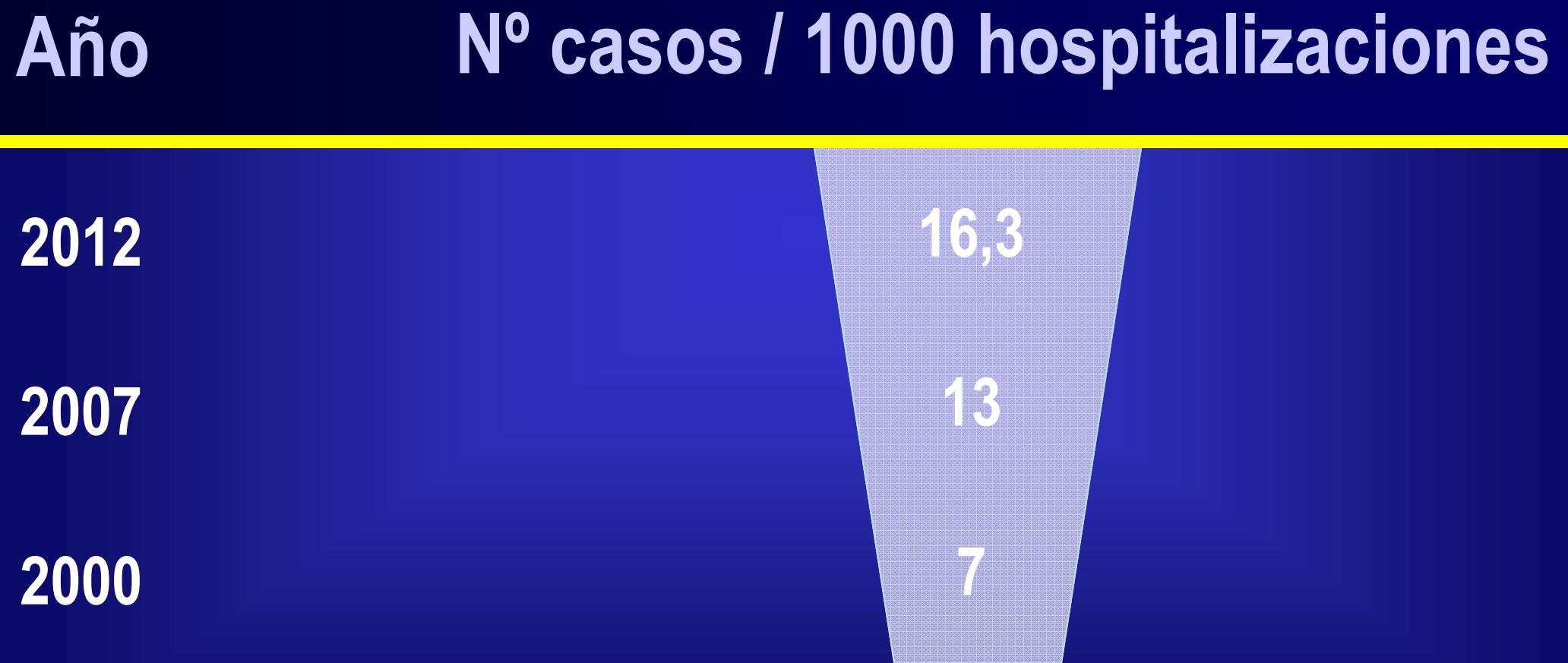
^c daily dose >30 mg prednisone (equivalent)

