NHS
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BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

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Review: July 2019

Bulletin 239 : Rifaximin for the management of chronic diarrhoea associated with gastro- intestinal disorders

JPC Recommendations:

- To support the East of England Priorities Advisory Committee (PAC) policy statement and recommendations (See attachment)

The East of England
Priorities Advisory Committee
A function of PrescQIPP

FULL EVIDENCE REVIEW

Rifaximin for the management of chronic diarrhoea associated with gastro-intestinal disorders

PAC recommendation

- Rifaximin is **NOT RECOMMENDED** for routine commissioning in patients with gastrointestinal disorders including Crohn's disease (CD), Ulcerative Colitis (UC), Diverticular disease (DD), Irritable bowel syndrome (IBS), recurrent Clostridium difficile infection and small intestinal bacterial overgrowth (SIBO).
- Rifaximin should be considered as an option for the treatment of pouchitis in ulcerative colitis patients where other treatments have failed, and where failure to treat would result in surgical intervention. Patients requiring treatment with Rifaximin for this indication should be considered through local individual funding request (IFR) procedures.

Key points/Evidence level

Key points

- The aetiology of inflammatory bowel diseases (IBD) is still obscure. There is increasing evidence that gut microflora is a further important factor, with the concentration of intestinal bacteria in IBD patients being higher than normal and increasing with the severity of the disease. Overgrowth of gut microflora has also been implicated in diverticular disease (DD) and irritable bowel syndrome (IBS).
- Ciprofloxacin and metronidazole are currently used in the management of acute exacerbations of IBD conditions. IBS and DD are managed conservatively. Diverticulitis, an acute inflammatory response in DD patients is usually more serious and often requires IV fluids and antibiotics.
- Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis. Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species and may inhibit the division of urea-de-aminating bacteria
- Two licensed products are available in the UK; Targaxan® 550mg for hepatic encephalopathy and Xifaxanta® 200mg for non-invasive traveller's diarrhoea.
- Rifaximin has been advocated as a possible treatment option for other gastrointestinal disorders as listed above due to its broad spectrum and poor oral absorption.
- There is currently very limited evidence, good quality randomised controlled trials (RCTS) are lacking. All the available trials are either small, short term uncontrolled and/or retrospective in design. There is very little long term data.
- There are currently no data regarding the impact of rifaximin treatment on hospitalisation rates and/or length of stay for patients with inflammatory bowel disease and diverticular disease.

- Whilst the evidence is weak, clinician feedback has indicated there may be a place in therapy for rifaximin in the treatment of pouchitis, a specific complication of ulcerative colitis, where other treatments have failed, and where failure to treat would result in surgical intervention.
- In addition to the indications mentioned above, observational data from hepatic encephalopathy trials has suggested a possible role in the treatment of recurrent Clostridium difficile infection; however data from retrospective analysis has proved inconclusive and metronidazole and vancomycin remain the treatments of choice.
- The impact of rifaximin on bacterial resistance rates including resistance to other rifamycin antibiotics, such as rifampicin, is unknown. Rifampicin is a mainstay of TB treatment and whilst the consequent risk to TB affected communities is likely to be low, it is still unknown. More data is required to further quantify the risk, if any of increased bacterial resistance.
- Rifaximin (550mg, Targaxan®) currently costs £259.23 for 28 days treatment and Xifaxanta® (200mg) is £15.15 for nine tablets.

Introduction

The aetiology of inflammatory bowel diseases (IBD) is still obscure, with genetic, immunological, environmental and psychological factors all playing a part. There is increasing evidence that gut microflora is a further important factor involved in promoting or maintaining the inflammatory process, with the concentration of intestinal bacteria in IBD patients being higher than normal and increasing with the severity of the disease. Overgrowth of gut microflora has also been implicated in diverticular disease (DD) and irritable bowel syndrome (IBS).[1-6]

Antibiotics such as metronidazole and ciprofloxacin have been successfully employed in the treatment of Crohn's disease (CD), ulcerative colitis (UC) and pouchitis.[7-8] Rifaximin has been suggested as a possible alternative due to its broad spectrum of activity and poor bioavailability, which theoretically minimises the risk of systemic side effects and bacterial resistance.[1-6]

The intervention mechanism of action

Rifaximin is an antibacterial drug of the rifamycin class that irreversibly binds the beta sub-unit of the bacterial enzyme DNA-dependent RNA polymerase and consequently inhibits bacterial RNA synthesis. Rifaximin has a broad antimicrobial spectrum against most of the Gram-positive and negative, aerobic and anaerobic bacteria, including ammonia producing species and may inhibit the division of urea-de-aminating bacteria.[7,8]

