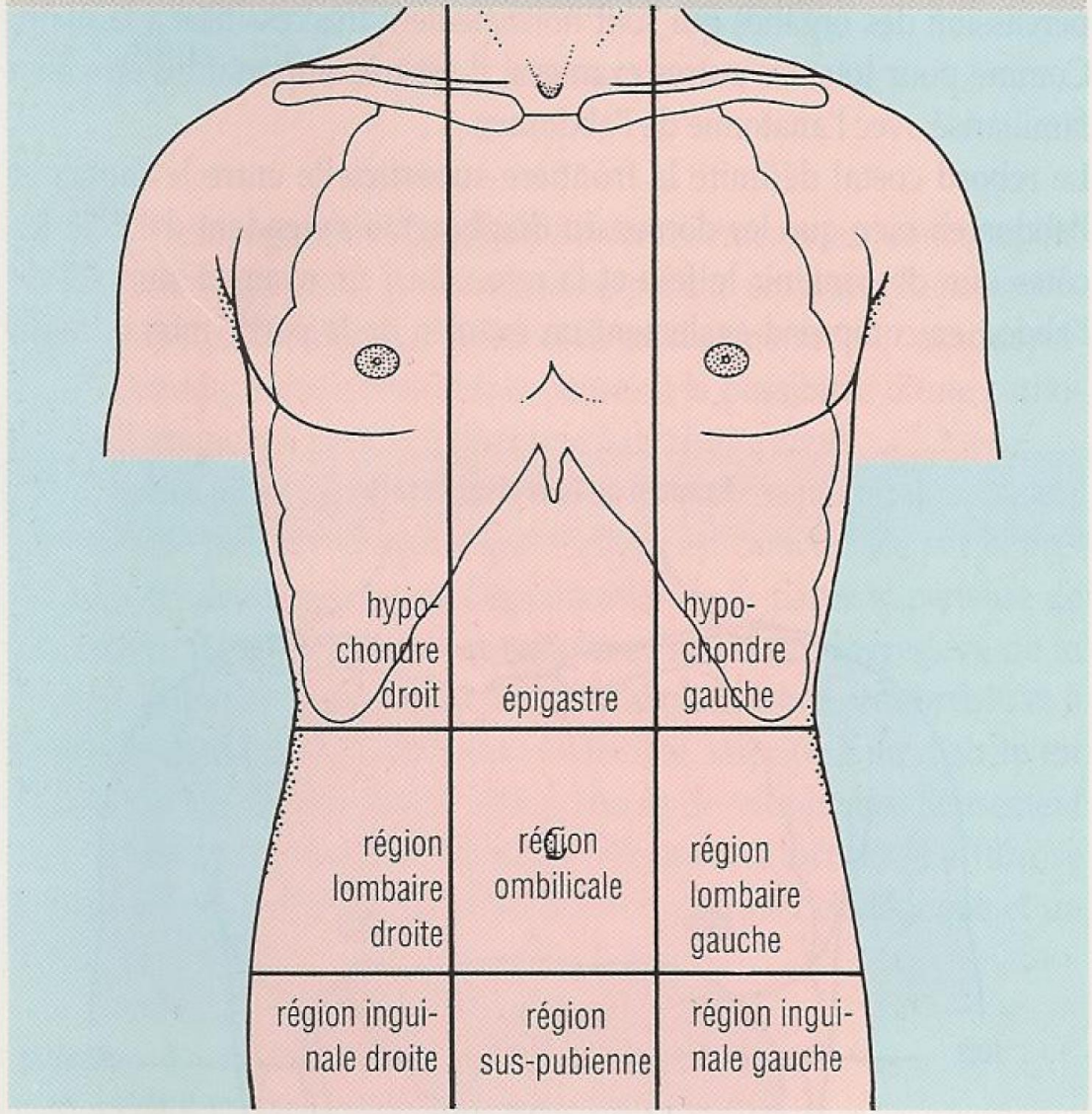
Douleurs abdominales (et ictère)

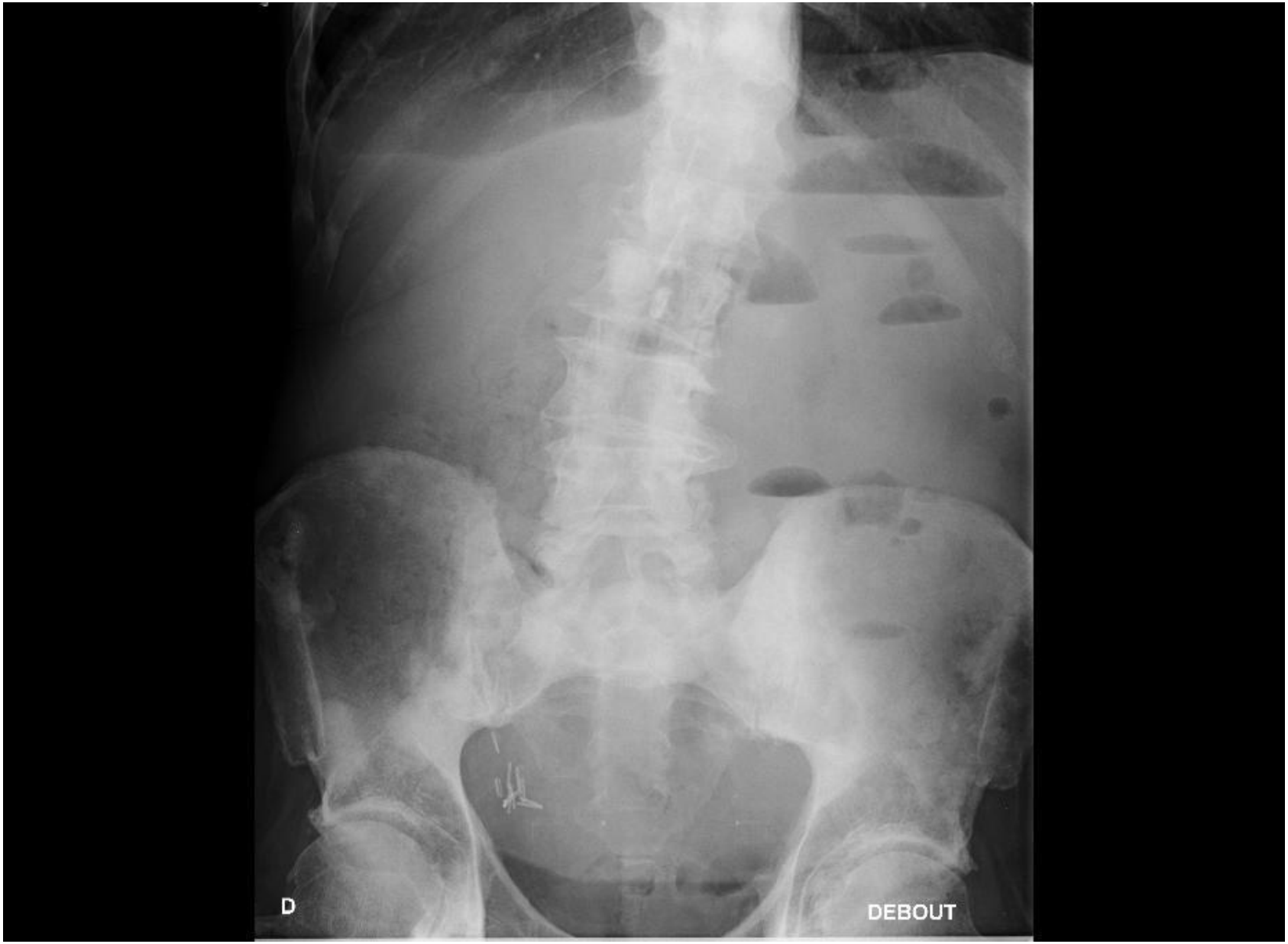
Segmentation anatomique de l'abdomen



Abdomen aigu

Les complications intestinales graves

- Iléus mécanique
- Iléus paralytique
  - Perforation
- *Hémorragie*



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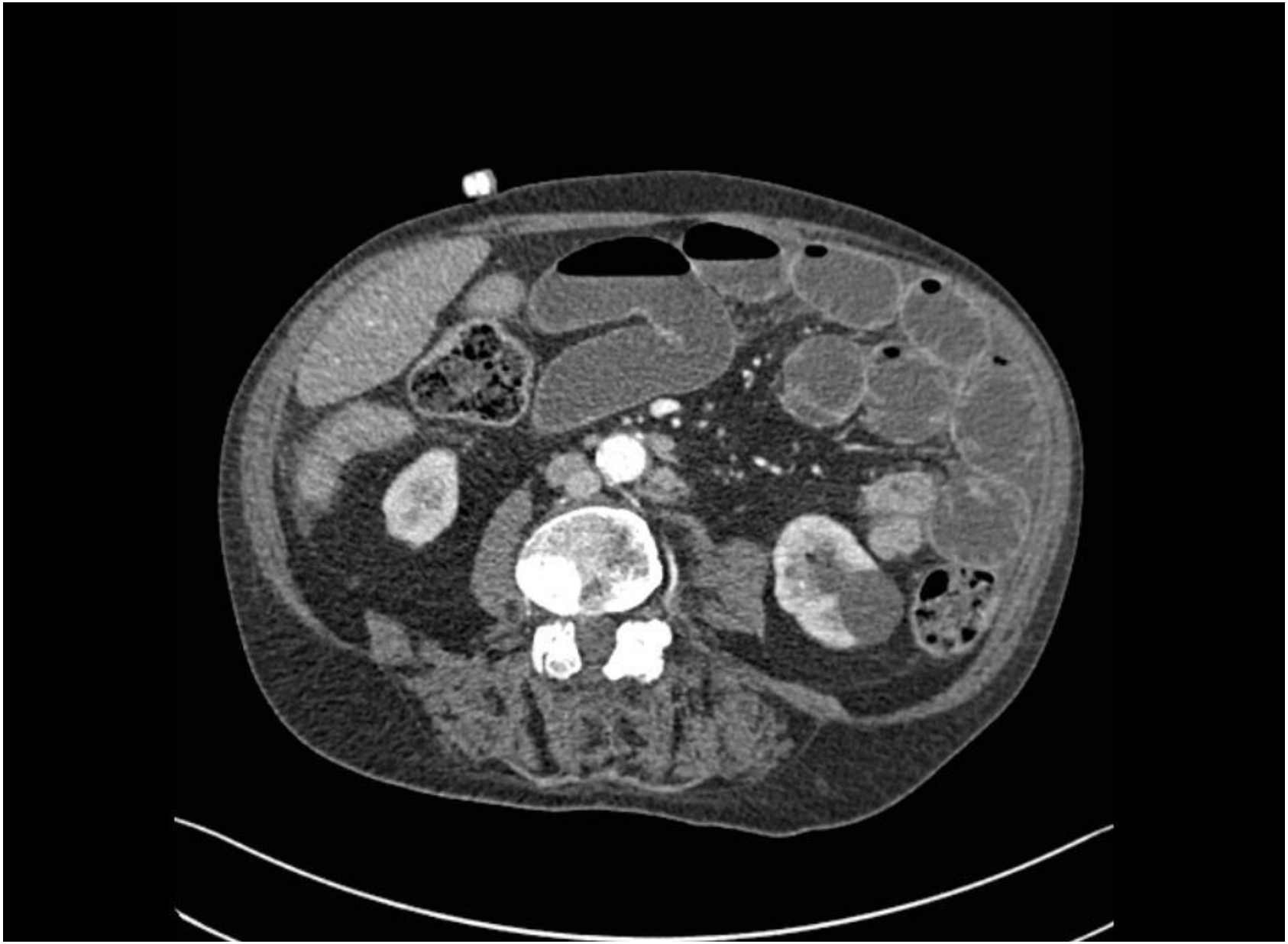