Lucena P et al. Rev Esp Quimioter 2010



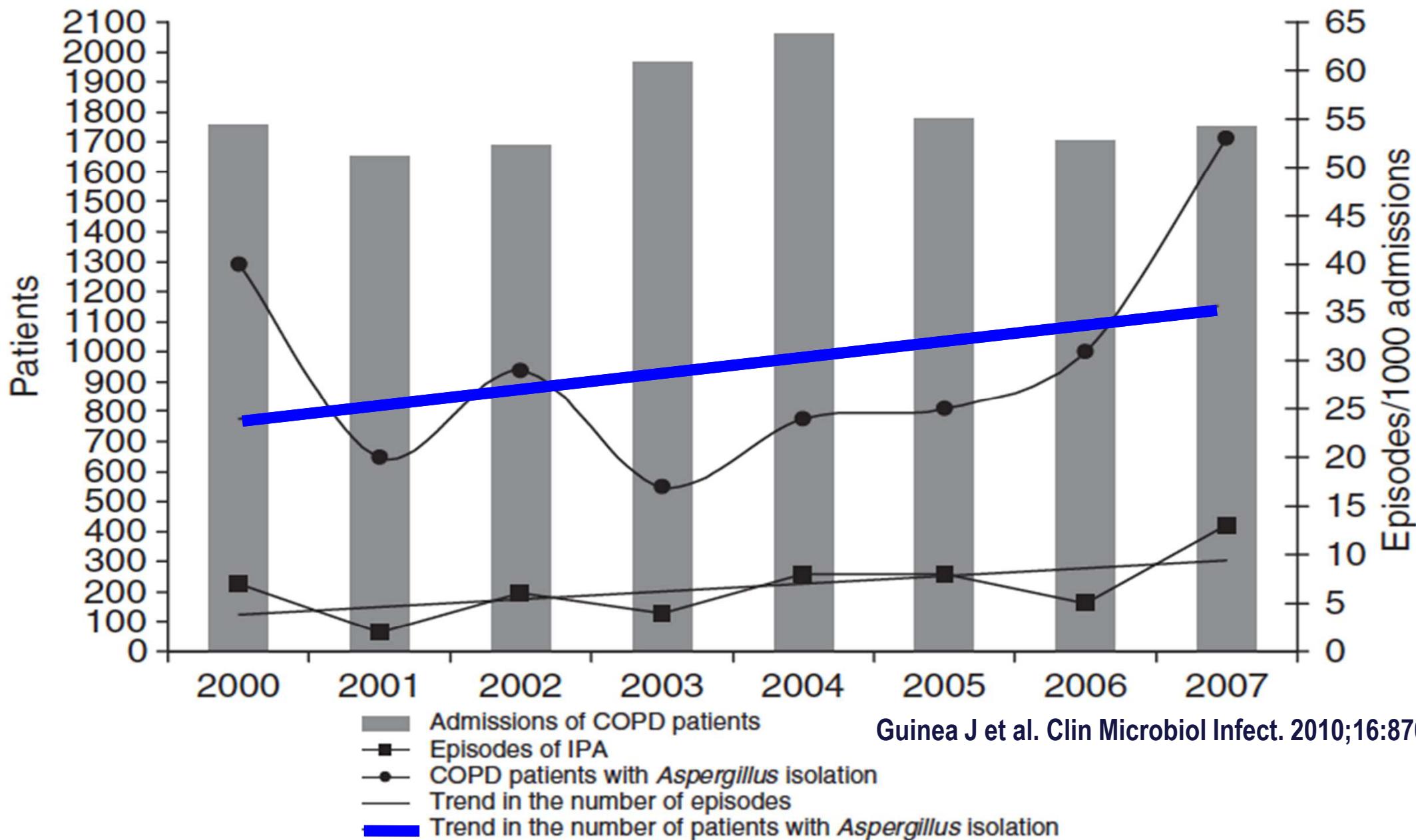
“Enfermedad pulmonar estructural”