Formulation/Available products

Rifaximin is available as two products, both of which are licensed for use in people aged 18 years and older:[9,10]

- Targaxan® 550 mg film-coated tablets
- Xifaxanta® 200 mg film-coated tablets

Licensed indication

TARGAXAN® is indicated for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients' ≥ 18 years of age.[9]

XIFAXANTA® 200mg film-coated tablets are indicated for the treatment of non-invasive travellers' diarrhoea that is not associated with fever, bloody diarrhoea, eight or more unformed stools in the previous 24 hours, occult blood or leucocytes in the stool.[10]

Usual dosage

The recommended dose of Xifaxanta® for non-invasive traveller's diarrhoea is 200mg 8 hourly for three days.[9-10]

The recommended dose of Targaxan® for OHE is 550 mg twice a day (BD).[7-9]

Rifaximin can be administered with or without food, with a glass of water.[7,9,10]

Treatment alternatives/place in therapy

Exacerbation of Inflammatory Bowel disease: Ciprofloxacin or metronidazole.[7,11]

Clostridium difficile associated diarrhoea: metronidazole or oral vancomycin.[7,11]

Irritable bowel syndrome: Antibiotics are not usually recommended for IBS. Treatment is usually aimed at symptomatic relief of symptoms i.e. antispasmodics, peppermint oil, anti-diarrhoeal agents etc.[11,12]

Diverticular disease: conservative management, increase fibre intake. Exacerbation causing diverticulitis, IV fluids and antibiotics may be needed.[7]

Future alternatives

None known.

National guidance

No relevant national guidance was identified. NICE recommend rifaximin as a treatment option for patients with overt hepatic encephalopathy only.[13]

Local guidance

None identified.

Evidence for use

There is limited evidence of increased benefit over existing treatments at this time and all the indications discussed below are unlicensed uses for rifaximin.

Crohn's Disease

An ongoing randomised, prospective, placebo controlled, cross over study, published as an interim analysis in a conference abstract included 22 patients with moderate to severe CD, who were randomised to either rifaximin 550mg BD or placebo for eight weeks. The primary efficacy endpoint was the proportion of patients achieving clinical response; defined as a decrease in the Crohn's disease activity score (CDAI of ≥100 points at week 8). The mean week 8 CDAI score was reported as 322 for placebo and 258 for rifaximin; p=0.2743 and for the mean Inflammatory Bowel Disease Questionnaire score was 143 vs 119; p=0.1414.[14] However, there is not enough data available on which to base a definitive conclusion.

In a double blind study by Prantera et al, 402 patients with moderately active CD (CDAI 220-400; mean 278), aged between 18 years and 70 years, were randomised to receive either placebo or 400mg, 800mg, 1200mg BD of an extended release formulation of rifaximin. It should be noted that this formulation is not currently available in the United Kingdom.[15]

The primary endpoint was remission (CDAI < 150) at 12 weeks. Remission was reported in 62% of patients in 800mg group; 54% in the 400mg , 47% in the 1200mg group compared with 43% who received placebo; 95% CI 1.26-3.92 (p=0.005).

However withdrawal rates and adverse effects were higher in the 1200mg group. The study authors concluded that 800mg BD of the extended release rifaximin formulation induced remission with few adverse events in patients with moderately active CD.

An earlier smaller dose ranging study by Prantera involving 83 patients with mild to moderate CD, demonstrated clinical remission in 52% of patients receiving 800mg BD compared with 32% in patients receiving 800mg once daily (OD) and 33% in the placebo group; again this study is too small to draw a definitive conclusion.[16]

In a preliminary, open label assessment, 39 patients with active Crohn's disease (symptoms for at least three months and CDAI score >220 and < 400 received rifaximin 200mg three times daily (TDS) for 16 weeks. At the end of month 4 mean CDAI score was reduced by 43% compared with baseline (baseline 278±51; month 4 159±102, p<0.0001). Clinical remission, defined as CDAI score < 150 was observed at the end of treatment months 1, 2, 3 and 4 in 41%, 56%, 56% and 59% of patients respectively.[17] 23 patients completed the four month course. The most common adverse events were abdominal pain, fatigue and headache.

