Atteinte digestive au cours de la sclérodermie systémique: quels traitements fondés sur des preuves ?

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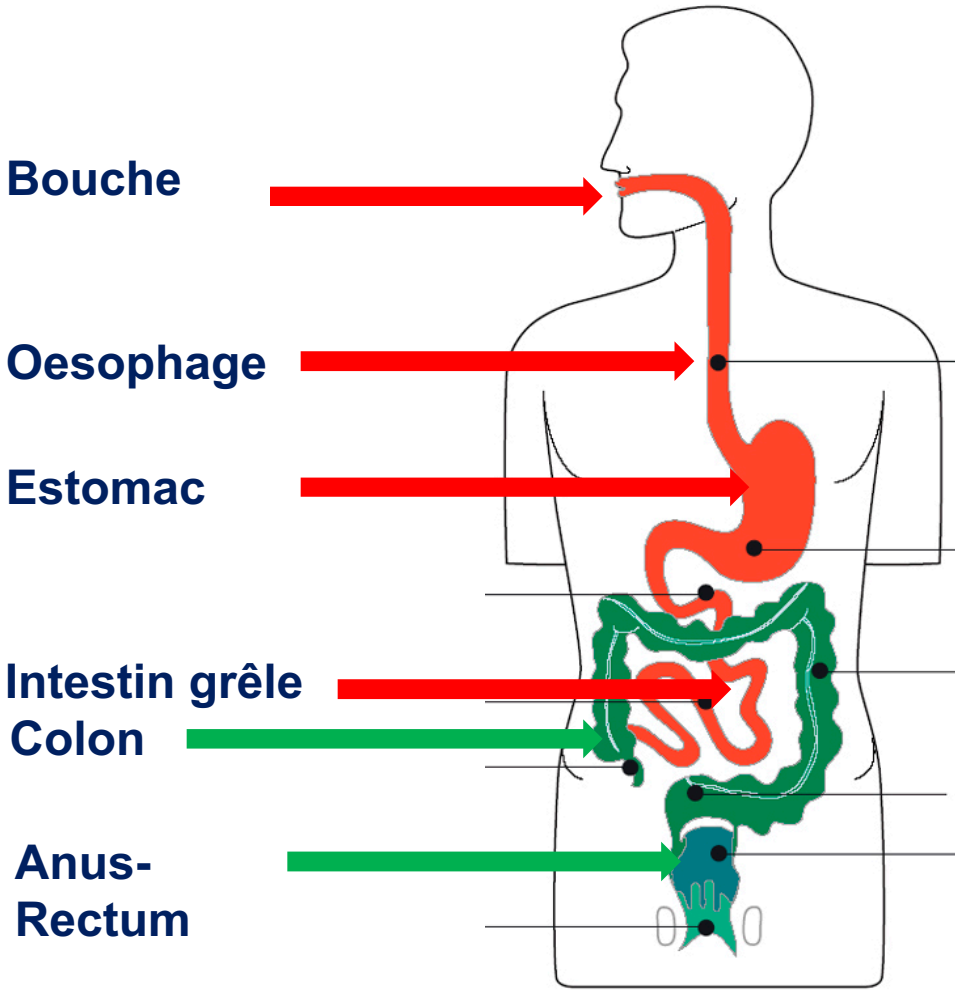
Sclérodermie systémique
Atteinte digestive: symptômes



Syndrome sec buccal
Limitation de l'ouverture buccal
Apparence physique

Reflux gastro-oesophagien
Dysphagie
Toux
Fatigue (anémie)
Vomissements
Douleurs abdominales
Constipation
Occlusion
Diarrhée
Amaigrissement