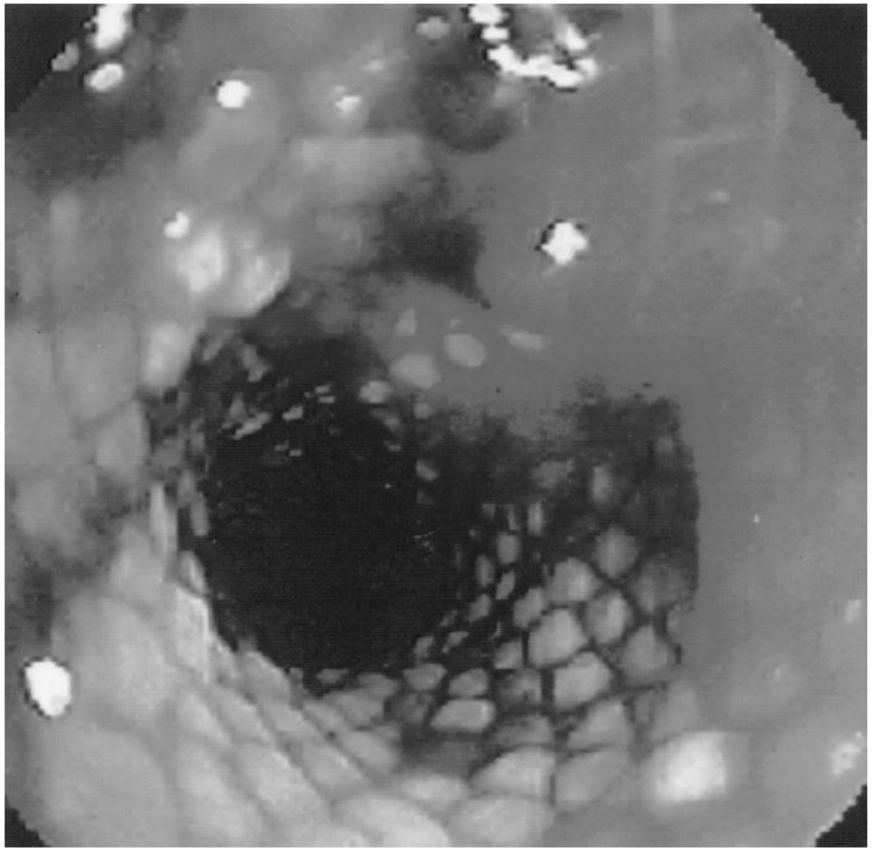
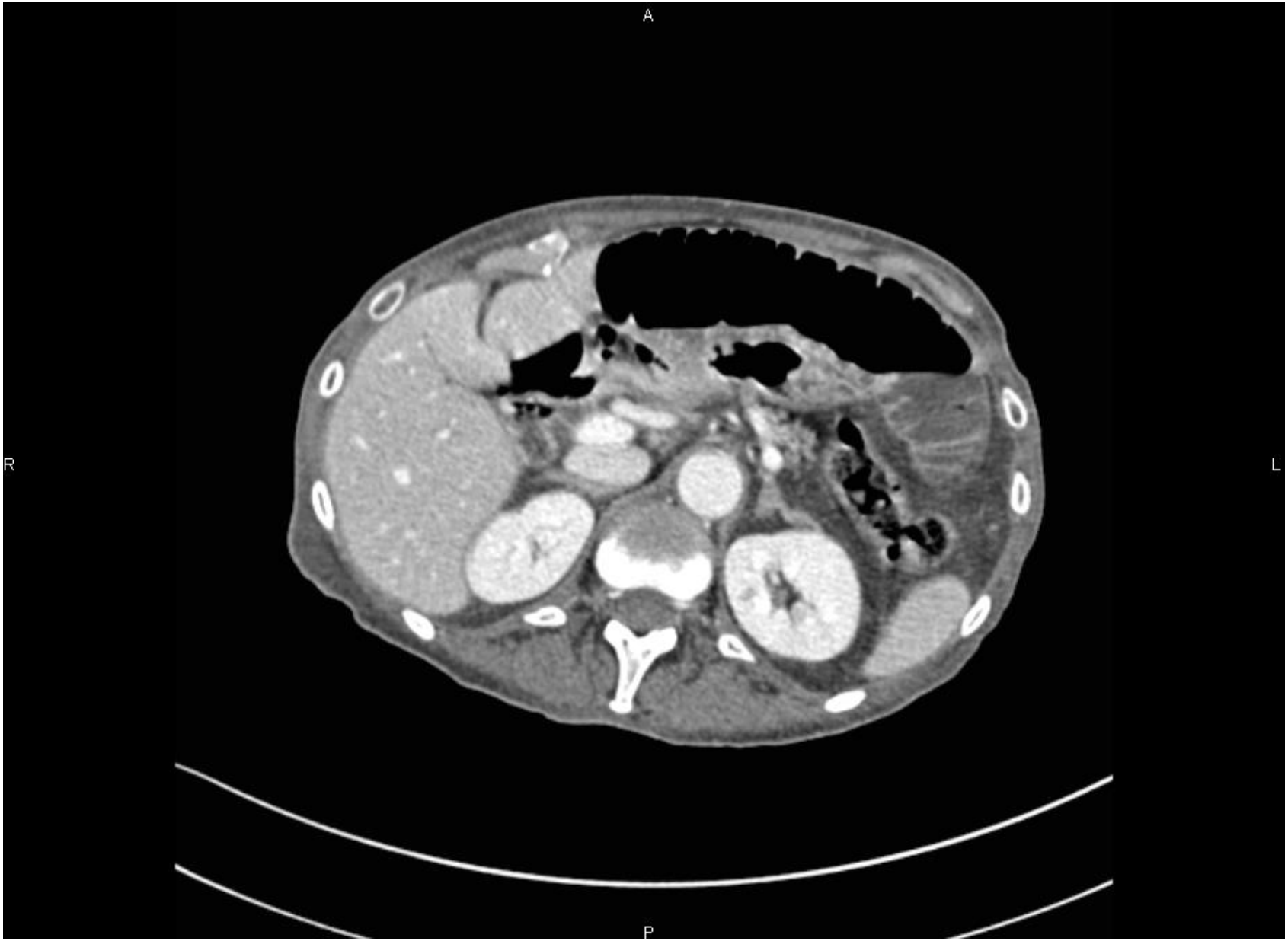
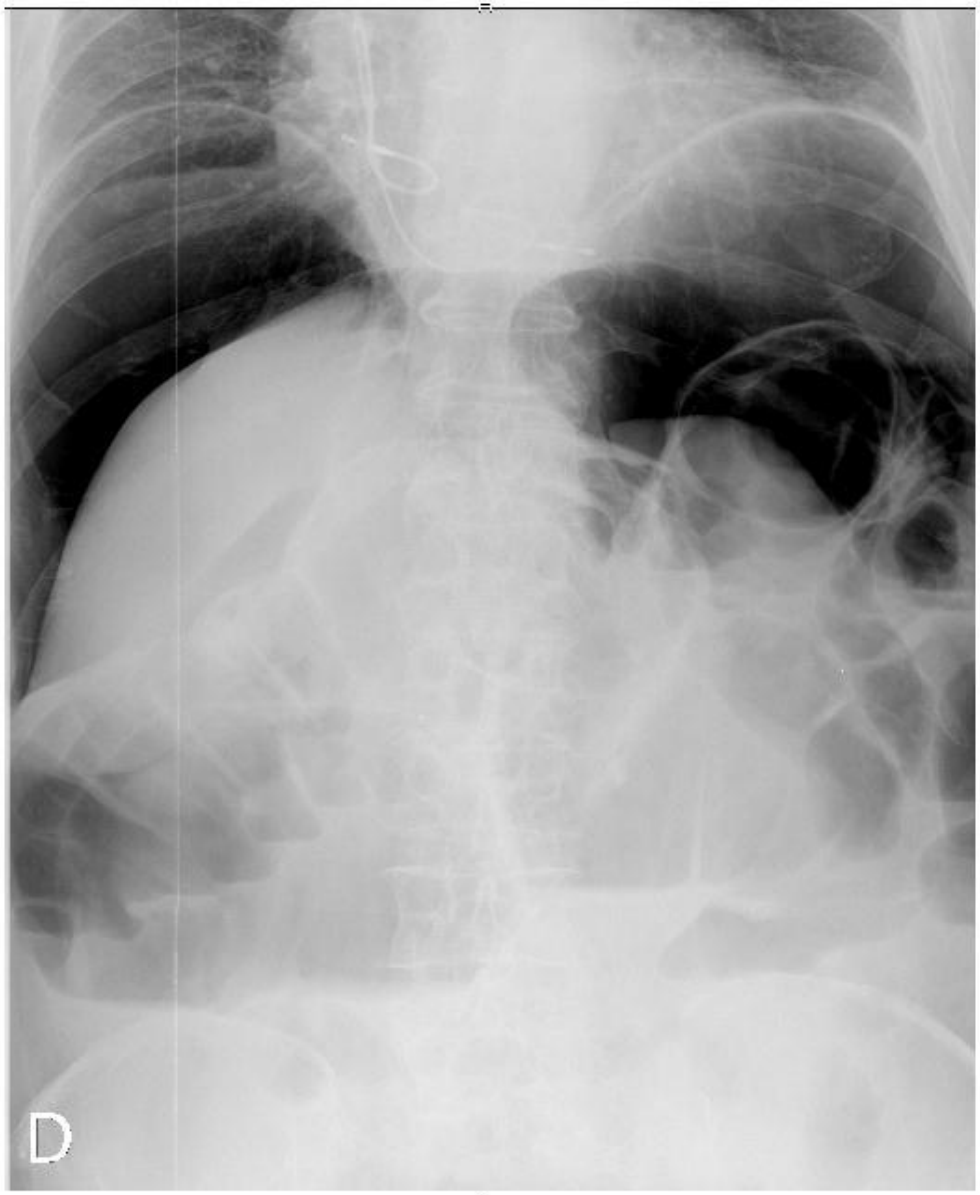


Fig. 1. Recanalized neoplastic colonic lesion. Fully expanded endolumenal Wallstent in situ.



