Démarche transversale clinique et thérapeutique appliquée aux infections parasitaires chez les transplantés

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- Toxoplasmose
- Anguillulose
- Chagas
- Cryptosporidiose
- Palu
- Leishmaniose

Toxoplasmose et transplantation d'organe solide

- Transplantation organe solide
  - Chez le patient D+/R-, transmise par le greffon
  - Fonction de la séroprévalence globale et de l'immunodepression
  - Tropisme parasite pour certains organes (risque plus élevé chez les transplantés cardiaques et cœur poumons)
  - Risque le plus élevé pour transplanté cardiaque D+/R sans prophylaxie: 55-75%
  - Présentation clinique:
    - Non spécifique
    - Fièvre initiale
    - Atteinte d'organe: poumon, cérébral, infection disséminée
  - Diagnostic: PCR sur le sang (89% des diag chez HSCT et SOT) et les liquides, histopath identifiant les tachyzoites , serologie difficile à interpreter

Toxoplasmose transplantation organe

- 2000-2009
- 22 cas toxoplasmose pour 15800 SOT
  - Cœur (12)
  - Rein (6), Foie (4)
- Incidence 0.61% T cardiaques vs 0.08% T rein ou foie chez D+/R-
- 92 jours en moyenne après la transplantation
- Sérologie négative en pretransplant associé à la survenue de toxoplasmose (OR 15)

Dhakal R, Curr Opin Organ Transplant 2018

Toxoplasmose chez transplantés non cardiaques

- 31 cas toxoplasmose
- 2004-2017
- Non cardiac SOT
- 90% rein, 16% foie
- 94% chez patients seronegatifs
- 63% Transmis par donneur
- Pas de prophylaxie au diagnostic
- 43% mortalité, 100% mortalité si survenue dans les 30 jours, 25% si survenue après J180, 69% mortalité si disséminé vs 33% CNS

Dhakal R, Curr Opin Organ Transplant 2018

- 52 cas toxoplasmoses chez SOT
- 34 rein
- 12 foie
- 86% ds 90 jours post transplant
- 35% décès
- D+/R-: J16, survie plus faible
- D-: J31

Campbell AL, Transplantation 2006

Données Européenne

- 46 centres, 11 pays
- 2010-2014
- 29 cas
- 59% non cardiaque transplant
- 46%: D+/R-
- 8/28 : après arrêt prophylaxie
- Survie 74% si prophylaxie avant survenue vs 37%

Robert-Gangneux F, EID, 2018

Table 4. Characteristics of transplant patients with toxoplasmosis, according to graft type and comparison to overall graft population, Europe, 2010–2014*

Characteristics	Allo-HSC		Kidney		Liver		Heart		p value
	Case-patients	All TP	Case-patients	All TP	Case-patients	All TP	Case-patients	All TP	
Patients, no.	58	4,108	9	6,507	8	2,983	12	998	NA
Age, y, mean ± SE	46.8 ± 5.3	50.7	44.6 ± 5.9	50.9	55.1 ± 1.5	51.6	44.4 ± 6.4	47.5	NA
Female sex, %	43	38	44	63	38	30	17	22	NA
Male sex, %	57	62	56	37	62	70	83	78	NA
Mean time diagnosis/graft, wk, mean ± SE	20.6 ± 4.6	NA	198 ± 68	ND	152 ± 144	ND	441 ± 155	ND	<0.0001
Mean time diagnosis/death, d, mean ± SE	47 ± 18	NA	33	ND	38 ± 17	ND	NA	ND	0.8595
Mismatched serologic results (D+/R−), no. (%)	0	NA	4 (33)	NA	3 (38)	NA	4 (33)	NA	0.8923
2-mo survival, no. (%)	36 (62)	ND	8 (89)	ND	5 (63)	ND	12 (100)	ND	<0.05
Deep site involvement	12 (43)	ND	3 (60)	ND	4 (57)	ND	6 (100)	ND	0.0513
Fever only	5 (100)	ND	3 (100)	ND	0	ND	2 (100)	ND	1
No clinical signs	18 (72)		1 (100)		1 (100)		4 (100)		0.1407
6-mo survival, %†	38	84‡	89	72	50	75§	100	60	<0.0001
Deep site involvement	25	NA	60	NA	28	NA	100	NA	<0.01
Fever only	40	NA	100	NA	0	NA	100	NA	0.2083

*D+, donor positive; NA, not applicable; ND, not determined; NS, not significant; R−, recipient negative; TP, transplant patients.
†The survival rate for the general TP population was calculated at a time similar to the mean time of diagnosis of toxoplasmosis after graft in case-patients.
‡p<0.01 compared with case-patients.
§p<0.05 compared with case-patients.