A retrospective analysis of inpatient charts at a medical centre in the US, identified 68 CD patients who had received rifaximin with most patients receiving 600mg/day for 16 weeks (overall range 200mg three times weekly to 200mg TDS). 31 patients were also treated with steroids.[18]

The primary endpoint of this analysis was successful remission in patient with CD treated with rifaximin, with remission defined as CDAI score < 150. CD remission was reported in 44 (65%) of patients, with a slightly higher remission rate being noted in patients who did not receive steroids (70%) and in patients who received concomitant medication other than steroids (65%) compared with those who received steroids (58%). Clinical remission was also observed in 12 of 18 patients (67%) who received rifaximin alone.

Ulcerative colitis

In an open-label study, 30 patients aged between 21 and 66 years, with a mild-to-moderate flare-up of ulcerative colitis during maintenance treatment with mesalazine 2.4g daily, and in whom steroid treatment was not advisable because of a history of poor tolerability, had rifaximin 400mg BD added for four weeks.[19] Clinical evaluation before and after treatment was performed by means of Rachmilewitz's Activity Index. Only patients with an initial score of > 8 were included. A final index score of < 6 was considered a sign of full clinical remission and was obtained in 23/30 (76.6%) of cases. Partial clinical improvement was observed in six of the remaining seven subjects.[19]

In a small placebo controlled, double blind randomised study, 28 patients refractory to steroid therapy received an adjunct therapy with either rifaximin 400 mg BD or placebo for 10 days, Patients were considered to be improved if they had ≤ 3 bowel movements per day. In the rifaximin group clinical improvement, as defined by any improvement from baseline to day ten, was observed in nine patients (64.3%) compared with placebo; five patients (41.7%).[20]

A small pilot study involving six mesalazine-intolerant patients with mild to moderate ulcerative colitis, who were in remission after a course of oral steroids who were reluctant to take immunosuppressants, received a combination of rifaximin 400mg + the probiotic agent Saccharomyces boulardii 500mg as a maintenance treatment for three months. At the end of the treatment period, all patients were still in clinical remission.[21]

Pouchitis

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with ulcerative colitis (UC) requiring colectomy. Pouchitis is a non-specific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC, occurring in up to 50% of IPAA patients within ten years. Diagnosis of pouchitis requires the presence of symptoms, together with characteristic endoscopic and histological abnormalities [EL3a, RGB]. Symptoms include increased stool frequency and liquidity, abdominal cramping, urgency, tenesmus and pelvic discomfort. Rectal bleeding, fever, or extraintestinal manifestations may occur, Optimum treatment has not been clearly defined but currently includes ciprofloxacin or metronidazole. Chronic pouchitis may require combined treatment. Other options include, budesonide and/or rifaximin. Infliximab has

been used for refractory chronic pouchitis unresponsive to other measures. Surgical revision may be necessary if medical treatments fail.[22]

NICE have published an evidence summary (ESUOM30) regarding the use of rifaximin either alone or in combination with ciprofloxacin for pouchitis, which confirms that there is limited evidence of benefit.[23]

A Cochrane review, published in 2010 assessed the treatment and prevention of pouchitis after IPAA for UC. The primary objective of the review was to determine the efficacy of medical therapies, including antibiotics, probiotics and other agents for pouchitis. 11 RCTs were identified and included in the review, assessing ten different pharmacologic agents. For the treatment of acute pouchitis; rifaximin was no better than placebo, although ciprofloxacin was more effective than metronidazole.[24]

Feedback from local clinicians and EoE medicines management teams has suggested that although the evidence is weak, there may be justification in offering rifaximin as an option for the treatment of pouchitis in ulcerative colitis patients where other treatments have failed, and where failure to treat would result in surgical intervention.

Diverticular disease

Diverticula are small hernias or pouches of mucosa that develop through the muscular wall of the gut (especially the colon) or other hollow organs; they increase in prevalence with increasing age. Diverticular disease (the presence of colonic diverticula) is usually asymptomatic, but may be associated with symptoms of abdominal pain and altered bowel habit (diverticulosis). This is usually conservatively managed by increasing fibre intake.[25]

Occasionally there may be severe life-threatening complications such as inflammation and necrosis of diverticula (diverticulitis), perforation, fistula formation, obstruction, or haemorrhage which require hospitalisation and treatment with intravenous fluid and antibiotics and even blood transfusion

Cyclical administration of rifaximin has been used in the management of diverticular disease; however the evidence is limited to small open label non-randomised trials.