Ulcère duodénal perforé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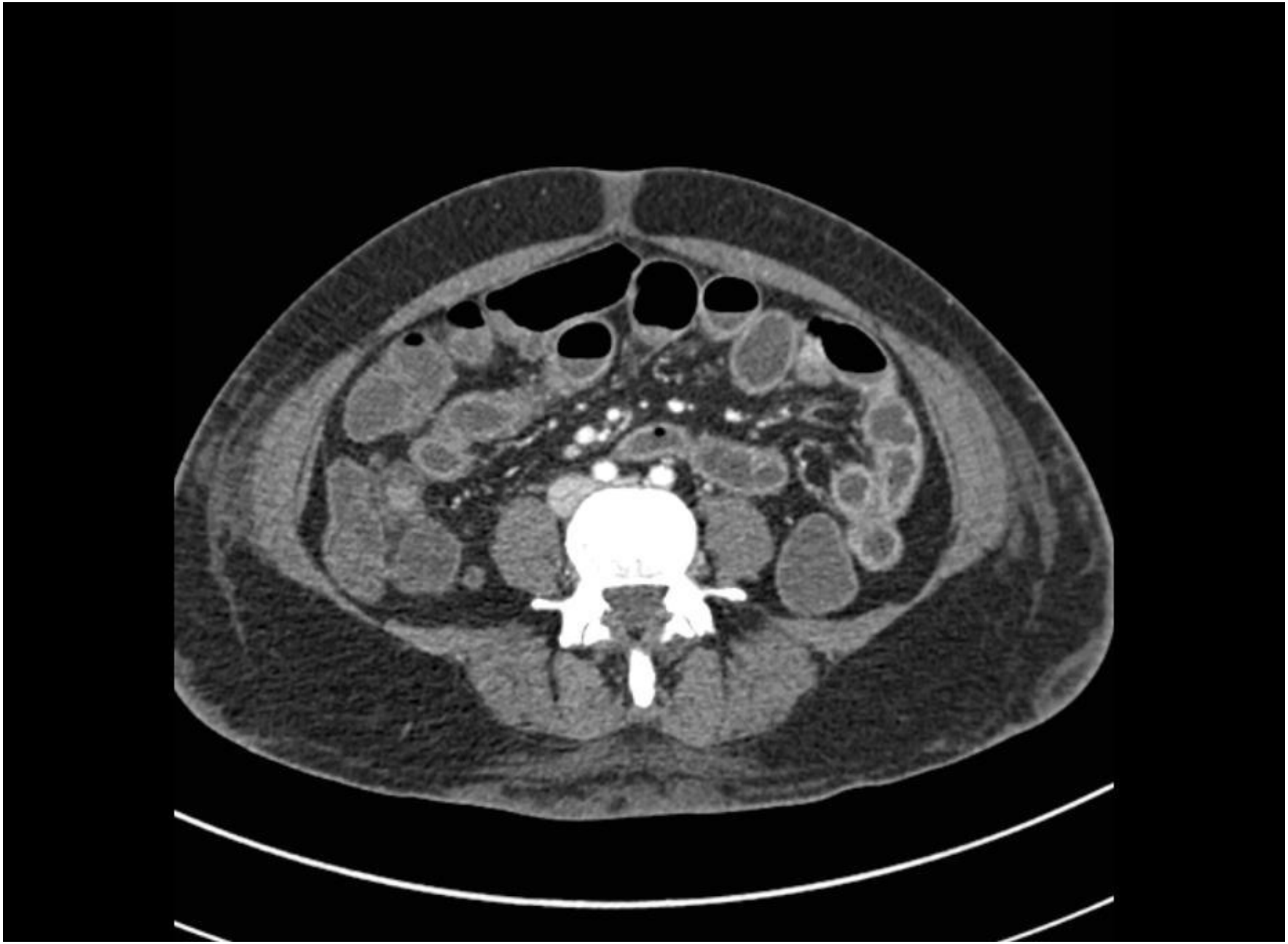

Colite

Les médicaments

- iléus paralytiques : morphiniques, alcaloïdes de la pervenche (vinblastine, vincristine, vindésine, vinorelbine)
- perforation (péritonite): inhibiteurs de tyrosine kinase (erlotinib, gefitinib, sunitinib, crizotinib)

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Gastrointestinal perforations in patients treated with erlotinib: A report of two cases with fatal outcome and literature review

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CHANGEMENT DE LIBELLÉ

Crizotinib : perforations digestives parfois mortelles

Nom de spécialité	Principales modifications
Ville - Hôpital **XALKORI°** gélules ***crizotinib*** Séc. soc 100 % et collect. **Prescription restreinte (a)** Liste I Pfizer	**Nouveau libellé des mises en garde** (texte ajouté) : « *Dans les études cliniques portant sur le crizotinib, des cas de perforation gastro-intestinale ont été rapportés. Après la mise sur le marché, des cas fatals de perforation gastro-intestinale ont été rapportés (…). Le crizotinib doit être utilisé avec prudence chez les patients à risque de perforation gastro-intestinale ((…) antécédents de diverticulite, métastases au niveau du tractus gastro-intestinal, utilisation concomitante de médicaments présentant un risque connu de perforation gastro-intestinale).* *Le traitement (…) doit être interrompu en cas de survenue d'une perforation gastro-intestinale. Les patients doivent être avertis des premiers signes de perforation gastro-intestinale et il doit leur être conseillé de consulter rapidement en cas d'apparition de tels signes* » (1).

a- Prescription hospitalière restreinte aux spécialistes en cancérologie ou en oncologie.

1- Commission européenne "RCP-Xalkori" 22 août 2014 + 21 mars 2014 : 102 pages.

● **La liste des effets indésirables du *crizotinib* s'allonge avec des perforations digestives, risque connu avec d'autres cytotoxiques inhibiteurs de tyrosine kinases.**

Le *crizotinib* (Xalkori°), un cytotoxique inhibiteur de tyrosine kinases, est autorisé en deuxième ligne chez les adultes ayant un cancer du poumon non à petites cellules avancé avec surexpression de la tyrosine kinase ALK (1).

l'Agence européenne du médicament (EMA), dix cas de perforation digestive ont été rapportés chez des patients traités par *crizotinib* (2). Le risque de perforation digestive est connu avec d'autres cytotoxiques inhibiteurs de tyrosine kinases, tels l'*erlotinib* (Tarceva°), le *géfitinib* (Iressa°), et le *sunitinib* (Sutent°) (3,4). Un effet indésirable à prendre en compte dans la balance bénéfices-risques de ces cytotoxiques.

©Prescrire

Rectal perforation after two years of treatment with sunitinib for metastatic kidney cancer

Perforation rectale après deux ans de traitement par sunitinib pour un cancer du rein métastatique

Case report

A 63-year-old man was admitted to our hospital at the beginning of November 2012. This patient is affected by a renal-cell carcinoma, clear-cell type, metastatic with thoracic lymph

Troubles du transit

diarrhée, constipation ou alternance des deux

Diarrhée aiguë

- Penser aux antibiotiques chez le patient hospitalisé

TABLEAU 2

Examens complémentaires potentiellement nécessaires dans l'exploration d'une diarrhée des antibiotiques

Examens	Contextes cliniques les indiquant
Recherche de toxine A ou B de *Clostridium difficile* (méthode immuno-enzymatique ou test de référence par cytotoxicité des selles) et recherche du germe par culture	D'emblée si diarrhée des antibiotiques accompagnée de fièvre ou de signes physiques faisant évoquer l'existence d'une colite (météorisme abdominal douloureux, signes péritonéaux) Secondairement si la diarrhée se prolonge après l'arrêt des antibiotiques
Coproculture standard comportant la recherche de *Salmonella, Shigella, Campylobacter, Yersinia*	Diarrhée des antibiotiques avec fièvre ou se prolongeant malgré une recherche de *Clostridium difficile* et de ses toxines négative
Recherche de *Klebsiella oxytoca* par ensemencement des selles sur milieu sélectif	Diarrhée hémorragique sous antibiotiques
Rectosigmoïdoscopie ou coloscopie	Diarrhée hémorragique Signes physiques faisant évoquer l'existence d'une colite (météorisme abdominal douloureux, signes péritonéaux)

Diarrhée chronique

- Le cancer peut se présenter comme une diarrhée chronique
- Penser aux médicaments
- GVHD
- Radiothérapie

Table 3. Cancers associated with diarrhoea as a symptom

Type of cancer
Carcinoid syndrome from neuroendocrine tumours (NETs)
Colon cancer
Lymphoma
Medullary carcinoma of the thyroid
Pancreatic tumours, particularly islet cell tumours (Zollinger-Ellison syndrome)
Pheochromocytoma

Annals of Oncology 29 (Supplement 4): iv126–iv142, 2018
doi:10.1093/annonc/mdy145

Médicaments associés aux diarrhées chroniques

MÉDICAMENTS	MÉCANISMES
Inhibiteurs de la recapture de la sérotonine	Colite microscopique
AINS	Colite macroscopique et microscopique, entéropathie aux AINS, diaphragme du grêle et du côlon, entérocolite à éosinophiles, atrophie villositaire
Bêtabloquants	Colite microscopique
Statines	Colite microscopique
Bisphosphonates	Colite microscopique
Paclitaxel	Nécrose épithéliale en aires
Colchicine	Apoptose des cellules épithéliales
Irinotécan	Apoptose des cellules éphitéliales, atrophie villositaire, sécrétion colique
Ticlopidine	Colite microscopique
Ranitidine	Colite microscopique
Veinotoniques	Colite microscopique
Inhibiteurs de la pompe à protons	Colite microscopique
Laxatifs	
Sels d'or	Colite macroscopique
Antibiotiques	Colites à *Clostridium difficile* ou à *Klebsiella oxytoca* (diarrhée aiguë)

Chimiothérapie

Table 4. Frequency and severity of diarrhoea with frequently used combinations of ChT agents

ChT	Incidence of grade 3 and 4 diarrhoea (%)
CapeIRI	47
FOLFOXIRI	20
mIFL	19
Bolus fluorouracil with folinic acid	16
Irinotecan with fluorouracil and folinic acid	15
Docetaxel with capecitabine	14
FOLFIRI	14
FLOX	10

CapeIRI, capecitabine/irinotecan; ChT, chemotherapy; FLOX, bolus fluorouracil/leucovorin/oxaliplatin; FOLFIRI, fluorouracil/leucovorin/irinotecan; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mIFL, irinotecan/bolus fluorouracil.