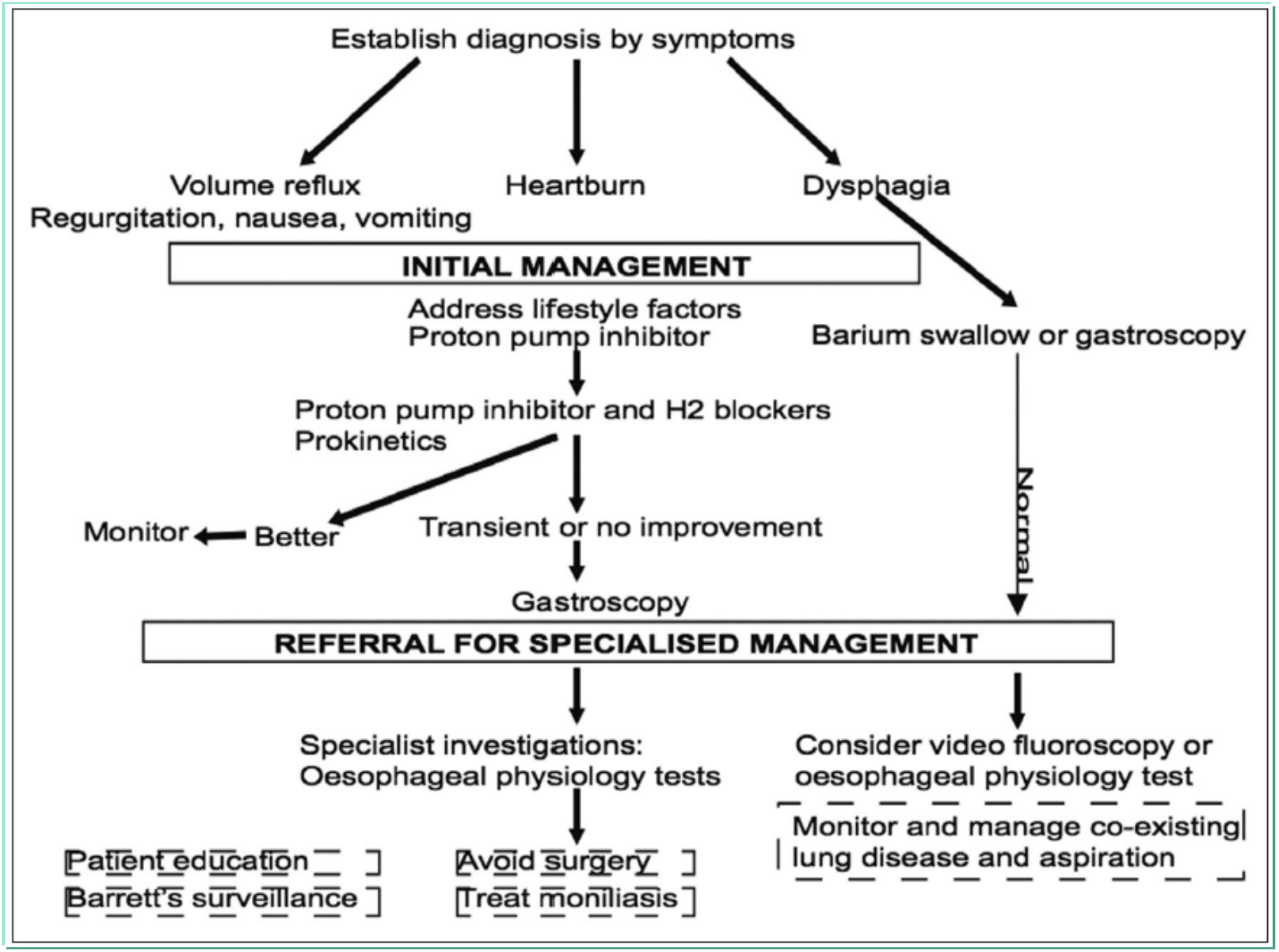
Incontinence annale

Prévalence des principaux symptômes digestifs au cours de la ScS

Symptômes	**Prévalence (%)**
RGO	50-80
Dysphagie	50
Douleurs et/ou ballonnement abdominal	20-30
Diarrhée	20
Constipation	30
Incontinence fécale	7-88

Marie I. Presse Med 2006

Algorythm for management of GORD



Hansi N et al. Clin Exp Rheum 2014

Mesures hygiéno-diététiques
Règles posturales

- Repas fractionnés
- Réduction/arrêt tabac, alcool, thé, café et chocolat.
- Consultation auprès d'un(e) diététicien(ne)
- ETP
- Surélévation de la tête du lit, évitement du décubitus durant les 3 heures suivant les repas.

Consensus Best Practice pathway of the UK Scleroderma Study Group: gastrointestinal manifestations of systemic sclerosis

- The efficacy of PPI in GORD in the general population is well documented in meta-analyses of randomised controlled trials despite there being a lack of randomised control trials in the efficacy of PPI in SSc. Use of ranitidine at night-time to reduce nocturnal acid breakthrough has not been shown to have a consistent effect on patient symptoms (*).