Table 6. Survival among transplant patients with toxoplasmosis, according to patients' characteristics, Europe, 2010–2014

Characteristic	2-mo survival		6-mo survival	
	No. patients/no. survived (%)	p value*	No. patients/no. survived (%)	p value*
All patients	61/87 (70)	Not applicable	46/87 (53)	Not applicable
Chemoprophylaxis				
Yes	30/35 (86)	<0.05	26/35 (74)	<0.01
No	27/43 (63)		16/43 (37)	
Recipient serologic status				
Positive	27/45 (60)	<0.05	15/45 (33)	<0.001
Negative	22/25 (88)		20/25 (80)	
Type of graft				
Hematopoietic stem cell	36/58 (62)	<0.05	22/58 (38)	<0.001
Solid organ	25/29 (86)		24/29 (83)	

*Exact χ^2 test.

Robert-Gangneux F, EID, 2018

Table 3. Overview of toxoplasmosis diagnosis strategies in transplant recipients based on clinical symptomatology.

Toxoplasmosis	Clinical features	Imaging	Sample(s) for diagnosis	Techniques	Main differential diagnosis	Ref.
Disseminated toxoplasmosis (multiple organ involvement)	Fever plus clinical signs, depending on organs involved	On organs potentially involved	Blood, Bone marrow aspirates, BAL, CSF Biopsies [a]	PCR[c] PCR, (Giemsa) PCR, histology	Other infections: viral (HSV, VZV, CMV); bacteremia, fungemia. GvHD	[7,11,12,20,29,54,64,72,73]
Cerebral toxoplasmosis	Brain abscess, encephalitis	MRI or CT scan: Brain abscesses: homogenous nodules, ring enhancement surrounding edema and mass effect. Diffuse encephalitis: non-focal and atypical lesions	CSF Brain biopsy [b]	PCR[c], (Giemsa) Intrathecal Ig synthesis[d] (WB) PCR, histology	Other infections: mycobacteria, cryptococcosis, bacterial abscess, Chagas disease; malignancies (CNS lymphoma), PML.	[11,74]
Retinochoroiditis (posterior uveitis)	Eye pain; decreased visual acuity, +/- vitreous inflammation	Funduscopic examination: yellow-white, cottony lesions showing nonvascular distribution; isolated or diffuse and multiple foci of active retinitis in one or both eyes	AH, vitreous fluid (and serum in parallel)	PCR, intraocular Ig synthesis: GWC* and comparative WB	Other infections: viral (HSV, VZV, CMV); bacterial (*Treponema pallidum*); parasitic (*Toxocara sp*)	[34,74–76,88]
Pneumonitis	Fever, dyspnea; non-productive cough, acute distress syndrome, hypoxia	Chest CT scan: Reticulonodular, diffuse or localized infiltrates; interstitial pneumonitis with alveolar condensations.	BAL, Blood	PCR, (Giemsa) PCR	Other infections: *Pneumocystis jirovecii*, *Mycoplasma pneumonia*, *Chlamydia pneumonia*, *Legionella pneumophila*, viruses, diffuse alveolar hemorrhage, acute drug reactions	[7,11,81,87]
Myocarditis (reactivation in heart tissue)	Congestive heart failure, arrhythmia, pericarditis	ND	Blood, Endomyocardial biopsy	PCR PCR, histology	CMV, EBV, bacteria, opportunistic and endemic fungi	[82–85]
Cutaneous toxoplasmosis	Rare diagnosis	None	Skin biopsy	PCR, histology	*Leishmania* sp, *Histoplasma* sp	[79]

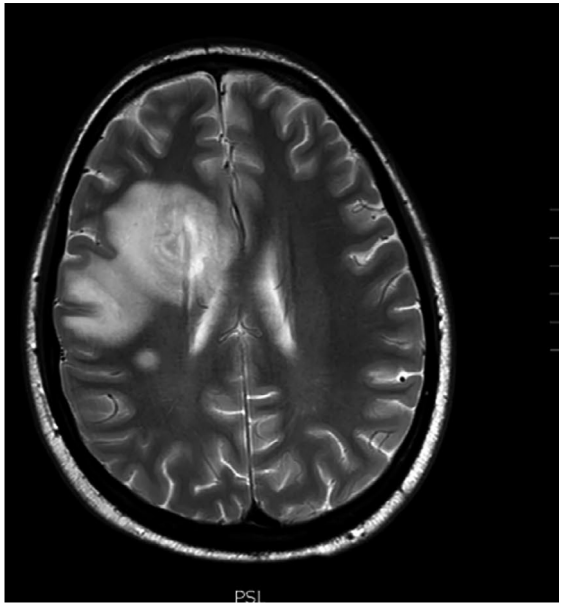
Table 1. Characteristics of 87 transplant patients with toxoplasmosis, according to clinical presentation, Europe, 2010–2014*