Aislamiento *Aspergillus* – EPOC



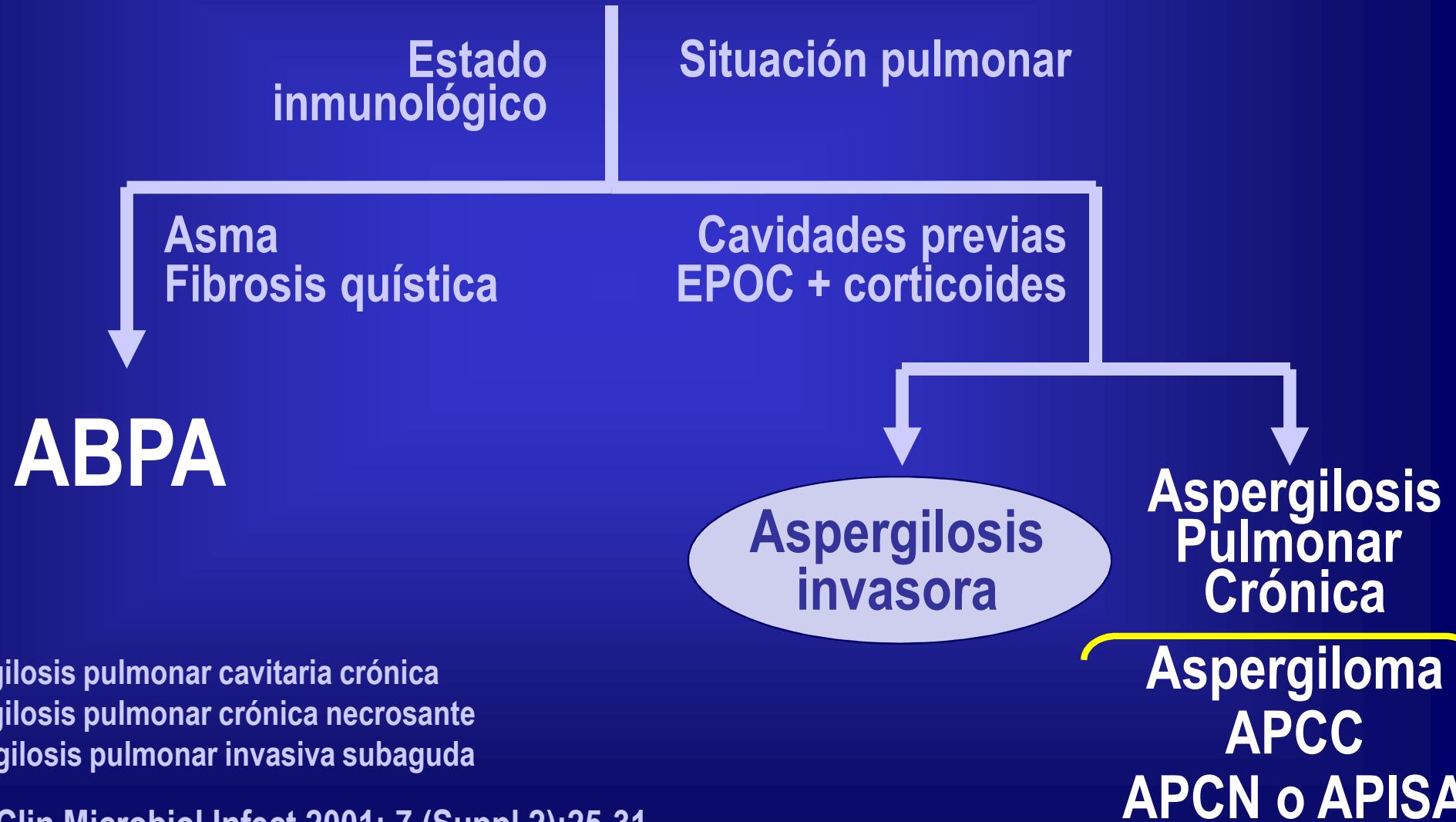
Xu H, et al. Clin Microbiol Infect 2012; 18:403-8.
Guinea J et al. Clin Microbiol Infect. 2010;16:870-7