*JANIAK P, THUMSHIRN M, MENNE D *et al.*: Clinical trial: The effects of adding ranitidine at night to twice daily omeprazole therapy on nocturnal acid breakthrough and acid reflux in patients with systemic sclerosis--a randomized controlled, cross-over trial. *Aliment Pharmacol Ther* 2007; 26: 1259-65.

Hansi N et al. Clin Exp Rheum 2014

Does long term therapy with lansoprazole slow progression of oesophageal involvement in SSc?

Method

- 24 SSc patients randomised : lansoprazole 30 mg vs placebo for 12 months.
- Gastroesophageal motility assessed by scintigraphy.
- Symptoms evaluated by self-reported gastrointestinal questionnaire.

Results.

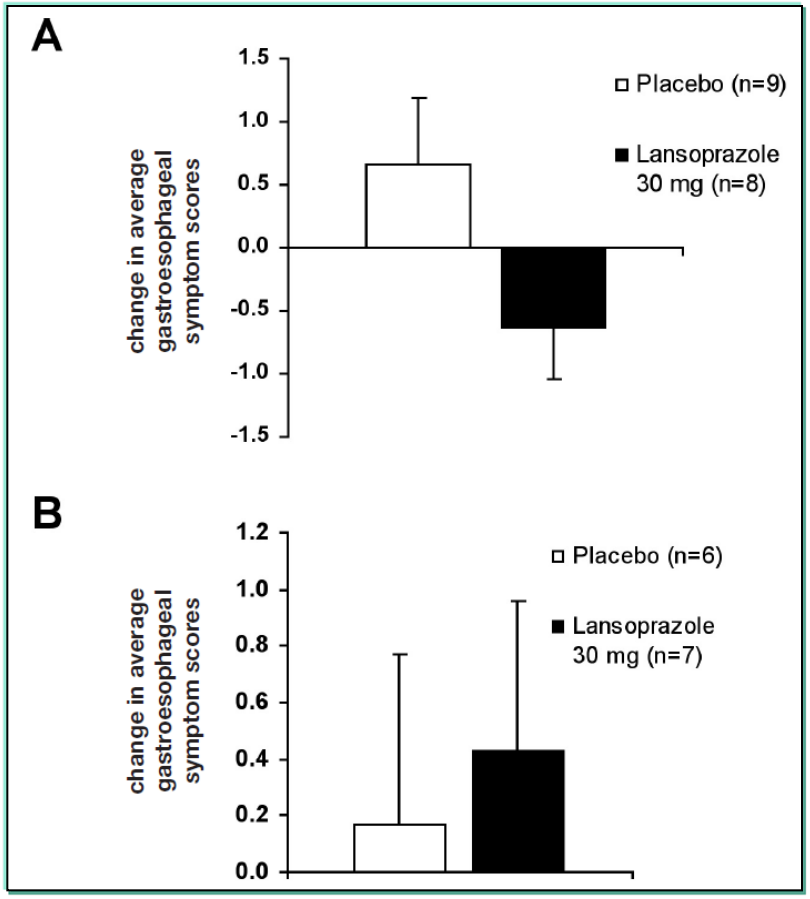
- 21 patients started treatment, 17 (81%) completed 6 months and 13 (62%) completed the study (3 patients in each group withdrawn/adverse events).
- Lansoprazole decreased frequency of gastroesophageal symptoms in the first 6 months of treatment, but long term benefit was not evident.
- Scintigraphy showed worsening oesophageal dysmotility irrespective of lansoprazole treatment.
- No correlation of scintigraphy findings with symptoms of gastroesophageal dysmotility.