Variables	Clinical type						p value
	Cerebral	Ocular	Disseminated	Pulmonary	Fever alone	No signs	
No. (%) patients	13 (15)	4 (5)	19 (22)	10 (11)	10 (11)	31 (36)	
Patient age, y, mean ± SE	37.0 ± 7.7	60.7 ± 0.8	47.8 ± 5.6	53.1 ± 4.8	35.5 ±4.4	46.4 ± 4.2	<0.0001
Time graft/diagnosis, wk, mean ± SE	123 ± 151	313 ± 175	163 ± 124	19 ± 11	73 ± 43	99 ± 51	<0.05
Diagnosis by, no. (%)							
PCR	13 (100)	3 (75)	17 (89)	9 (90)	9 (90)	26 (84)	<0.001
Serology	3 (23)	3 (75)	9 (47)	2 (20)	5 (50)	5 (16)	0.2278
Imaging	12 (92)	3 (75)	8 (42)	7 (70)	0	2 (6)	<0.01
Microscopy	1 (8)	0	6 (32)	1 (10)	0	0	<0.01
Graft type, no. (%)							<0.05
Liver, n = 8	1 (8)	1 (25)	3 (16)	2 (20)	0	1 (3)	
Kidney, n = 9	1 (8)	1 (25)	1 (5)	2 (20)	3 (30)	1 (3)†	
Heart, n = 12	0	1 (25)	5 (26)	0	2 (20)	4 (13)‡	
Allo-HSC, n = 58	11 (85)	1 (25)	10 (53)	6 (60)	5 (50)	25 (81)§	
No. with mismatch, n = 11	0	1 (25)	5 (26)	1 (10)	4 (40)	0	<0.05
Survival, no. (%)							
2 mo	5 (38)	4 (100)	13 (68)	5 (50)	10 (100)	24 (77)	<0.0001
6 mo	2 (15)	4 (100)	10 (53)	5 (50)	7 (70)	18 (58)	<0.001

*HSC, hematopoietic stem cell.
†This patient was receiving chemoprophylaxis.
‡1 patient was receiving chemoprophylaxis.
§11 patients were receiving chemoprophylaxis.

Table 2. Characteristics of transplant donors and recipients at transplantation, according to *Toxoplasma* serologic status, Europe, 2010–2014*

Serologic status of donor/recipient†	Prophylaxis, no. (%)	Graft type, no.				Survived 6 mo, no. (%)	Wks between diagnosis and graft, mean ± SE
		Liver	Kidney	Heart	HSC		
Positive/positive, n = 9‡	5 (56)	2	0	1	6	3 (33)	21 ± 9
Positive/negative, n = 11§	4 (36)	3	4	4	0	9 (82)	309 ± 275
Negative/positive, n = 36¶	12 (33)	0	0	1	35	12 (33)	15 ± 3
Negative/negative, n = 14	9 (64)	2	2	5	5	11 (79)	123 ± 31
p value	0.1975	NA	NA	NA	NA	<0.01 (0.0029)	<0.05



Robert-Gangneux F, EID, 2018

Diagnostic

- Tachyzoites en histologie (hematoxylin ou Giemsa)
- Ou à l'examen direct marqué au Giemsa sur myélo, LBA, CSF
- PCR sur sang, LBA, CSF, tissu
  - Plus sensible que Giemsa
  - PCR sur sang

Table 4. **Definitions of *Toxoplasma* infection and *Toxoplasma* diseases.** Adapted from the recommendations of the European Group for Blood and Marrow Transplantation Infectious Diseases Working Party (EBMT-IDWP) [91].

Definitions		Criteria
Toxoplasma Infection		Seroconversion in a previously *T. gondii* seronegative person or presence of detectable *Toxoplasma* PCR in the blood without evidence of organ involvement, with or without fever
Toxoplasma disease (*Toxoplasma* infection + organ involvement demonstration)	✓ **Possible disease**	Radiologically (CT scan or MRI) and clinically consistent with organ involvement
	✓ **Probable disease**	Radiologically and clinically consistent with organ involvement + detectable *T. gondii* DNA (by PCR) in blood, tissue (biopsy) or body fluid (BAL, CSF).
	✓ **Definite disease**	Histological or cytological evidence of organ disease: tachyzoites evidence in tissue (biopsy), body fluid (BAL, CSF) or at autopsy.