Aislamiento de *Aspergillus* – EPOC



Enfermedad pulmonar – Aspergilosis

Exposición pulmonar a *Aspergillus*



APCC: aspergilosis pulmonar cavitaria crónica

APCN: aspergilosis pulmonar crónica necrosante

APISA: aspergilosis pulmonar invasiva subaguda

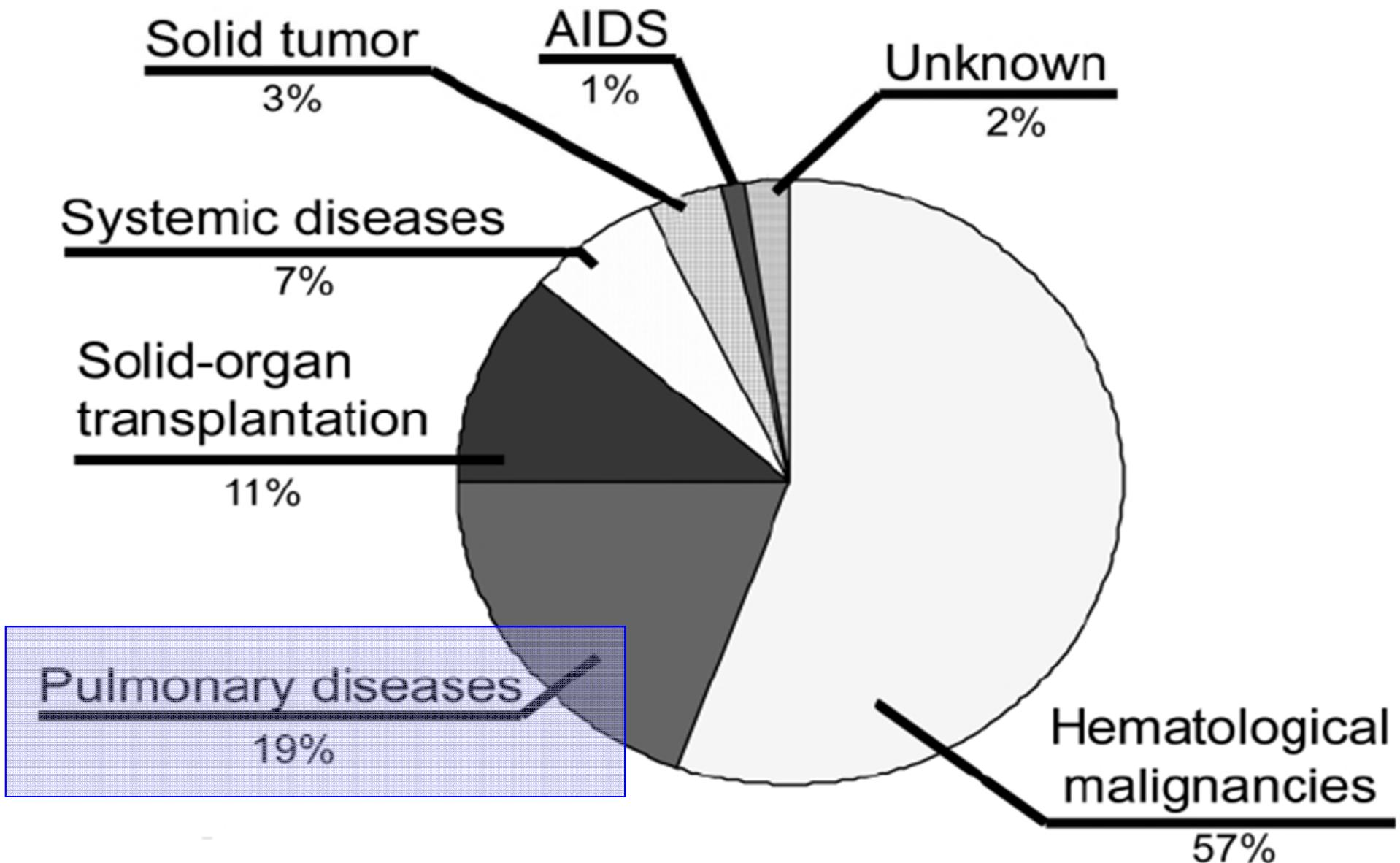
Aspergilosis invasora - Enfermedad de base

Enfermedad de base	Nº pacientes (%)
Trasplante mo	
Autólogo	43 (7)
Alogénico	151 (25)
Enfer hematológica	169 (29)
Trasplante de órgano sólido	52 (9)
SIDA	48 (8)
Tumor órgano sólido	25 (4)
Enfer granulomatosa crónica	9 (2)
Enfer pulmonares	56 (9)
Miscelánea	33 (5)
Ninguna	9 (2)
TOTAL	595 (100)

Enfermedad de base – *Aspergillus* spp

Enfermedad de base	Nº pacientes	Nº aislados	Aspergilosis invasora
Tumor órgano sólido	29	39	3 (10,3%)
EPOC + corticoides	100	179	10 (10%)
Leucemia	10	18	6 (60%)
Linfoma	6	8	1 (16,7%)
Trasplante	17	29	2 (11,8%)
VIH	27	50	4 (15%)
Otros factores riesgo	71	91	5 (7%)
TOTAL	260	404	31

Aspergillosis pulmonar invasora – Enf. base



API en EPOC – Mortalidad

Primary disease/underlying condition and case classification	No. (%) of patients, by outcome		
	Death (n = 63)	Recovery (n = 19)	Unknown (n = 6)
Primary disease/underlying condition			
Hematological malignancy			
All (n = 49)	29 (59)	16 (33)	4 (8)
Acute leukemia (n = 19)	8 (42)	11 (58)	0 (0)
Other hemopathy (n = 30)	21 (70)	5 (17)	4 (13)
Solid-organ transplantation (n = 10)	9 (90)	1 (10)	0 (0)
Chronic pulmonary disease (n = 18)	16 (89)	1 (5.5)	1 (5.5)
Vasculitis disease (n = 5)	5 (100)	0 (0)	0 (0)
Solid tumor (n = 3)	2 (67)	0 (0)	1 (33)
AIDS (n = 1)	1 (100)	0 (0)	0 (0)
Unknown (n = 2)	1 (50)	1 (50)	0 (0)