In a multicentre open trial 217 patients with symptomatic uncomplicated diverticular disease were treated with glucomannan (n=110) or glucomannan plus rifaximin 400mg BD for seven days each month (n=107). Clinical evaluation was performed bimonthly for 12 months using a global symptom score of eight clinical variables. After 12 months the study authors reported a 63.9% reduction in symptom score for the combined group compared to 47.6% in the glucomannan only group ($p<0.001$).[26]

In a second similar study 168 patients were treated with either glucomannan 2g/day plus rifaximin 400mg BD for 7 days every month (n=84) or glucomannan 2g/day plus placebo two tablets BD for seven days each month (n=84). After 12 months 68.9% of the patients treated with rifaximin were mildly symptomatic or symptom free compared to 39.5% in the placebo group; $p=0.001$.[27]

In a small non- randomised trial 218 consecutive eligible patients aged between 51-79 years with diverticulitis, 109 patients (group A) were treated with rifaximin 400mg BD plus mesalazine 800mg TDS for seven days followed by rifaximin 400mg BD plus 800mg BD for seven days each month. 109 patients (Group B) were treated with rifaximin BD for seven days followed by rifaximin 400mg BD for seven days each month. Colonoscopy was performed at three, six and 12 months of therapy. The primary outcome of the trial was not stated and limited details of the results are available.

At the end of follow up, symptomatic recurrence of diverticulitis occurred in three patients taking rifaximin and mesalazine and 13 patients taking rifaximin alone. Severity of symptoms improved in group A vs. group B.[28]

In a multi-centre, prospective open label trial, 968 outpatients aged between 40-80 years, with uncomplicated but symptomatic diverticular disease were randomised to either fibre supplementation with glucomannan 4g/day plus 400mg rifaximin BD for seven days each month or 4g/day glucomannan alone. The primary objective of the study was to evaluate the efficacy of cyclic long term administration of rifaximin in obtaining symptom relief, measure as a reduction at 12 months in both frequency of symptoms and global symptomatic score. At 12 months the frequency of symptoms was lower in the group treated with glucomannan plus rifaximin with the study reporting 56.5% of patients in the rifaximin plus glucomannan group and 29.2% in the glucomannan alone group were symptom free at 12 months.[29]

The overall global symptomatic score was similar but slightly lower compared to baseline in the rifaximin plus fibre group compared with fibre alone; (-5.5 vs -4.3 change from baseline respectively; $p<0.05$).

Colcheccia et al have also evaluated the use of rifaximin plus fibre versus fibre alone in a multicentre, open prospective randomised controlled study of 307 patients aged between 40-80 years of age, with symptomatic uncomplicated colonic diverticular disease. At enrolment and every two months patients were clinically examined and required to complete a questionnaire about their symptoms. Five clinical variables (lower abdominal pain/discomfort, bloating, tenesmus, diarrhoea and abdominal tenderness) were graded according to the following scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, sufficient to interfere with daily activities and 3 = severe, incapacitating. A global score was calculated which could range from 0, absence of symptoms to 15, presence of all symptoms with high degree of severity.[30]

Both treatments induced a reduction in symptom frequency in all patients by 12 months. After 24 months, rifaximin produced further reductions in symptom frequency, whilst no further reduction was observed in the fibre only group. Change from baseline in symptom score was higher in the rifaximin group, than in the fibre only group (-5.0 vs -3.0 respectively; $p<0.001$). Overall mild adverse events reported as headache, nausea and weakness were similar between the 2 groups, although frequency of complications was higher in the fibre group than in the rifaximin group; nine reports including four cases of intestinal infections, one of rectal bleeding and four of diverticulitis vs. four reports; two cases of rectal bleeding and two cases of diverticulitis respectively.

A systematic review published in 2011, which combines the results of the four trials which compared rifaximin plus fibre to fibre alone, concluded that the trials failed to show a significant difference between treatments, however cumulative data could suggest a benefit for the rifaximin plus fibre on the one year rate of acute diverticulitis 11/970 vs. 20/690; $p=0.012$.[31]

Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is a common, long-term condition of the digestive system. It can cause bouts of stomach cramps, bloating, diarrhoea and/or constipation.[12]

The symptoms vary between individuals and affect some people more severely than others. They tend to come and go in periods lasting a few days to a few months at a time, often during times of stress or after eating certain foods.[12]

IBS is thought to affect up to one in five people at some point in their life, and it usually first develops when a person is between 20 and 30 years of age. Around twice as many women are affected as men. The condition is often life-long, although it may improve over several years.[12]