BAL: broncho-alveolar lavage, CSF: cerebro-spinal fluid, CT: computed tomography, MRI: magnetic resonance imaging

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
2018, VOL. 16, NO. 6, 447–460
https://doi.org/10.1080/14787210.2018.1483721

Taylor & Francis
Taylor & Francis Group

REVIEW

Management of toxoplasmosis in transplant recipients: an update

Céline Dard[a,b], Pierre Marty[c,d], Marie-Pierre Brenier-Pinchart[a,b], Cécile Garnaud[a], Hélène Fricker-Hidalgo[a], Hervé Pelloux[a,b] and Christelle Pomares[c,d]

Country	population	in allo-HSCT (R^+ and R^-)	(R^+ only)	toxoplasmosis in allo-HSCT	Period of the study	Ref
France	Intermediate	3.2 – 3.9 %	*Toxoplasma* disease: 5.7 – 6 % *Toxoplasma* infection: 12.8 %	ND	2006 – 2015 2004 – 2006 2009 – 2011	[7] [29] [43]
Germany	Low to intermediate	9.3%	13.2%	2.7%	ND	[24]
Spain	Low to intermediate	ND	*T.* disease: 6% *T.* infection: 16%	2.8%	2001 – 2002	[45]
Italy	Low to intermediate	2.1%	ND	ND	2011 – 2015	[23]
Multi-center studies in Europe	NA	0.93% for all allo-HSCT	2.7% in seropositive recipients under prophylaxis	ND	1994 – 1998	[19]
USA	Low	0.3%	2.1%	40%	Before 1994 over a period of 20 years	[33]
Brazil	High	1.1%	7.6%	4.6%	1987 – 1998	[25]
Japan	Low	2.2%	19.6%	13%*	1998 – 2016	[87]
China	Low to intermediate	2%	0%	0%	1990 – 2001	[26]
Review	NA	ND	ND	66%	1966 – 2000	[73]

SOT

Country	Overall seroprevalence in the general population	Incidence of toxoplasmosis in			Mortality related to toxoplasmosis	Period of the study	Ref
		Heart and heart-lung	Renal	Liver			
France	Intermediate	1.4%	0.2%	0.16%	29%	2009 - 2011	[29]
Spain	Low to intermediate	0.61%	0.08%	0.08%	13.6%	2000 - 2009	[54]
Switzerland	Low to intermediate	13%	NA	NA	ND	1985 - 1991	[27]
USA	Low	25% (D^+/R^- with no prophylaxis)	NA	NA	25% (D^+/R^- with no prophylaxis)	1980 - 1996	[28]
Canada	Low	No patient with clinical disease	NA	NA	ND	1984 – 1997	[64]
Review	NA	NA	ND	NA	50% (renal transplant)	1966 - 2009	[72]

Recommandations prise en charge toxxoplasmose et SOT

- 2019
- Screening doneurs et recevurs toxxoplasmose
- IgG Toxoplasma
- Identification haut risque D+/R-
- Prophylaxie par TMP/SMX
- Sinon: Monitoring PCR Toxoplasma sang /sem en post transplant précoce et traitement pré emptif

La Hoz RM Clin Transplant 2019

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

A matched case–control study of toxoplasmosis after allogeneic haematopoietic stem cell transplantation: still a devastating complication

A. Conrad [1,2,3], M. Le Maréchal [4], D. Dupont [3,5,6], S. Ducastelle-Leprêtre [7], M. Balsat [7], H. Labussière-Wallet [7], F. Barraco [7], F.-E. Nicolini [7], X. Thomas [7], L. Gilis [7], C. Chidiac [1,3], T. Ferry [1,2,3], F. Wallet [8], M. Rabodonirina [3,5,9], G. Salles [3,7], M. Michallet [3,7], F. Ader [1,2,3,*] on behalf of the Lyon HEMINF study Group