Thérapies ciblées

Table 5. Incidence of diarrhoea from targeted therapies

Class of drug	Drug	Incidence of diarrhoea (%)	Incidence of grade 3 and 4 diarrhoea (%)
Anti-EGFR	Gefinitib	26–52	1–5
	Erlotinib	18–57	3–6
	Afatinib	87–95	14–22
	Cetuximab	13–28	4–28
	Panitumumab	21	8–20
Anti-HER2	Lapatinib	47–75	3–14
	Trastuzumab	2–63	2–6
	Pertuzumab	67	5–8
Anti-BRAF	Vemurafenib	5–6	0
	Dabrafenib	1	0
Anti-MEK	Cobimetinib	45–50	4
	Trametinib	45–50	4
Anti-EML4/ALK	Crizotinib	50–60	0
Anti-VEGF	Bevacizumab	20	2–7
	Aflibercept	58–69	13–19
Multi-targeted TKI	Imatinib	20–26	1
	Pazopanib	52	4
	Sunitinib	44–55	5–8
	Axitinib	55	11
	Sorafenib	43–55	2–8
	Vandetanib	74	10
	Regorafenib	34–40	5–8
	Cabozantinib	64	12
	Levantinib	59	8
Anti-mTOR	Everolimus	30	1–3
	Temsirolimus	27	1
Anti-CDK4/6	Palbociclib	21–26	1–4
	Ribociclib	35	1.2
	Abemaciclib	86–90	13–20
Anti-PARP	Olaparib	11–18	0
	Rucaparib	13–20	0

Toxicities are considered with single drug arm or in combination with other drugs.

Immunothérapie

Table 1. Immunotherapy Toxicity

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Vaccines	Fevers, chills, lethargy	Maculopapular, vitiligo[1]	Rare diarrhea[5]	Rare[5]	None	Local reactions, back pain,[8] rare hypotension[5]
Cytokines: IFN	Fevers, chills, and flu-like symptoms[19]	Maculopapular[19]	Nausea, diarrhea, and rare vomiting[22]	Elevated LFTs common[23]	Thyroiditis; often associated with benefit[24]	Congestive heart failure,[19] anemia,[26] thrombocytopenia,[26] leukopenia,[26] depression[21]
Cytokines: IL-2	Fevers, chills, and lethargy[31]	Petechial and macular[31]	Transient nausea, vomiting, and diarrhea[31]	Elevated LFTs and bilirubin common[31]	Thyroiditis; often associated with benefit[36]	Pulmonary edema,[32] hypotension,[32] azotemia,[32] myocarditis,[32] altered mental status[31]
Cell therapy: TILs	Fevers, chills, and fatigue[43-45]	Maculopapular[43]	Rare diarrhea[43-45]	Elevated LFTs rare[43-45]	Thyroiditis; often associated with benefit[43-45]	Prolonged lymphopenia, CMV infections[43-45]
Cell therapy: CAR	Fevers, chills, and lethargy	Maculopapular	Rare diarrhea	Elevated LFTs with CA-IX CAR[56]	None	Cytokine release with tachycardia, hypotension, oliguria; B-cell aplasia[54]; pulmonary edema[55]
Cell therapy: TCR	Fevers, chills, and lethargy[47]	Maculopapular,[47] vitiligo [52]	Colitis with CEA TCR[53]	Elevated LFTs rare[47]	None	Encephalopathy[59] and carditis[60] with MAGE-3 TCR
Checkpoint protein inhibition: CTLA-4	Fevers, chills, and lethargy[62]	Maculopapular[62]	Diarrhea and colitis with ulceration[62]	Elevated LFTs[62]	Hypophysitis, thyroiditis, and adrenal insufficiency[62]	Neuropathy, nephritis, Guillain-Barré, myasthenia gravis, sarcoid, and thrombocytopenia all rare[62,63]
Checkpoint protein inhibition: PD-1	Fevers, chills, and lethargy[68-72]	Maculopapular[68-72]	Diarrhea and colitis with ulceration: uncommon[68-72]	Elevated LFTs uncommon[68-72]	Hypophysitis, thyroiditis more common, adrenal insufficiency[68-72]	Pneumonitis not common; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[68-72]
Checkpoint protein inhibition: PD-L1	Fevers, chills, and lethargy[81,82]	Maculopapular[81,82]	Diarrhea and colitis with ulceration: rare[81,82]	Elevated LFTs rare[81,82]	Hypophysitis, thyroiditis more common, adrenal insufficiency[81,82]	Pneumonitis rare; anemia rare[81,82]
Combination checkpoint protein inhibition	Fevers, chills, and lethargy[100]	Maculopapular[100]	Diarrhea and colitis with ulceration; pancreatic lab elevation common[100]	Elevated LFTs common[100]	Hypophysitis, thyroiditis more common, adrenal insufficiency[100]	Pneumonitis not common[100]; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[100]

Abbreviations: CA-IX, carbonic anhydrase IX; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; IFN, interferon; IL-2, interleukin-2; LFTs, liver function tests; TCR, T-cell receptor; TILs, tumor-infiltrating lymphocytes.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Enterocolitis in Patients With Cancer After Antibody Blockade of Cytotoxic T-Lymphocyte–Associated Antigen 4

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ABSTRACT

Purpose

Cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) is an inhibitory receptor on T cells. Knocking out CTLA4 in mice causes lethal lymphoproliferation, and polymorphisms in human CTLA4 are associated with autoimmune disease. Trials of the anti-CTLA4 antibody ipilimumab (MDX-010) have resulted in durable cancer regression and immune-mediated toxicities. A report on the diagnosis, pathology, treatment, clinical outcome, and significance of the immune-mediated enterocolitis seen with ipilimumab is presented.

Table 2. Symptoms on Presentation in 41 Patients With Grade 3/4 Gastrointestinal Toxicity

Presenting Symptom	No. of Patients
Diarrhea	40
Abdominal pain	8
Nausea/vomiting	6
Fever	5
Anal pain	4
Rectal bleeding	1
Constipation	1

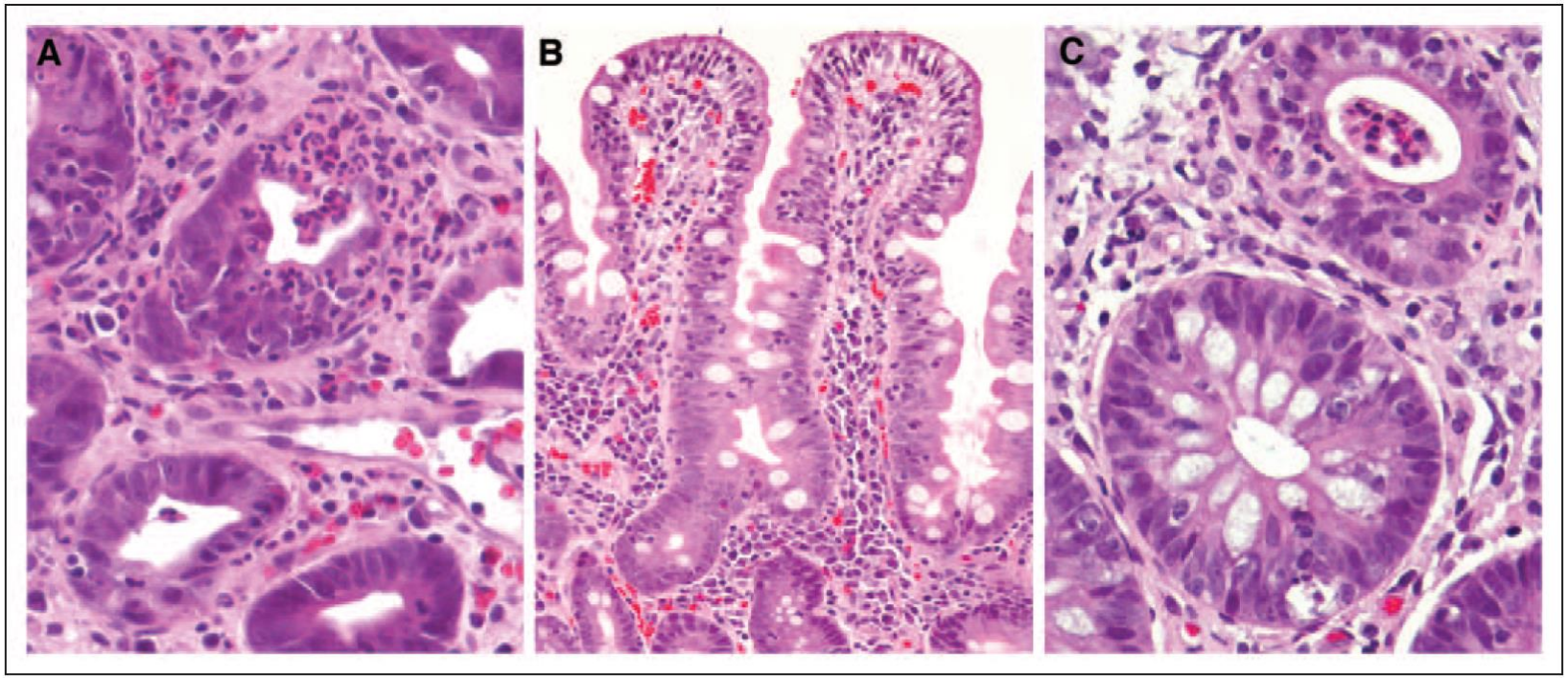

Fig 3. Representative photomicrographs of histopathologic features of enterocolitis. (A) Neutrophilic infiltration with colonic crypt destruction (hematoxylin and eosin, ×400). (B) Small bowel mucosa showing markedly increased surface intraepithelial lymphocytes and expansion of lamina propria with mononuclear cells (hematoxylin and eosin, ×200). (C) Two adjacent colonic glands showing cryptitis in the upper gland and intraepithelial lymphocytosis and crypt cell apoptosis in the lower gland (hematoxylin and eosin, ×400).

Table 4
Management of immune-related diarrhoea, colitis and hepatitis.