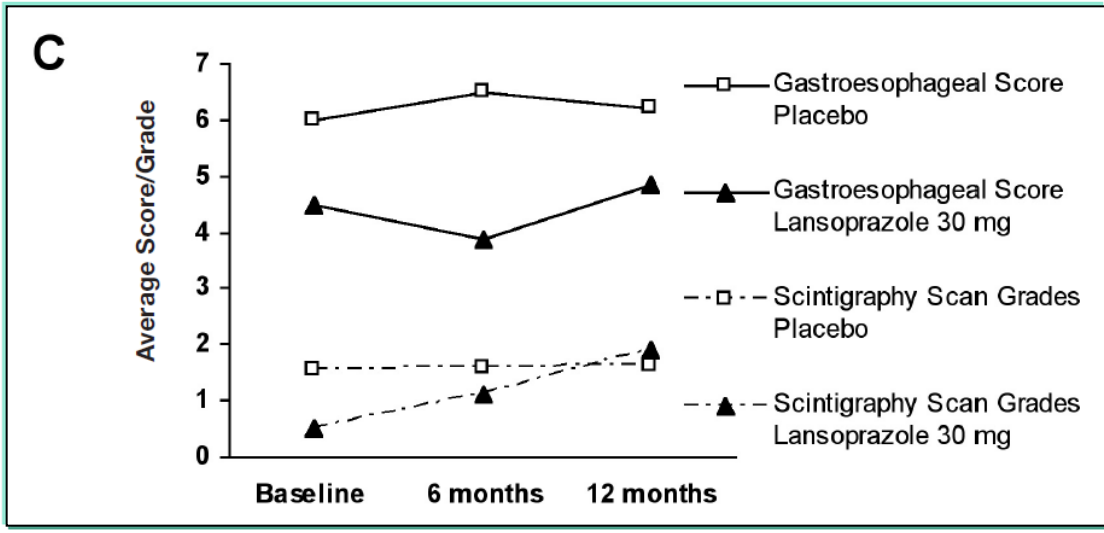
Conclusion.

- Lansoprazole 30 mg daily appears to suppress SSc-related gastroesophageal symptoms in the short term, but a benefit was not sustained at 12 months.
- No evidence that progression of gastroesophageal motility was prevented.
- Scintigraphy findings did not correlate with symptoms of dysphagia.

Pakozdi A. et al. Clin Exp Rheum 2009

Does long term therapy with lansoprazole slow progression of oesophageal involvement in SSc?





Pakozdi A. et al. Clin Exp Rheum 2009

NIFEDIPINE AND ESOPHAGEAL DYSFUNCTION IN PROGRESSIVE SYSTEMIC SCLEROSIS

- **We evaluated the effect of the calcium channel blocking agent, nifedipine, on esophageal dysfunction in 15 patients with progressive systemic sclerosis, using a double-blind, randomized, crossover, placebo-controlled manometric study.**
- **Nifedipine significantly decreased lower esophageal sphincter pressure in these patients; this reduced lower esophageal sphincter ressure may cause gastroesophageal reflux.**
- **Thus, nifedipine may have detrimental effects on progressive systemic sclerosis patients.**

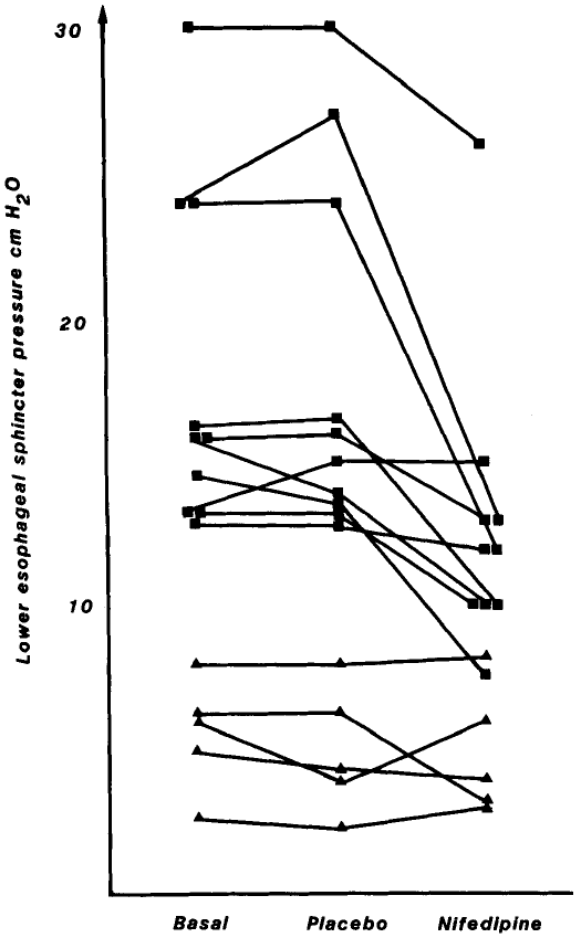


Figure 1. Effect of nifedipine on lower esophageal sphincter pressure (LESP) in 15 patients with progressive systemic sclerosis and diffuse scleroderma. Lower esophageal sphincter pressure in each individual patient is shown for the baseline state and after placebo and nifedipine administration. ■ = group I: 10 patients with normal baseline LESP; ▲ = group II: 5 patients with low baseline LESP.