- 2006-2015
- HSCT; cas contrôle 2:1
- 33 cas (3.9%)/588
- Pour appariement 20 maladies (14 poumon), 3 infections
- J62 après allogreffe
- 14 atteintes pulmonaires
- 87% sérologie + en pré transplant, 62% R-/D-
- 19: pas de prophylaxie, 4 prophylaxie par TMP/SFX (n=3) ou pyrimethamine-sulfadiazine (n=1)
- Survenue précoce si mismatch unrelated, tardif si GVH avec cot refractaire
- FDR: absence de prophylaxie efficace, GVH aigue grade III-IV, anti TNF
- Mortalité 43%

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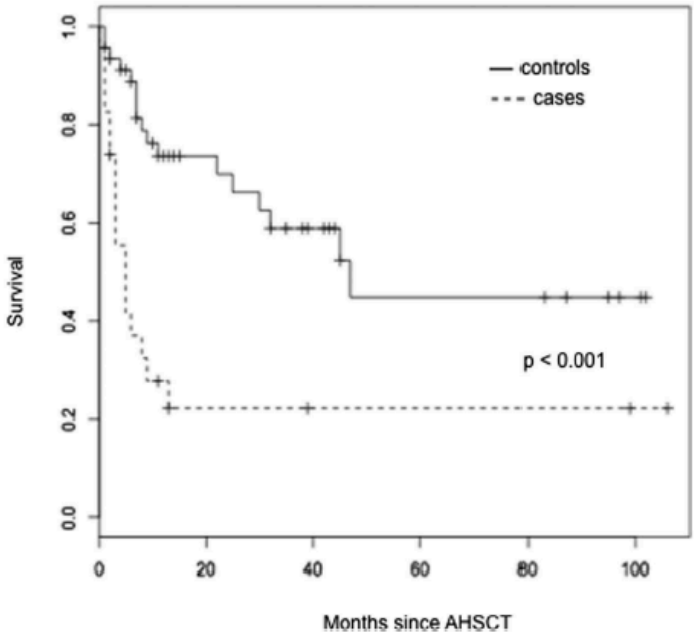
Présentation clinique:

-Pneumopathie interstitielle n=14

-SNC n=10-encéphalits n=6, abces cerebral n=4, 2 SAM

Pas de myocardite ni de choriorétinite



Biol Blood Marrow Transplant 25 (2019) 2510–2513

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Toxoplasmosis as an Early Complication of Allogeneic Hematopoietic Cell Transplantation

Christine Robin[1,2,*], Mathieu Leclerc[1,2], Cécile Angebault[2,3], Rabah Redjoul[1], Florence Beckerich[1], Ludovic Cabanne[1], Francoise Foulet[3], Cécile Pautas[1], Andréa Toma[1], Sébastien Maury[1,2], Francoise Botterel[2,3,4], Catherine Cordonnier[1,2]

- 419 allo
- 17 (4%) toxoplasmose
- Survenue J45
- 7 cas avant J30
- 2 diagnostiqué sur PCR: traitement préemptif
- 5 autres: fièvre et pneumopathie
- Devant absence prophylaxie et screening PCR: diagnostic tardif:
- 5 decès /7

J Antimicrob Chemother 2017; 72: 2602–2606
doi:10.1093/jac/dkx198 Advance Access publication 22 June 2017

Journal of Antimicrobial Chemotherapy

Plasma concentrations of atovaquone given to immunocompromised patients to prevent *Pneumocystis jirovecii*

Christine Robin[1,2], Minh Patrick Lê[3,4], Giovanna Melica[5], Laurent Massias[3,4], Rabah Redjoul[1], Nihel Khoudour[6], Mathieu Leclerc[1,2], Florence Beckerich[1,2], Sébastien Maury[1,2], Anne Hulin[6] and Catherine Cordonnier[1,2]*

- 82 dosages 33 patients traités par atovaquone pour PCP
- 58% patients sous doasgeen attovuone Cmin <15microg/ml
- Associé avec mauvaise réponse au traitement

Bull Cancer 2019; 106S: S23–S34
en ligne sur / on line on
www.em-consulte.com/revue/bulcan
www.sciencedirect.com

Info.suppl.

Prophylaxie des infections post-allogreffe : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire (SFGM-TC)

Philippe Lewalle [1], Cécile Pochon [2], Mauricette Michallet [3], Pascal Turlure [4], Eolia Brissot [5], Catherine Paillard [6], Mathieu Puyade [7], Gabrielle Roth-Guepin [8], Ibrahim Yakoub-Agha [9,10], Sylvain Chantepie [11]

- Patients à haut risque:
  - Sérologie positive avant allogreffe
  - Prophylaxie dès que possible
  - TMP/SMXX 400mg/j ou 800mg/j 3 X / sem 6 à 12 mois
  - Peu de données sur traitement alternatif: atovaquone 750mg X 2/j alternative valide
- Traitement pré emptif guide par monitoring PCR en l'absence de prophylaxie
- sur TMP/SFX 3X/sem ou atovaquone en pré prise de greffe ?