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Diarrhoea and Enterocolitis	*<4 bowel actions per day over baseline; mild:* supportive measures such as increasing oral fluid, anti-motility agents such as loperamide	*4–6 bowel actions per day over baseline; moderate:* withhold ICPI. As per Grade 1 if patient is well. If no improvement in 5 days, or if worsening of symptoms, commence steroids at a dose of 0.5–1 mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to G1. If no improvement occurs, manage as per G3. Steroids can be tapered over 2–4 weeks. Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the macroscopic and microscopic inflammation evident	*⩾7 bowel actions per day over baseline; severe symptoms:* admit patient to hospital for intravenous hydration and clinical observation as appropriate. Commence steroids at 1–2 mg/kg prednisolone or IV equivalent. If no improvement in 2–3 days, commence infliximab 5 mg/kg and continue steroids. Infliximab is contraindicated in patients with sepsis or a perforation. Sigmoidoscopy and biopsy recommended to exclude other causes. Once symptoms resolve to G1, taper steroids over minimum 1 month (up to 3 months for severe cases). Infliximab may be re-administered at 2 and 6 weeks if symptoms persist or recur. Dietician input recommended	*Life threatening consequences, urgent intervention indicated:* management as per G3. Involve gastroenterologist and surgeon in management. Permanently discontinue ICPI

L'entérocolite du neutropénique

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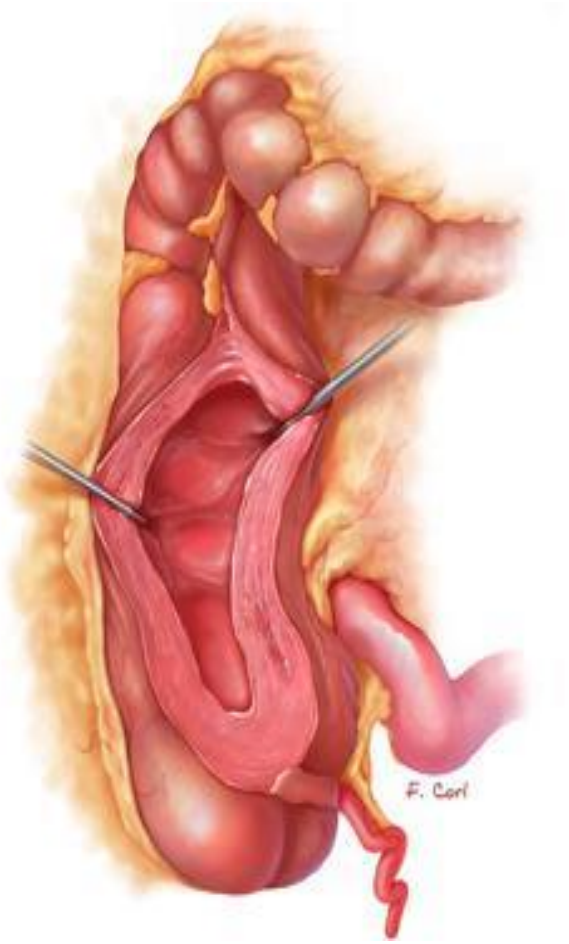


Caractéristiques

- principale cause d'abdomen aigu observée chez le neutropénique
- encore appelée entérocolite nécrosante, colite agranulocytaire ou typhlite (en cas d'atteinte du caecum)
- mortalité de 20 à 60 % selon les séries

Tableau clinique

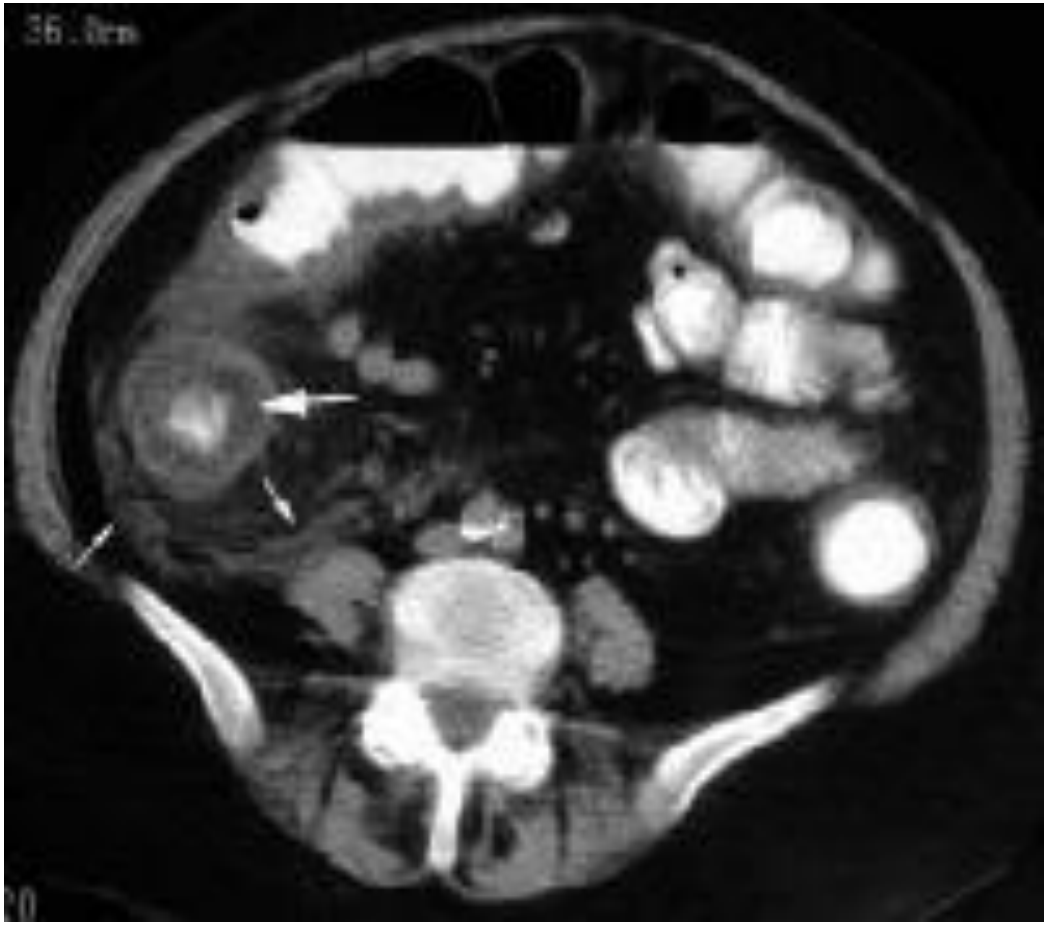
très variable:

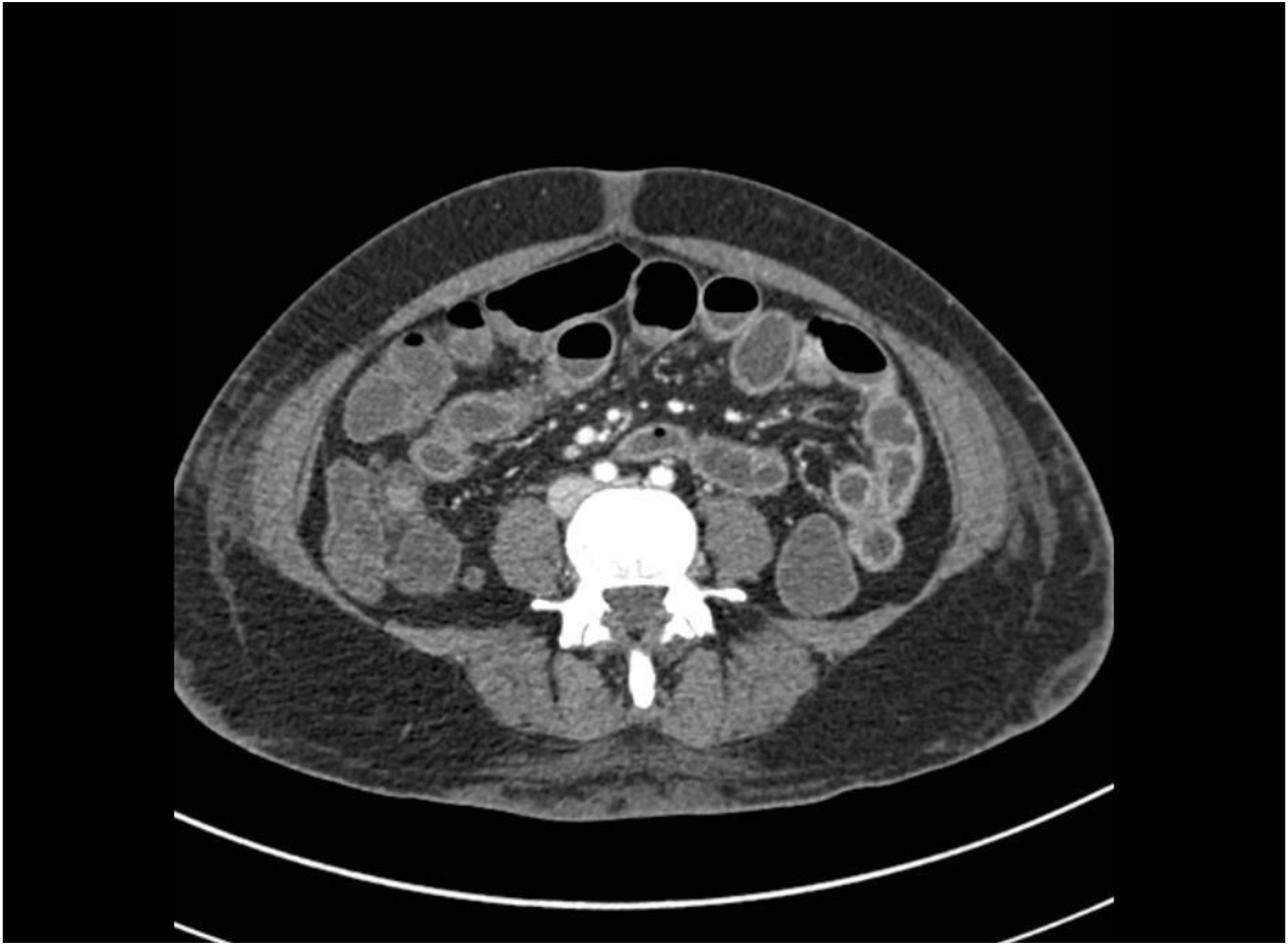
- neutropénie fébrile
- diarrhée aqueuse
- douleurs abdominales diffuses ou localisées
- complications : perforation digestive, abcès, *pneumatosis intestinalis*, hémorragie digestive, obstruction, sepsis et choc septique

Mise au point

- abdomen à blanc
- échographie abdomen
- TDM abdomen
- hémocultures: positives dans 30 à 40 % des cas

diagnostic d'exclusion en fait : exclure la pancréatite, la candidiase hépatique, la diverticulite, la perforation digestive, l'obstruction colique, l'infarctus splénique, la cholécystite lithiasique, l'appendicite, la gastrite ...





Ne pas oublier les champignons pathogènes

- Dans une série de 50 patients, une aspergillose digestive a été retrouvée chez 11 patients dont neuf à l'autopsie.
- Dans une série de 134 patients admis en soins intensifs avec une entérocolite du neutropénique patients avec une mortalité hospitalière de 38,8 % (20), un pathogène a été documenté chez 81 patients dont 17 infections fungiques (20 %).