In two identically designed phase 3 double-blind placebo controlled trials TARGET-1 and TARGET-2, patients who had IBS without constipation were randomly assigned to either rifaximin at a dose of 550mg or placebo, three times daily for two weeks and were followed for an additional ten weeks. The primary end point was the proportion of patients who had adequate relief of global IBS symptoms. The secondary endpoint was the proportion of patients who had adequate relief of IBS related bloating. Both were assessed weekly.[32,33]

A total of 1260 patients with IBS enrolled on the studies; 623 patients in TARGET-1; (n=309 for rifaximin, 314 for placebo), and 637 patients in TARGET-2; (n=316 for rifaximin and 321 for placebo). More patients in the rifaximin group than the placebo group met the criteria for the primary endpoint of adequate relief of global IBS symptoms for at least two of the first four weeks after treatment 40.8% vs. 31.2%; p=0.01 in TARGET-1; 40.6% vs. 32.2%, p=0.003 in TARGET-2; and 40.7% vs. 31.75%, p<0.0001 in the two studies combined. Similar results were seen for the secondary endpoint. The proportion of patients with adequate relief of IBS related bloating was 39.4% vs. 28.7%, p=0.005 in TARGET-1; 41.0% vs. 31.9%, p=0.02 in TARGET-2 and 40.2% vs. 30.3%, p<0.001 in the 2 studies combined.

The safety profile of rifaximin was reported to be similar to placebo. A total of 92.3% of the patients in TARGET-1 and 94.7% in TARGET-2 completed the study. Serious adverse events were recorded in ten patients in the rifaximin group and 15 patients in the placebo group. There were no cases of C. difficile associated diarrhoea reported or ischemic colitis. The two studies did not specifically assess the effect of rifaximin treatment of bacterial resistance rates. A subsequent pooled analysis of safety data has also suggested a similar adverse effect profile of rifaximin and placebo, but did not provide any additional data about the possible effect of rifaximin on increased bacterial resistance.[33]

Clostridium difficile associated diarrhoea

Clostridium difficile (C. difficile) can cause severe antibiotic associated colitis. Current treatments include vancomycin and metronidazole. Rifaximin has been suggested as a possible alternative option due to its poor bioavailability and effectiveness against C. difficile.[34]

Data for clinical trials relating to is use in hepatic encephalopathy has indicated that rifaximin may prevent C. difficile infections however, there are limited data from clinical trials specifically designed to assess the efficacy and safety in relation to the prevention and treatment of C difficile infection.[35]

In a randomised, double blind placebo controlled pilot study, 68 patients aged 18 years who had been treated for a confirmed C difficile associated diarrhoea, with either metronidazole and vancomycin for 10-14 days, received either rifaximin 400mg TDS (n=33) or placebo (n=35) for 20 days. Study treatments were given immediately after completing standard antibiotic treatments and patients were followed for three months. 24 patients had recurrent diarrhoea either due to recurrent C. difficile infection or self-reported diarrhoea. Recurrent diarrhoea occurred in 17 patients given placebo and seven given rifaximin, p=0.018. C. difficile infection recurrence occurred in 11 patients treated with placebo and five patients treated with rifaximin; p=0.11.[36]

A small retrospective study included 32 patients who had received rifaximin for recurrent C. difficile infection, who had received several courses of metronidazole and/or oral vancomycin. 25 patients received oral rifaximin 400mg BD for 14 days, which was immediately preceded by an oral course of vancomycin 125 mg QDS for 14 days. Seven patients received differing combinations and courses of metronidazole, vancomycin and rifaximin. Patients were followed for three months and assessed for recurrent diarrhoea that included C. difficile recurrence. After 12 weeks follow up, 15 patients were recorded as treatment failures and 17 patients were reported as being resolved.[37]

Small intestinal bacterial overgrowth (SIBO) not associated with irritable bowel disease

Small intestine bacterial overgrowth has been suggested as a possible cause in patients with gastrointestinal symptoms such as chronic diarrhoea and abdominal pain not associated with any gastrointestinal disorders. SIBO has also been postulated as a possible contributory factor to Coeliac disease and associated with symptoms of interstitial cystitis and arthritis.[38-57] Treatment with proton pump inhibitors such as omeprazole may increase the risk of developing SIBO.[58-65]

Current treatment options include a high fat, low carbohydrate diet, prebiotic and probiotic or a seven to ten day course of antibiotics such as metronidazole, co-amoxiclav or ciprofloxacin. Rifaximin has also been suggested as a possible treatment option due to its low systemic bioavailability.[38-39]

However as with all antibiotics, used to treat SIBO, the limited data so far, from small observational studies and anecdotal reports, does not support the routine use of rifaximin in these patients. Recurrence of SIBO, is common after treatment.[49,55-57] In a study involving 80 patients with SIBO who were treated successfully with rifaximin, recurrence rates were 13%, 28%, and 44% after three, six and nine months, respectively. Recurrence was more likely in older adults, those with a history of an appendectomy and with chronic PPI use.[49] Successful treatment of recurrence with rifaximin has been reported.[55]

In addition, there is also limited comparative evidence between all antibiotics including rifaximin.