Kahan A et al. Arthritis and Rheumatism, Vol. 28, No. 5 (May 1985)

RGO: Prokinétiques

Métoclopramide et dompéridone

- avec prudence
- à posologie minimale
- risque d'allongement du QT pour la dompéridone
- au moins 30 minutes avant le repas.
- 2014, domperidone, ANSM a informé les professionnels de santé afin qu'ils prescrivent à la dose efficace la plus faible possible et pour une durée de traitement la plus courte possible (< une semaine).
- Certains patients en tirent cependant bénéfice sur le long cours.

Protocole National de Diagnostic et de Soins (PNDS) 2017
Sclérodermie systémique

Effectiveness of add-on therapy with domperidone vs alginic acid in proton pump inhibitor partial response gastro-oesophageal reflux disease in systemic sclerosis: randomized placebo-controlled trial

- Objectives. To compare the efficacy of omeprazole in combination with domperidone vs in combination with algycon in reducing the severity and frequency of reflux symptoms of PPI partial response (PPI-PR) GERD in SSc.
- Methods. Adult SSc patients having PPI-PR GERD were randomly assigned to receive domperidone plus algycon placebo or algycon plus domperidone placebo in a 1:1 ratio plus omeprazole for 4 weeks.
- Results. 148 SSc-GERD patients were enrolled, of whom 88 had PPI-PR. 80 cases were randomized for either domperidone (n = 38) or algycon (n = 37) therapy. No significant difference in symptom grading was found between groups. After treatment and compared with baseline, the severity of symptoms, frequency scale for symptoms of GERD and QoL significantly improved in both groups. Five (13.2%) and 8 (21.6%) respective cases in the domperidone and algycon groups did not respond.
- Conclusion. Domperidone and algycon are equally effective treatments in combination with omeprazole.

Foocharoen C et al. Rheumatology 2017

Gastric motility

- Use of metoclopramide has been found to improve gastric motility and motor activity (1,2) but the studies involved small numbers and the drug has extrapyramidal side effects.
- There is no published data for domperidone in SSc.
- There is limited evidence from the 1990s advocating erythromycin (3,4) and cisapride was withdrawn from the market due to its association with cardiotoxicity and prolonged QT syndrome. Mosapride, has been shown to accelerate gastric emptying in a study of 60 patients who were randomized to receiving mosapride or nothing, however there is no data for its use in SSc (5).

1. SRIDHAR KR et al. *J Lab Clin Med* 1998; 132: 541-6.
2. JOHNSON DA et al. *Arch Intern Med* 1987; 147: 1597-601.
3. FIORUCCI S et al. *Scand J Gastroenterol* 1994; 29: 807-13.
4. FIORUCCI S et al. *Am J Gastroenterol* 1994; 89: 550-5.
5. WEI W, GE ZZ et al. *J Gastroenterol Hepatol* 2007; 22: 1605-8.

Erythromycine et gastroparésie

- Agoniste des récepteurs gastriques de la motiline
- Augmentation des contractions antrales, accélération de la vidange gastrique
- Efficacité prouvée dans de petites séries de gastroparésies (diabète et ScS)
- Posologie : de 125 x 2/j à 250 x 2/j PO
- Si inefficace par voie orale, voie IV (1,5-3 mg/kg/6-8h)
- Tachyphylaxie possible après prise prolongée

Gastroparésie

- Echec érythromycine:
  - acide clavulanique prokinétique pour l'estomac.
- Traitement prokinétique (métoclopramide ou métopimazine) buvable en l'absence de contre-indication neurologique et/ou électrocardiographique.
- Si dénutrition sévère: alimentation entérale (jéjunale) prolongée.

Protocole National de Diagnostic et de Soins (PNDS) 2017
Sclérodermie systémique

Pseudo-obstruction

- Somatostatin analogues such as octreotide have also been used to induce contractile activity throughout the bowel (1). Octreotide with erythromycin has been found useful in patients with abdominal discomfort associated with pseudo-obstruction (2). Octreotide does have its own disadvantages with increased risk of cholelithiasis, with inhibitory effects on gastric emptying, pancreatic secretions and gallbladder contractions and we would not advocate its use routinely.