Approche thérapeutique

conservatrice si possible :

- mise au repos digestive : aspiration digestive, alimentation parentérale
- antibiothérapie i.v. à large spectre (couvrant les anaérobies) et, si pas de réponse, envisager antifongiques
- examens radiologiques (TDM, écho) répétés avec ponction transpariétale des collections identifiées ou intervention chirurgicale en cas de complication ou de sepsis prolongé de plus de 24 h

Ascite

EUROPEAN JOURNAL OF CANCER 42 (2006) 589–597

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Review

Malignant ascites: Systematic review and guideline for treatment

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Table 2 – Management by abdominal paracentesis

Author/year/ level of evidence	Study design	No. of subjects	Primary tumour	Number of paracenteses	Symptom relief	Duration of effect	Complications
Fischer (1979),[13] level 3	Case series	300	–	–	–	–	No severe hypotension under concurrent infusion with 5% dextrose
Appelqvist (1982),[11] level 3	Case series	100	Varied	127	–	–	4 died because of complications (3%): 2 died from pulmonary embolism, 1 from perforation, 1 peritonitis
Ross (1989),[57] level 3	Case series	43	Varied	109	39 (87%)	4–45 days mean 10.4 days	2 fatal hypotension (2%) 1 nonfatal hypotension (1%)
Gotlieb (1998),[10] level 3	Prospective uncontrolled trial	15	Ovary	35	100% (89% complete relief 11% partial relief)	–	No hypotension, no perforation, no peritonitis
McNamara (2000),[19] level 3	Prospective uncontrolled trial	44	Varied	48	100% in 4 symptoms (discomfort, nausea, vomiting dyspnoea) improvement of at least 2 units on a score from 0 to 10 for reading 2 h after paracentesis compared with mean score baseline	For all 4 symptoms improvement in the mean scores at 72 h compared with baseline, reaching statistical significance in discomfort, vomiting and dyspnoea	No associated adverse effects in 35 procedures (73%). 11 pts reported pain (7 requiring analgesia), 1 patient vomited soon after drain insertion
		102			Mean 94%		

Table 3 – Management by diuretics

Author/year/ level of evidence	Study design	No. of subjects	Diuretics used	Relief of ascites	Duration of effect	Renal dysfunction	Other adverse effects
Razis (1976),[58] level 2	Cohort study	12	IV furosemide 100–200 mg or IV bumetanide 3–5 mg/day	5	–	–	–
Greenway (1982),[21] level 2	Cohort study	15	Spironolactone 150–450 mg	13 (8 until death 5 at 1–4 months)	–	0	Two uncontrolled nausea and vomiting
Pockros (1992),[20] level 2	Cohort study	16	Sodium diet Spironolactone +/− furosemide (dose adjusted for weight loss of 0.5 kg/day)	3 (those with massive hepatic metastases and ↑↑ plasma renin levels)	Uncertain (study lasted 7.8 ± 3.2 days)	2 (both in the group of non-responders)	1 symptomatic hypotension (non-responder)
Gough (1993),[59] level 3	Study is not randomized open controlled trial, level 2. Concerning diuretics descriptive subgroup analysis of 68 pts, level 3	68 (38 also had shunt*)	Methylclothiazide 5 mg/day and spironolactone 50–100 mg/day	26 (12 with shunt)	15 < 8 weeks 11 > 8 weeks	–	–
Sharma et al. (1995),[60] level 3	Case report	2	Spironolactone 100–200 mg/day and furosemide 40–80 mg/day	2	One 4 months until death. One 5.5 months until lost of follow up	0	0
		Total 113		Mean 43%			

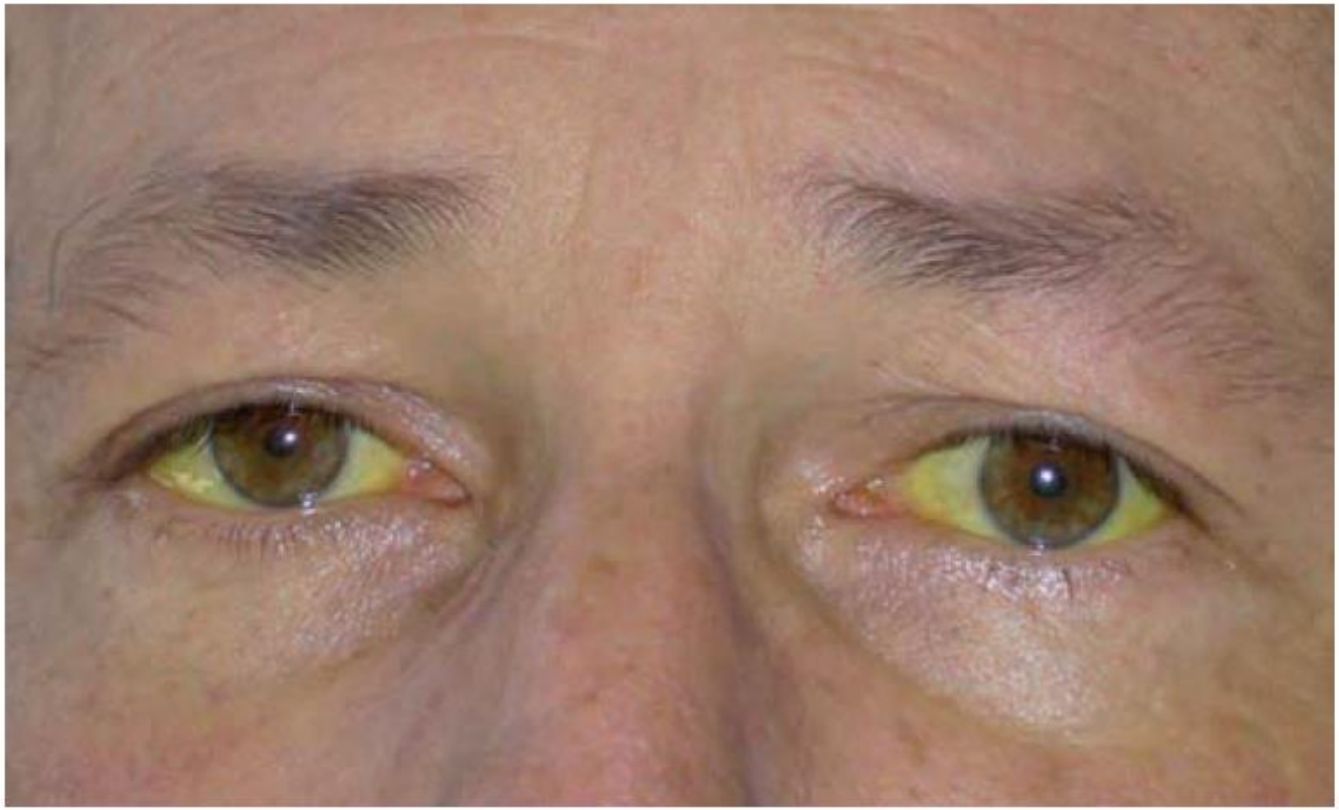
Table 4 – Management by peritoneovenous shunts

Author/year/ level of evidence	Study design	Primary tumour	No. of patients	Type of shunt	Control of ascites	Shunt block	Pulmonary oedema	Pulmonary emboli	DIC subclinial	DIC clinical	Infection	Tumour emboli at autopsy	Shunt patency
Straus (1979),[61] level 3	Case series	Varied	33	Le Veen	27	4	1	1	–	1	1	0/9	Mean 10.6 weeks
Kudsk (1980),[62] level 3	Case series	Varied	10	Le Veen	8	2	0	1	5	1	1	0/2	–
Lokich (1980),[63] level 3	Case series	Varied	8	Le Veen	8	2	4	1	4	1	–	–	–
Raaf (1980),[64] level 3	Case series	Varied	5	Le Veen	5	1	–	1 (suspected)	1	0	0	–	–
Cheung (1982),[65] level 3	Case series	Varied	22	19 Le Veen 3 Denver	–	–	3	2	6	0	4	1/6	Pts with neg. cytology = median 120 days, pos. cytology = median 26 days
Gough (1982),[66] level 3	Case series	Varied	10	Le Veen	8	3	–	–	–	0	1	–	1–64 weeks, mean 16 weeks
Qazi (1982),[67] level 3	Case series	Varied	40	Le Veen	28	–	4	–	6/10	0	1	0/8	–
Souter (1983),[28] level 3	Case series	Varied	26	17 Le Veen 9 Dencer	23	8	3	–	0/6	0	2	–	–
Gough (1984),[27] level 3	Case series	Varied	17	13 Le Veen 4 Denver	13	4	3	–	2	0	2	–	1–104 weeks, mean 24 weeks
Timon (1987),[68] level 3	Case series	Varied	7	1 Le Veen 6 Denver	6	2	–	1	2	0	0	–	5–14 weeks, mean 9 weeks
Millard (1988),[69] level 3	Case series	Varied	11	Denver	10	1	0	0	–	0	0	–	Mean 11 weeks
Li (1988)[70], level 3	Case series		7	Denver	6	0	0	0	–	0	0	0	Mean 10 weeks
Smith (1989),[71] level 3	Case series	Varied	50	12 Le Veen 38 Denver	–	6 Le Veen 10 Denver	6	–	–	3	2	–	Mean 10 weeks for Le Veen
Edney (1989),[72] level 3	Case series	Varied	45	29 Le Veen 26 Denver	34	7	6	–	"Virtually all patients"	1	0	–	–
Gough (1993),[59] level 2–	Not randomized open controlled trial	Varied	42	16 Le Veen, 26 Denver	27	–	–	–	32/32	0	–	–	–
Schumacher (1994),[73] level 3	Case series	Varied	89	Not specified	57	26	12	1	"Nearly every patient"	2?	6	–	Mean 12 weeks
Faught (1995),[74] level 3	Case series	Varied, 21 with ovary	25	Le Veen or Denver	22	4	–	1	5	1	0	–	–
Wickremesekera (1997),[29] level 3	Case series	Varied	19	Denver	16	2	4	–	10	1	0	–	–

5. Guideline on the management of symptomatic malignant ascites in advanced cancer

1. Paracentesis is indicated for those patients who have symptoms of increasing intraabdominal pressure. Available data show good, although temporary relief of symptoms in most patients. Symptoms like discomfort, dyspnoea, nausea and vomiting seem to be significantly relieved by drainage of up to 5 L of fluid. (Grade of Recommendation: D)
2. When removing up to 5 L of fluid, intravenous fluids seem to be not routinely required. (Grade of Recommendation: D)
3. If patient is hypotensive or dehydrated or known to have severe renal impairment and paracentesis is still indicated, intravenous hydration should be considered. Infusion therapy is not sufficiently studied. The only investigated therapy in malignant ascites is infusion of dextrose 5%. There is no evidence of concurrent albumin infusions in patients with malignant ascites. (Grade of Recommendation: D)
4. To avoid repeated paracenteses a peritoneovenous shunting may be considered. Major complications (pulmonary oedema, pulmonary emboli, clinically relevant disseminated intravascular coagulation, and infection) have to be expected in about 6% of patients. (Grade of Recommendation: D)
5. There are no randomized controlled trials assessing the efficacy of diuretic therapy in malignant ascites. The available data are controversial and there are no clear predictors to identify which patients would benefit from diuretics. The use of diuretics therefore should be considered in all patients, but has to be evaluated individually. Patients with malignant ascites due to massive hepatic metastasis seem to respond more likely to diuretics than patients with malignant ascites caused by peritoneal carcinomatosis or chylous ascites. (Grade of Recommendation: D)
6. Choice of diuretics is not evaluated. As available data suggest that the efficacy of diuretics in malignant ascites depends on plasma renin/aldosterone concentration, aldosterone antagonists like spironolactone should be used, either alone or in combination with a loop diuretic. (Grade of Recommendation: D)
7. Dose regimens of diuretics are not evaluated in patients with malignant ascites. There is no evidence to diverge from standard clinical practice. Therefore dosage should be performed according to manufacturer's instructions and package inserts. (Grade of Recommendation: D)