Bone Marrow Transplantation (2020) 55:93–99
https://doi.org/10.1038/s41409-019-0641-y

ARTICLE

Features of *Toxoplasma gondii* reactivation after allogeneic hematopoietic stem-cell transplantation in a high seroprevalence setting

Olivier Paccoud[1] · Juliette Guitard[2] · Myriam Labopin[1,2] · Laure Surgers[4,5] · Florent Malard[1,3] · Giorgia Battipaglia[1] · Rémy Duléry[1] · Christophe Hennequin[3] · Mohamad Mohty[1,3] · Eolia Brissot[1,3]

- 138 allo HSCT 4 ans
- 49% not receiving TMP-SMZ at D30
- M6: 11.6% reactivation,9 infections, 7 diseases
- 56% reactivation before D30
- 38% in patients with atovaquone prophylaxis
- After study: TMP-SMZ use from the day of engraftment. M16: in 89% of elligible patients; 1.5% reactivation

Traitement curatif

- TMP/SFX
- Pyrimethamine (50-100mg/j) et Sulfadiazine (4-6g/j)
- Pyrimethamine: toxicité hématologique
- Substitution acide folique
- Si allergie sulfadiazine: clindamycine ou azithromycine
- Atovaquone, doxycycline et dapsone agents anti toxoplasma alternatifs

Maladie de Chagas

- *Trypanosoma cruzi*
- Amérique Latine
- Transmission lié au greffon
- Réactivation
- Fièvre, hépatosplénomégalie, myocardite
- Sérologie pré transplant en cas de voyage en zone d'endémie non recommandée par les guidelines internationales

Leishmaniose

- Leishmaniose viscérale
- Fièvre, hépatosplénomégalie, pancytopénie: 1/3 des patients
- 11 mois post transplant
- Prévention: pas de recommandation de dépistage avant greffe
- Diagnostic:
  - Moelle le plus sensible
  - Buffy coat: Èxamen direct, histopathology, culture, PCR
  - PCR sur sang (Se 65%) ou moelle (Se 75%)
- Traitement:
  - L Amb: 4mg/kg/j J1-5, 10, 17, 24, 31, 38 (total 40mg/kg)
  - Réduction IS
  - Monitoring PCR
  - Pas de prophylaxie secondaire

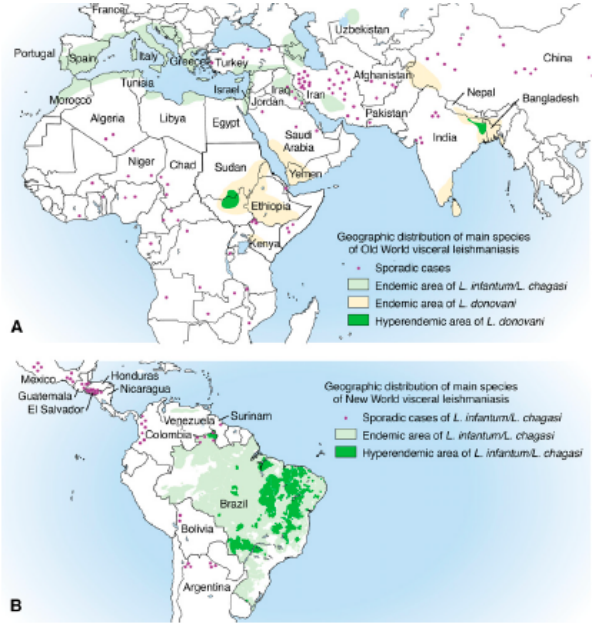


Figure 3. Maps of the Geographic Distribution of Visceral Leishmaniasis (VL)

Aronson N, Am J Trop Med Hyg 2017

Anguillulose

- *Strongyloides stercoralis*
- Risque de Strongyloides hyperinfection syndrome (SHS)
- Risque important au cours de la GVH
- Présentation: pulmonaire, digestive, disséminée
- Fièvre, bactériémies, exanthème, douleurs abdominales, diarrhée, hémoptysies, sibiliants, méningite à Gram négatifs
- Hyperéosinophilie (peuvent être normaux)
- Sérologie (sensibilité chez l'immunodéprimé?), EPS
- Ivermectine à répéter à 2 semaines