Contraindications and precautions

Hypersensitivity to rifaximin, rifamycin-derivatives or to any of the excipients.[9,10]

Do not use in patients with intestinal obstruction.[9,10]

The safety and efficacy of rifaximin in paediatric patients (aged less than 18 years) has not been established.[9,10]

No dosage adjustment is necessary in elderly patients as the safety and efficacy data of rifaximin showed no differences between the elderly and the younger patients.[9,10]

No dosage adjustment is necessary for patients with hepatic insufficiency. [9,10]

With respect to renal impairment, although dosing change is not anticipated, the SPC advises that rifaximin should be used with caution in patients with impaired renal function. [9,10]

As rifaximin is an antibacterial, consideration should be given to official guidance on the appropriate use of antibacterial agents. No evidence of bacterial resistance developing in patients treated with rifaximin appears to have been reported to date.[7-10]

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended. [9,10]

Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. To date, such interactions have not been commonly reported. The SPC for rifaximin currently recommends taking additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50µg. [9,10]

Safety and tolerability

Rifaximin is a rifamycin type antibacterial and has a similar sounding name to rifampicin, which is commonly used for management of tuberculosis. Unlike rifampicin, rifaximin is not absorbed and therefore is associated with fewer side effects.

Healthcare professionals are advised to exercise caution and double check prescriptions for rifaximin and rifampicin to ensure that the correct drug is supplied and to avoid inadvertent administration of the wrong drug.

Pharmacokinetic studies in rats, dogs and humans demonstrated that after oral administration rifaximin in the polymorph α form is poorly absorbed (less than 1%). After repeated administration of therapeutic doses of rifaximin in healthy volunteers and patients with damaged intestinal mucosa (IBD), plasma levels are negligible (less than 10 ng/mL). A clinically irrelevant increase of rifaximin systemic absorption was observed when administered within 30 minutes of a high-fat breakfast.[9 10,66]

Since rifaximin is poorly absorbed from the gastrointestinal tract, adverse effects have generally been restricted to gastrointestinal disturbances such as abdominal pain, diarrhoea, and nausea. Headache may also occur. Hypersensitivity reactions, including exfoliative dermatitis and

angioedema have been reported. Patients should be informed that despite the negligible absorption of the drug (less than 1%), like all rifamycin derivatives, rifaximin may cause a reddish discolouration of the urine.[9,10,65]

Rifaximin has a less adverse side-effect profile compared to neomycin. Neomycin is not licensed for long-term use in the prevention of hepatic encephalopathy; patients require regular renal function tests for potential nephrotoxicity and auditory tests due to ototoxicity. Rifaximin has few monitoring requirements.[9,10,66]

Drug interactions

In vitro data show that rifaximin did not inhibit the major cytochrome P-450 (CYP) drug metabolizing enzymes (CYPs1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4). In in vitro induction studies, rifaximin did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4.[9,10,67]

In healthy subjects, clinical drug interaction studies demonstrated that rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however, in hepatic impaired patients it cannot be excluded that rifaximin may decrease the exposure of concomitant CYP3A4 substrates administered (e.g. warfarin, anti-epileptics, anti-arrhythmics), due to the higher systemic exposure with respect to healthy subjects. There is one isolated case report of rifaximin reducing the anticoagulant effects of warfarin. [9,10,67]

An in vitro study suggested that rifaximin is a moderate substrate of P-glycoprotein (P-gp) and metabolized by CYP3A4. It is unknown whether concomitant drugs which inhibit P-gp and/or CYP3A4 can increase the systemic exposure of rifaximin. [9,10,67]

The potential for drug-drug interactions to occur at the level of transporter systems has been evaluated in vitro and these studies suggest that a clinical interaction between rifaximin and other compounds that undergo efflux via P-gp and other transport proteins is unlikely (MDR1, MRP2, MRP4, BCRP and BSEP). [10,67]