Ictère



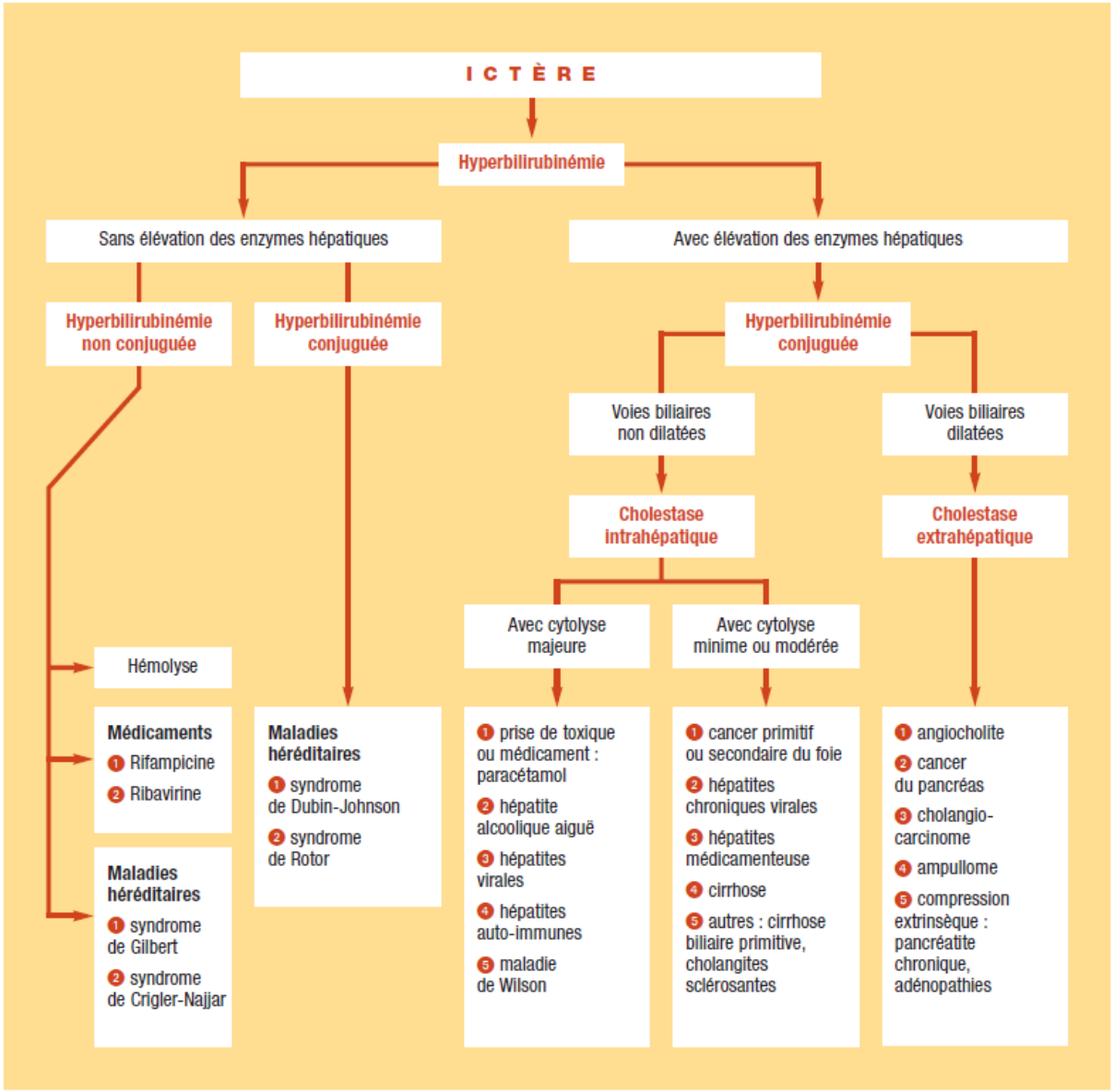


FIGURE 3 **Mécanismes de l'ictère.**

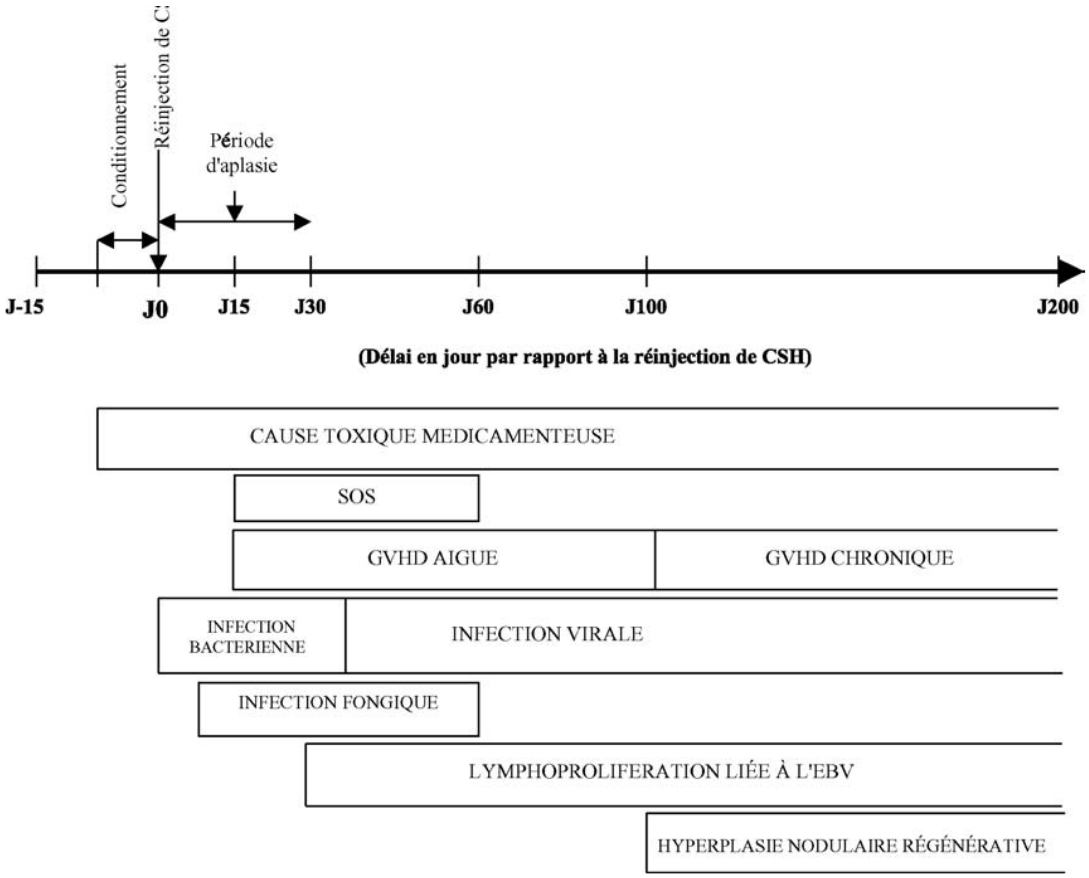
Quelques causes spécifiques d'ictère

- Hémolyse (microangiopathie thrombotique)
- Métastases hépatiques
- Compression des voies biliaires
- Médicaments
- Maladie veino-occlusive du foie
- GVHD
- Auto-immunes (inhibiteurs des points de contrôle immunitaire)

Maladie du greffon contre l'hôte (GVHD)

Les tableaux cliniques

- Forme aiguë: tableau d'hépatite avec ictère.
  - diagnostic différentiel : VOD, toxicités médicamenteuses, infections (surtout virales)
  - aidé par le contexte clinique et éventuellement par une biopsie hépatique.
- Forme chronique : cirrhose biliaire secondaire


Conditionnement
Réinjection de C
Période
d'aplasie
J-15
J0
J15
J30
J60
J100
J200
(Délai en jour par rapport à la réinjection de CSH)
CAUSE TOXIQUE MEDICAMENTEUSE
SOS
GVHD AIGUE
GVHD CHRONIQUE
INFECTION BACTERIENNE
INFECTION VIRALE
INFECTION FONGIQUE
LYMPHOPROLIFERATION LIÉE À L'EBV
HYPERPLASIE NODULAIRE RÉGÉNÉRATIVE

Maladie veino-occlusive du foie

= syndrome d'obstruction sinusoïdale

SOS

VOD

« veno-occlusive disease »

Définition

Oblitération fibreuse des veinules hépatiques (centrolobulaires et sus-lobulaires) causant une obstruction postsinusoïdale et une hypertension portale intrahépatique

Tableau clinique

- prise de poids (> 5%) avec développement d'ascite
- ictère (↑ bilirubine)
- hépatomégalie douloureuse

- souvent thrombopénie précoce et réfractaire

dans un contexte de chimiothérapie intensive avec greffe de moëlle osseuse pratiquée dans les 3 semaines précédentes

Inhibiteurs des points de contrôle immunitaire

Table 1
Immune-related adverse event rates associated with immune checkpoint inhibitors in advanced melanoma.

	Pembrolizumab (2 mg/kg 2- and 3-weekly) [5]		Nivolumab (3 mg/kg 2-weekly) [7,8,10]		Ipilimumab (3 mg/kg 3-weekly) [5,10]		Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks) [10]	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Diarrhoea (%)	14–17	1–3	11–19	0–2	23–33	3–6	44	9
Colitis (%)	2–4	1–3	1	<1	8–12	7–9	12	8
Hepatitis* (%)	1–2	1–2	3–6	2–3	1–7	0–2	30	19
Pruritus (%)	14	0	16–19	<1	25–35	<1	33	2
Rash (%)	13–15	0	9–22	<1	15–21	1–2	28	3

Table 2
Immune-related adverse events associated with immune checkpoint inhibitors in advanced lung cancer.