1. NIKOU GC et al. *J Clin Rheumatol* 2007; 13: 119-23.
2. VERNE GN et al. *Dig Dis Sci* 1995; 40: 1892-901.
   TOSKES P. NEJM 1991

Traitement de l'atteinte grêlique de la ScS (1)

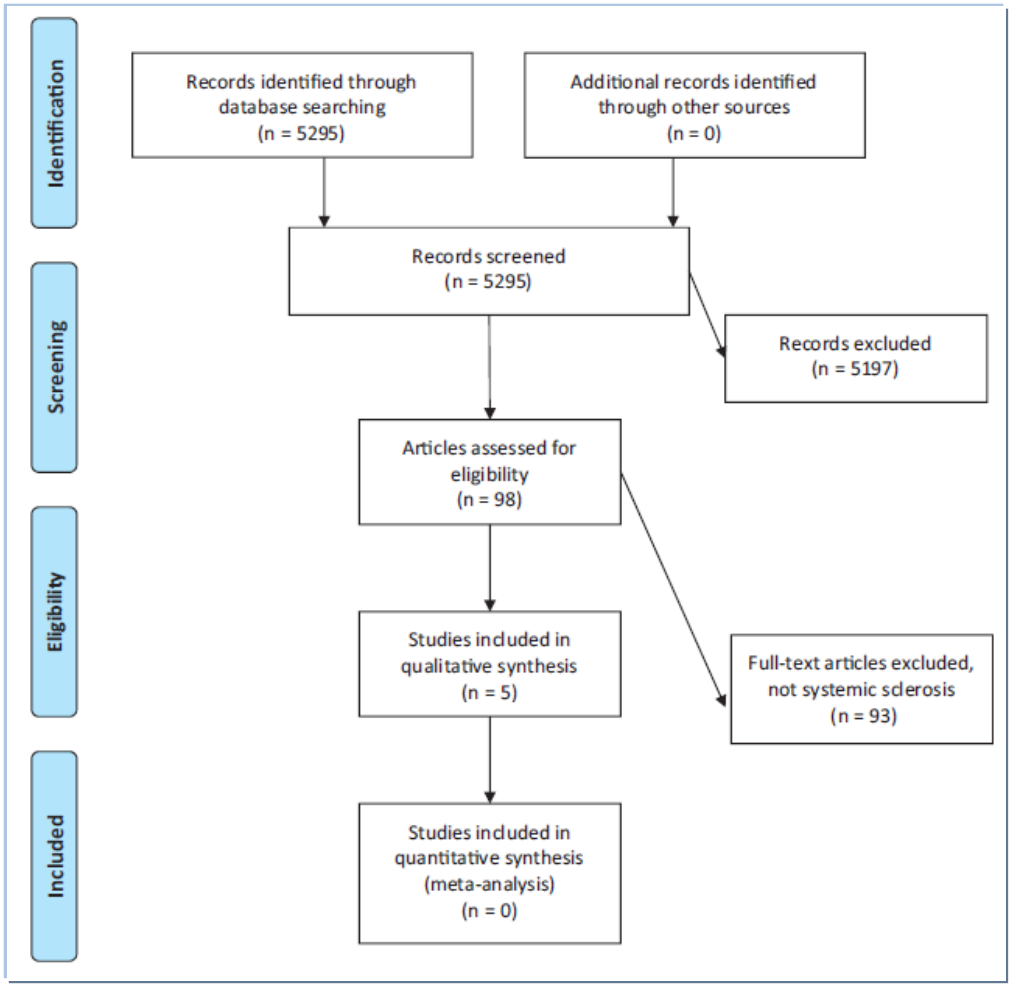
- Traitement de l'hypomotilité intestinale:
  - Prokinetiques :
    - ! Plus l'intestin est dilaté, moins le médicament est efficace!
    - Metoclopramide 10 mg x 3/j
      - Souvent utilisé pour atteinte oesogastrique associée
    - Octreotide : action plus spécifique sur intestin grêle
      - Début à 50 µg/j sous-cutané
      - Augmenter à 50 µg x 2/j, maximum 100 µg x 2/j
      - Si perte d'efficacité, « wash-out » pendant 3 à 4 semaines
    - Pyridostigmine - Neostigmine
  - Mesures diététiques
    - Régime pauvre en fibres, pauvre en graisses, fractionnement des repas
  - En cas de pseudo-occlusion aiguë :
    - Aspiration naso-gastrique – hydratation intraveineuse – analgésie (sans opiacés)

Small intestinal bacterial overgrowth (SIBO)

- A trial of empirical antibiotics for bacterial overgrowth may be started as per local guidelines such as ciprofloxacin or metronidazole, but cyclical courses may be needed. Studies of Rifaximin use in the general population have shown significant improvement in its eradication of SIBO (1) and can be administered at high doses of 800mg twice daily (2).