API en EPOC – Mortalidad

	AI n (%)	No AI n (%)	p
Supervivencia	15 (28,3)	128 (69)	<0,001
Mortalidad por AI	11 (20,7)	0	<0,001
Mortalidad por AI y otros	26 (49)	3 (1,6)	<0,001
Mortalidad NO po AI	1 (1,9)	44 (23,6)	<0,001

Aspergilosis pulmonar invasiva - EPOC

Manifestaciones clínicas	Bulpa	Samarakoon
■ Disnea	85%	32%
■ Tos		26%
■ Hemoptisis	9%	15%
■ Expectoración		12%
■ Dolor torácico	7%	8%
■ Pérdida de peso		8%

Bulpa P et al. Eur Respir J 2007; 30:782-800

Samarakoon P et al. Chorn Respir Dis 2008; 5:19-27

Aspergilosis pulmonar invasiva - EPOC

Manifest radiológicas	Bulpa	Samarakoon
■ Alteraciones	64%	78%
■ Infiltrados	25%	63%
■ I	Signo del halo: 1 paciente	
■ Cavitacion	5%	20%
■ Nódulo solitario	5%	6%
■ Derrame pleural	-	5%

Bulpa P et al. Eur Respir J 2007; 30:782-800
Samarakoon P et al. Chorn Respir Dis 2008; 5:19-27

Exacerbación EPOC – Indicación esputo

- Hospitalización con riesgo de microorganismos poco frecuentes o resistentes:
 - Antibióticos en 4 meses previos
 - Corticoides largo tiempo
 - > 4 exacerbaciones en año previo
 - FEV₁ < 30%
- Ingreso en UCI
- Mala respuesta en las primeras 72 h

Aislamiento *A. fumigatus* – Probabilidad API

Nº aislados	Probabilidad de API	p
1	5,8%	< 0,001
2	18,4%	
≥ 3	38,2%	

Diagnóstico API - *Galactomanano en suero*

Tipo paciente	S	E
Neutropénico	85	95
EPOC	41	93

Pfeiffer CD, et al. Clin Infect Dis 2006; 42:1417-27.
He H et al. Crit Care 2011;15:R5.

Galactomanano en BAL – Paciente EPOC

	BALF GM (95%CI) (cut-off 0.8)	BALF GM (95%CI) (cut-off 0.5)	Serum GM (95%CI) (cut-off 0.5)
Sensitivity (%)	88.9 (76.8 to 101)	88.9 (76.8 to 101)	77.8 (61.8 to 93.8)
Specificity (%)	100 (100 to 100)	47.1 (27.9 to 66.3)	100 (100 to 100)
PPV (%)	100 (100 to 100)	47.1 (27.9 to 66.3)	100 (100 to 100)
NPV (%)	94.4 (85.6 to 103.2)	88.9 (76.8 to 101)	89.5 (77.7 to 101.3)
TCR (%)	96.1 (88.7 to 103.5)	61.5 (42.8 to 80.2)	92.3 (82.1 to 102.5)

For probable IPA and control patients ($n = 26$).

IFI paciente hematológico - *Definición*

Host factors	Clinical features	Micology	Infection
-	+	+ ¹	Proven
+	+	+	Probable
+	+ ²	-	Possible
-	+	+	?
+	-	+	?
+	-	-	?

¹Tissue

²Halo sign

Aspergilosis invasora – Definición en EPOC

Proven IPA

Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with Aspergillus and evidence of associated tissue damage, if accompanied by any one of the following:

- 1) Positive culture of Aspergillus spp. from any LRT sample.
- 2) Positive serum antibody/antigen test for *A. fumigatus* (including precipitins).
- 3) Confirmation that the hyphae observed are those of Aspergillus by a direct molecular, immunological method and/or culture.

Probable IPA

As for proven IPA but without confirmation that Aspergillus is responsible (points 1, 2 and 3 are not present or tested).

OR

COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months⁺) and one of the following:

- 1) Positive culture[§] and/or microscopy for Aspergillus from LRT.
- 2) Positive serum antibody test for *A. fumigatus* (including precipitins).
- 3) Two consecutive positive serum galactomannan tests.