There is no experience regarding administration of rifaximin to subjects who are taking another rifamycin antibacterial agent to treat a systemic bacterial infection.[10] Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Due to the lack of data and the potential for severe disruption of gut flora with unknown consequences, concomitant administration of rifaximin with other rifamycins is not recommended.[9,10,67]

Due to the effects on the gut flora, the effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. To date, such interactions have not been commonly reported. The SPC for rifaximin currently recommends taking additional contraceptive precautions, in particular if the oestrogen content of oral contraceptives is less than 50µg. [9,10,67]

Pregnancy and lactation

There are no or limited data from the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus. As a precautionary measure, use of rifaximin during pregnancy is not recommended.[9,10]

It is unknown whether rifaximin or its metabolites are excreted in human milk. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.[9,10]

Costs/Tariff status/Activity costs

Comparative costs (BNF, eMIMs and Drug Tariff January 2016). Costs are indicative only and do not imply therapeutic equivalence.

Drug	Indication	Dose and frequency	Cost	Cost/28 days or course
Rifaximin	CD	550mg BD	£259.23/56	£259.23
	CD	200mg TDS	£15.15/9	£141.40
	UC	400mg BD		£161.60
	DD/IBS	400mg BD for 7 days each month		£47.13
	Pouchitis	200-1800mg daily for 3 months		£141.40-£424.20
	C difficile	400mg TDS for 20 days		£201.99
Metronidazole	Various	400mg BD- TDS for 10-14 days	£1.36/21	£1.94
Ciprofloxacin	Various	500mg BD for 10 days	£1.10/10	£2.20
Vancomycin	Various	125mg QDS for 10 days	£88.31/28	£126.16

CD = Crohn's disease, UC = Ulcerative Colitis, DD = Diverticular disease, IBS = Irritable Bowel Syndrome, C diff = Clostridium difficile infection

Rifaximin is included in the national PbR Tariff. Rifaximin is listed as category C in the PPA Drug Tariff.

Cost effectiveness (if available)

Not available at present.

Impact per 100,000 population/Affordability/Considerations

The current reported incidence rate per 100,000 of the UK population is 5.9 - 11.7 cases for Crohn's disease, and 240 for ulcerative colitis. Inpatient non elective hospital admissions for inflammatory bowel disease have an associated unit reference cost of between £289 and £1,531.[11,68,69]

Approximately 50% of the population have diverticula by the time they are 50 years of age, and nearly 70% of all people have diverticula by the time they are 80 years of age, with 9.8 cases/100,000 of perforated sigmoid diverticular.[11]

Irritable Bowel syndrome is estimated to affect at least one in five people (i.e. 20% of the population) at some point during their lifetime.[11,12]

It is unclear from current available data, how many patients with these conditions would be eligible and require treatment with rifaximin. As the incidence and prevalence of some of these conditions is quite large, the demand for rifaximin treatment could be high.

Decisions from other bodies

SMC: have assessed for the management of hepatic encephalopathy only.[70]

AWMSG: None.[71]

NICE has recommended rifaximin as a possible treatment option for hepatic encephalopathy only and have published an evidence summary only regarding its use in pouchitis.[13,23]

Comments sought from

Local gastroenterologists via PAC members.

Dr Sani Aliyu, Consultant in Microbiology and Infectious diseases. Cambridge University Teaching Hospitals. Addenbrookes.

Evidence strengths and limitations

There is currently very limited evidence to support the use of rifaximin over licensed treatments for the indications reviewed above.

Good quality RCTs are lacking. All the available trials are either small, short term uncontrolled and/or retrospective in design. There is no long term data and there is not enough data to determine the effect, if any, of long term rifaximin use on bacterial resistance rates. Rifaximin has not been shown to be superior to alternative antibiotics, including oral vancomycin, which is also poorly absorbed for the gastrointestinal tract.

There is currently no data regarding the impact of rifaximin treatment on hospitalisation rates and/or length of stay for patients with inflammatory bowel disease and diverticular disease.

Options considered by PAC

Option 1: Not recommended for routine commissioning.

Consider as an option for the treatment of pouchitis in ulcerative colitis patients where other treatments have failed and where failure to treat would result in surgical intervention.

Option 2: Recommended for Crohn's disease, Ulcerative Colitis (including pouchitis and Diverticular disease only). Not recommended for IBS and Clostridium difficile infection.