1. *PIMENTEL M. Expert Opin Investig Drugs 2009; 18: 349-58.*
2. *SCARPELLINI E et al. Aliment Pharmacol Ther 2007; 25: 781-6.*

Treatment of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review



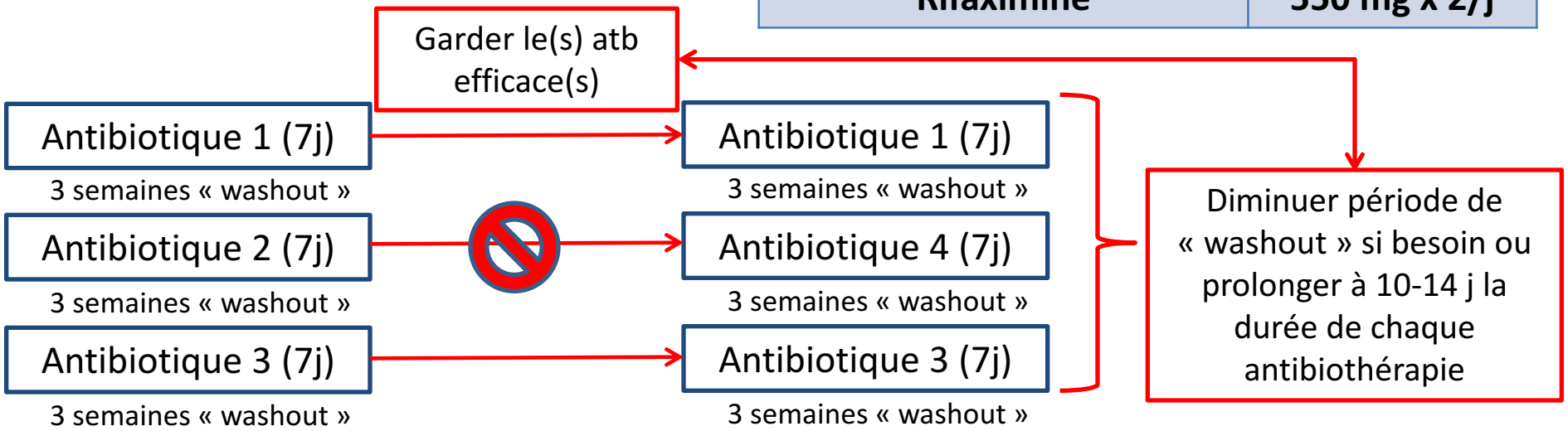
- There is a paucity of evidence to determine whether prokinetics or probiotics are beneficial in the treatment of SIBO in patients with SSc.
- Based on low quality data, there is some evidence that antibiotics can be effective in eradicating SIBO in some patients with SSc.

Pittman N et al. Rheumatology 2018

Traitement de l'atteinte grêlique de la ScS (2)

- Traitement de la pullulation microbienne:
  - Diagnostic clinique
  - Test respiratoire souvent inutile
  - Antibiothérapie alternée:

Amoxicilline	**500 mg x 3/j**
Norfloxacine	**400 mg x 2/j**
Doxycycline	**100 mg/j**
Metronidazole	**250 mg x 3/j**
Gentamycine	**80 mg/j**
Cotrimoxazole	**800 mg x 2/j**
Amoxicilline-clavulanate	**500 mg x 2/j**
Rifaximine	**550 mg x 2/j**



Traitement de l'atteinte grêlique de la ScS (3)

- Traitement de la dénutrition :
  - Supplémentation des carences (vitamines, ions)
  - Compléments alimentaires oraux
  - **Nutrition parentérale** :
    - Catheter veineux central
    - Verrous antibiotiques
    - Centres spécialisés (si prolongée)

Protocole National de Diagnostic et de Soins (PNDS) 2017
Sclérodermie systémique

Atteinte digestive au cours de la sclérodermie systémique: quels traitements fondés sur des preuves ? Conclusions

- L'atteinte digestive est très fréquente au cours de la sclérodermie
- Très peu d'essais prospectifs randomisés
- Manque de puissance des essais disponibles
- Le plus souvent il s'agit de recommandations d'experts
- PNDS sclérodermie systémique
- Importance de l'expérience clinique