Possible IPA

COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months⁺), but without positive Aspergillus culture or microscopy from LRT or serology.

Colonisation

COPD patient with positive Aspergillus culture from LRT without exacerbation of dyspnoea, bronchospasm or new pulmonary infiltrate.

API probable* en EPOC – Factores predictores

Estudio multivariante

	Wald	p	OR	95% CI Inferior	Superior
ICU admission	4.758	0.029	2.406	1.093	5.294
Chronic heart failure	3.649	0.056	2.102	0.981	4.504
Accumulated dose of corticosteroids prior to admission ^a	6.213	0.013	2.987	1.263	7.060
Accumulated dose of corticosteroids during admission ^b	13.338	0.000	4.568	2.022	10.324
Antibiotic treatment ^a	5.924	0.015	2.570	1.202	5.497
Constant	66.327	0.000	0.034		

ICU, intensive-care unit.

^aIn the 3 months prior to admission.

^bFrom admission to the first clinical isolation of *Aspergillus* from LRT samples.

EPOC – API vs. colonización

Estudio multivariante

	API (n 48)	Colonización (n 70)	p
GOLD III + IV	71,1%	57,1%	0,025
Charlson index	$3,5 \pm 2,5$	$2,6 \pm 2,2$	0,027
Estancia en UCI	27,1%	4,3%	0,001

EPOC – Factores asociados con aspergilosis

Estudio multivariante

	p	OR
Cavitación Rx o TC	< 0,001	10,68
Empeoramiento radiológico	0,001	5,22
Necesidad más O ₂	< 0,001	3,52
UCI	0,012	2,82
IC	0,044	2,39
Corticoides previos	0,021	2,19

Aspergillus en EPOC – Factores mortalidad

Estudio multivariante

	API (n 48)	Colonización (n 70)	p
Global	58%	10%	<0,001
GOLD III	54%	0%	<0,001
Corticoides	78%	50%	0,038
Ab previos	60%	30%	0,036
Estancia en UCI	39%	10%	0,046

API - Escala diagnóstica

Scoring level	%			
	Sensitivity	Specificity	PPV ^a	NPV ^a
0	100	0	12	
1	90.3	50.65	19.9	97.5
2	67.7	74.7	26.6	94.5
3	54.8	92.1	48.6	93.8
4	32.3	98.7	77.0	91.5
5	22.6	98.7	70.0	90.4
7	16.1	99.6	83.3	89.8
9	6.5	99.6	66.7	88.7
10	3.2	100	100	88.4

Muestra (invasiva), ≥ 2 muestras, leucemia, neutropenia, corticoides

^aIA incidence 1.6 cases/10,000 admissions

Bouza E et al. J Clin Microbiol 2005

Paciente EPOC - Aislamiento hongo filamentoso muestras respiratorias

Barberán J and Mensa J. Rev Iberoam Micol 2014 (In press)

Identificación/aislamiento de un hongo filamento o de *Aspergillus spp* en una muestra de secreción respiratoria



Obtener una segunda muestra (aspirado traqueal o lavado broncoalveolar) para tinción de calcoflúor, cultivo y determinación del AGA



¿El paciente tienen factores de riesgo, clínica o imagen radiológica de infección respiratoria?

SI

Considerar la práctica de una TC de tórax, la determinación de AGA en sangre y el comienzo de tratamiento antifúngico empírico

NO

Esperar el resultado de las pruebas microbiológicas

positivas

negativas
fin del estudio

Tratamiento antifúngico empírico – Criterios de elección

Barberán J and Mensa J. Rev Iberoam Micol 2014 (In press)

Imagen radiológica (Rx simple o TC) o fact riesgo de IFI

SI

Voriconazol iv^{1,2}

Anfotericina B
liposomal iv^{1,2}

NO³

Probable colonización
endobronquial.
Considerar el tratamiento
con anfotericina B
liposomal inhalada

¹No en caso de:

- Hongo diferente de *Aspergillus*
- Tratamiento con fármacos que prolongan QT*
- Hepatopatía (transaminasas valor normal x5)

²Si la evolución no es favorable considerar:

- La adición de anfotericina B liposomal inhalada o
- Las asociaciones de antifúngicos

³Al menos en dos muestaras

** Citalopram, difenhidramina, fluxetina, foscarnet, granisetron,
metronidazol, nortriptilina, ondansetron, pentamidina, macrólidos

¿Qué ha pasado con los colonizados?

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