	Pembrolizumab (2 mg/kg or 10 mg/kg every 3 weeks or 10 mg every 2 weeks) [17,19]		Nivolumab (3 mg/kg every 2 weeks) [14,16,18]	
	All grade	Grade 3/4	All grade	Grade 3/4
Diarrhoea (%)	8	1	8–10	0–3
Colitis (%)	1	1	1	<1
Hepatitis* (%)	1–3	<1	1–3	<1
Pruritus (%)	11	0	6–8	0–1
Rash (%)	10	0.2	4–11	0–1
Vitiligo (%)	NR	0	NR	NR
Pneumonitis (%)	5	2**	3–5	1–3
Hypothyroidism (%)	8	<1	4–7	0
Hyperthyroidism (%)	2–4	0	1–2	0
Hypophysitis (%)	<1	<1	NR	NR
Renal injury (%)	<1	0	0–4	1
Rheumatological (%)				
Myalgia	3	0	2–5	0–1
Arthralgia	9	<1	5	NR
Arthritis	NR	NR	NR	NR
Uveitis (%)	NR	NR	NR	NR
Neurological (%)	NR	NR	NR	1
Cardiac (%)	NR	NR	1	0
Fatigue (%)	14	1	16	1–4
Haematological (%)				
Anaemia	3	1	2	1

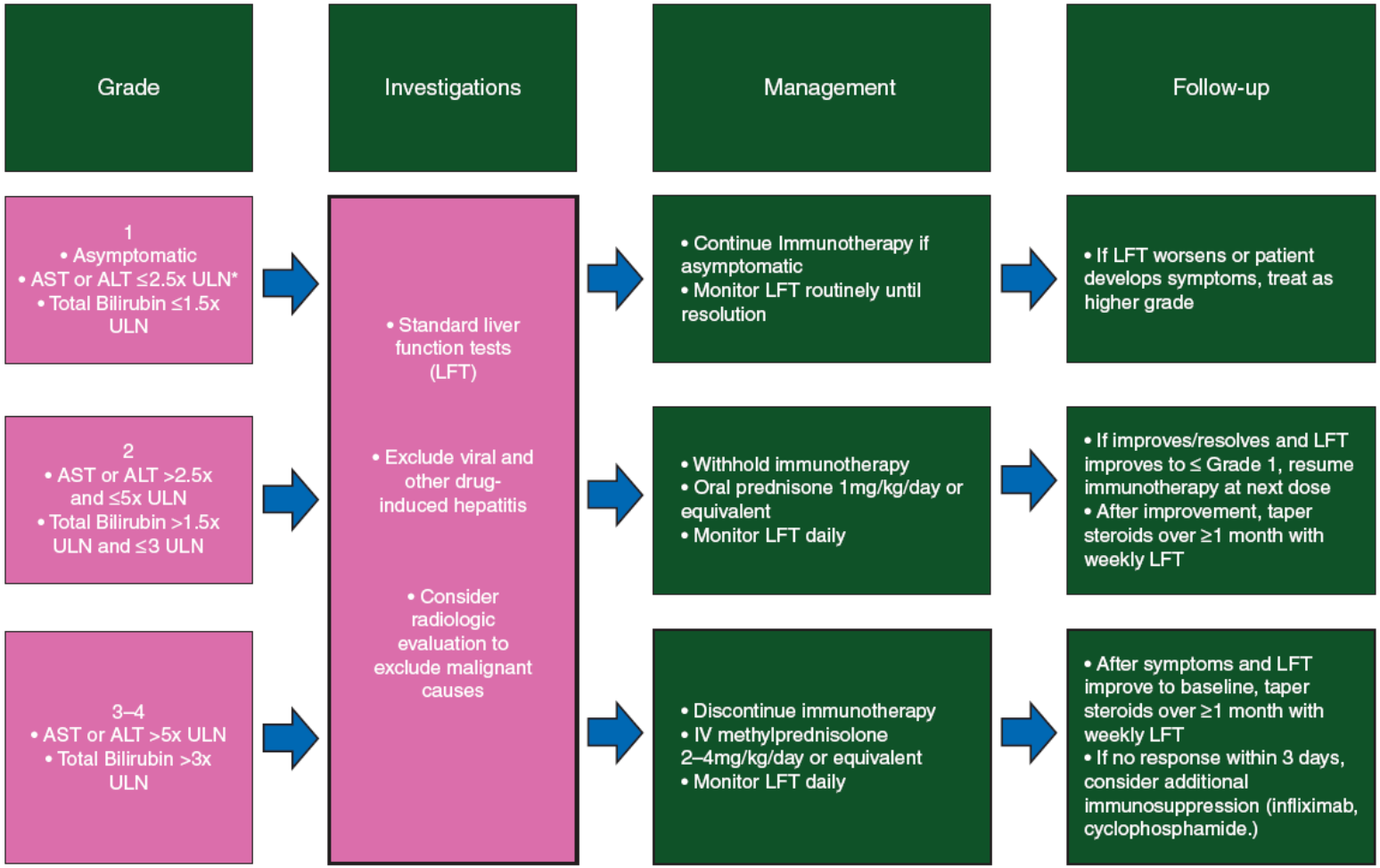


Figure 2. Adapted management algorithm for hepatitis with immune checkpoint blockade. *ULN, upper limit of normal.

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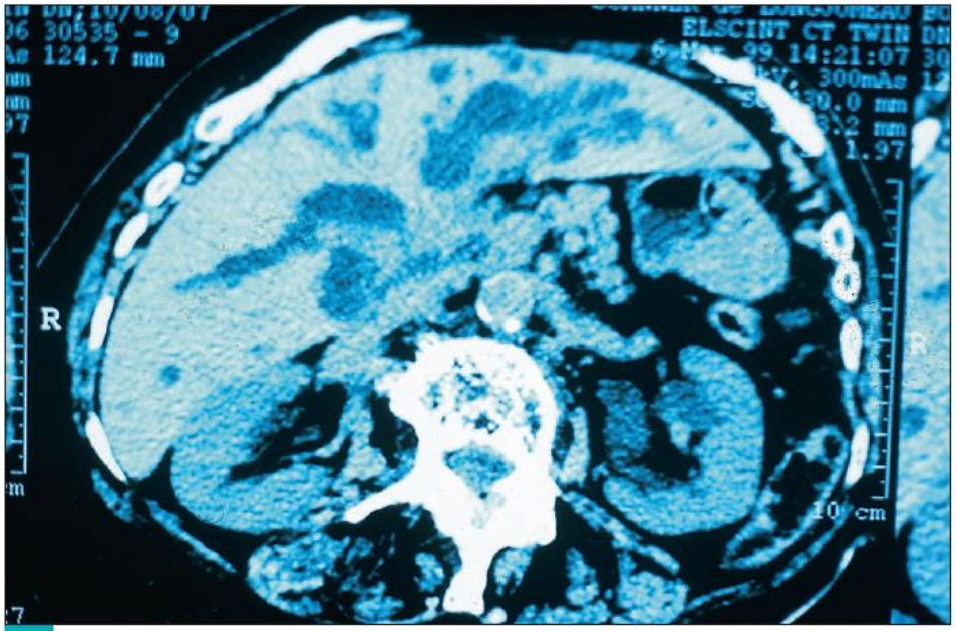

5 *Examen tomodensitométrique abdominal : on visualise une dilatation très importante des voies biliaires intrahépatiques droites et gauches sans communication entre elles et une masse tissulaire hilaire compatible avec le diagnostic de cancer du hile au stade II.*

Table 1. Primary and Secondary Tumors Associated With Biliary Tract Obstruction

Tumor	% Relative Frequency
Primary tumors	
Pancreas	80
Bile Duct	5
Ampulla periampulla	1
Duodenum	1
Secondary tumors in porta hepatis	
Gastric	10-50
Colon	20-40
Breast	10
Melanoma	15
Lung cancer	1
Lymphoma	1

Table 3. Therapeutic Options in the Management of MBTO

Surgical decompression
Curative resections
Pancreaticoduodenectomy
Skeletonization and resection of the biliary tree
Hepatic resection
Palliative bypass
Choledochoduodenostomy
Choledochojejunostomy
Cholecytojejunostomy
Cholangioenteric anastomosis
Intubation
Radiographic decompression
Endoscopic Decompression
Sphincterotomy
Endoprostheses
Radiation therapy
External beam
Intraoperative radiation
Brachytherapy
Chemotherapy

Table 5. Complications of Percutaneous Transhepatic Biliary Tract Drainage

Report	No. of Patients	Cholangitis (%)	Catheter Complications (%)	30-Day* Mortality
Mueller et al[53]	200	77 (39)	18 (9)	1%
Carrasco et al[54]	161	75 (47)	51 (32)	27%
Robison et al[55]	35	9 (26)	4 (11)	51%
Smith et al[49]	15	4 (27)	ND	6%
Clouse et al[42]	53	19 (36)	ND	ND

Abbreviation: ND, no data.
*Related to disease.

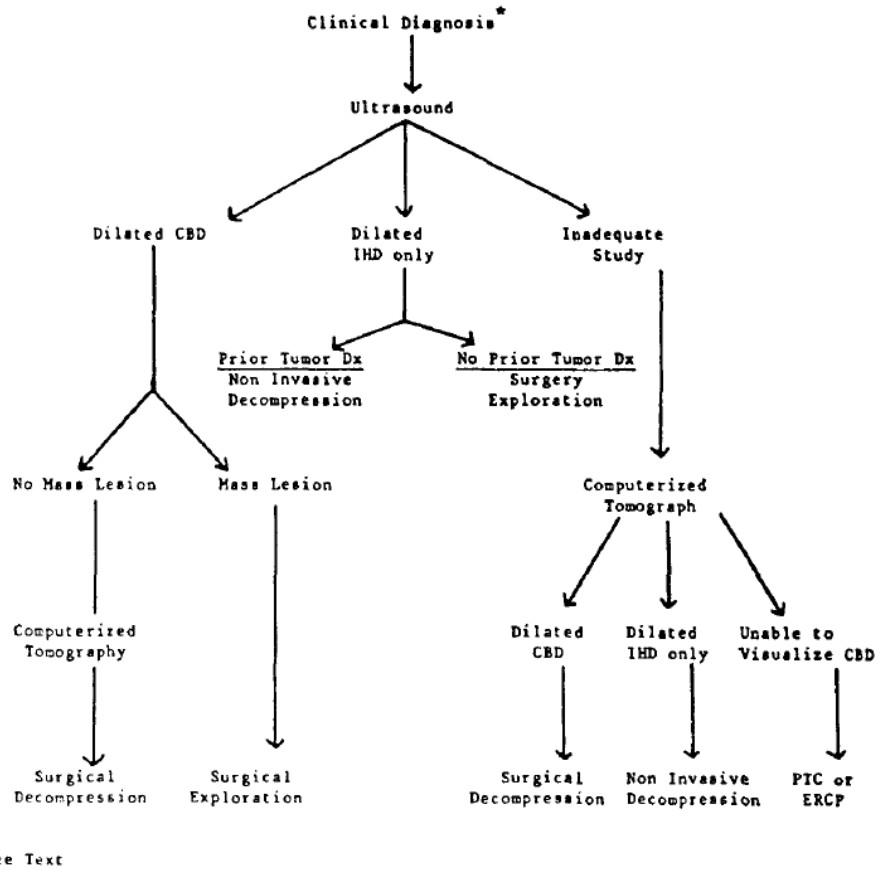

Fig 2. Algorithm for diagnosis and management of malignant obstructive jaundice. CBD, common bile duct; IHD, intrahepatic ducts; PTC, percutaneous transhepatic catheterization; ERCP, endoscopic retrograde cholangiopancreatography.