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

***Consult Summary of Prescribing Characteristics for full prescribing details.**

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Author: Vicky Gibson on behalf of PAC

Document history

PAC approval date	7th September 2015
Consultation process	PAC members and Consultant Gastroenterologists across the East of England
Version	v1.1 v1.1 Published July 2016. Correction to PbR tariff status
QA process	Katie Smith, Regional Medicines Information Director, East Anglia Medicines Information Service, 25th January 2015

References

1. Van Assche G, Axel Dignass A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis. Part 3 Special situations. Journal of Crohn's and Colitis 2013; 7: 1–33.
2. Biancone L, Michetti P et al on behalf of the ECCO. European evidence-based consensus on the management of ulcerative colitis: Special situations. Journal of Crohn's Colitis 2008; 1: 63-92.
3. Prantera C, Scribano ML. Crohn's disease: the case for bacteria. Italian Journal of Gastroenterology & Hepatology 1999; 31: 244–6.
4. Landers C, Cohavy O, Misra R, et al. Selected loss of tolerance evidenced by Crohn's disease-associated immune response to auto- and microbial antigens. Gastroenterology 2002; 123:

689–99.

5. Swidsinski A, Ladhoff A et al. Mucosal flora in inflammatory bowel disease. Gastroenterology 2002; 122: 44-54.
6. Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. Gut 2004; 53: 1-4.
7. Martin J, editor. British National Formulary. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain January 2015. Accessed 08/01/2015 via www.evidence.nhs.uk
8. Sweetman S, editor. Martindale: The Complete Drug Reference. Rifaximin. Date of revision of the text 15/04/2014. Accessed 02/01/2015 via www.medicinescomplete.com
9. Summary of Product Characteristics. Targaxan 550mg film coated tablets. Norgine Pharmaceuticals. Last updated 22/02/2013 Accessed 22/05/2015 via http://www.medicines.org.uk/emc/medicine/27427/SPC/TARGAXAN+550+mg+film-coated+tablets/
10. Summary of Product Characteristics. Xifaxanta 200mg film coated tablets. Norgine Limited. Last updated 09/09/2011. Accessed 22/05/2015 via http://www.medicines.org.uk/emc/medicine/24974/SPC/XIFAXANTA+200+mg+Film-coated+Tablets/
11. Patient UK website. Accessed 21/05/2015 via http://www.patient.co.uk
12. Irritable Bowel Syndrome. NHS Choices. Last updated 16/09/2015. Accessed 21/05/2015 http://www.nhs.uk/Conditions/Irritable-bowel-syndrome/Pages/Introduction.aspx
13. NICE TA337. Hepatic encephalopathy - rifaximin maintenance. March 2015. Accessed 22/05/2015 via https://www.nice.org.uk/guidance/ta337
14. Lee S, Wheat C et al. Assessment of the safety and efficacy of rifaximin for the treatment of moderate to severe Crohn's disease: a randomised, prospective crossover study in a single academic medical centre. American Journal of Gastroenterology 2013; 108: S559-S560.
15. Prantera C, Lochs H et al. Rifaximin extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology 2012; 142: 473-481.
16. Prantera C, Lochs H et al. Antibiotic treatment of Crohns' disease: results of a multicentre double blind randomised placebo controlled trial with rifaximin. Alimentary Pharmacology and Therapeutics 2006; 23: 1117-1125.
17. Shafran I, Burgunder P. Adjunctive antibiotic therapy with rifaximin may help reduce Crohn's diease activity. Digestives Diseases and Science 2010; 55: 1079-1084.
18. Shafran I, Johnson LK. An open label evaluation of rifaximin in the treatment of active Crohns' disease. Current Medical Research and Opinion 2005; 21: 1165-1169.
19. Guslandi M, Petrone MC, Testoni PA. Rifaximin for active ulcerative colitis. Inflammatory Bowel Disease 2006; 12: 335.
20. Gionchetti P, Rizzello F, Ferrieri A, et al. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. Digestive Diseases & Science 1999; 44: 1220-1221.
21. Guslandi M. Saccharomyces boulardii plus rifaximin in mesalamine-intolerant ulcerative colitis. Journal of Clinical Gastroenterology 2010; 44: 385.
22. Wall GC, Schirmer LL et al. Pharmacotherapy for acute pouchitis. Annals of Pharmacotherapy 2011; 45:1127-37.
23. NICE Evidence Summary: ESUOM30: Pouchitis: rifaximin. March 2014. Accessed 22/05/2015 via https://www.nice.org.uk/advice/esuom30

24. Holubar SD, Cima RR, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. Cochrane Database System Rev 2010 Jun 16;(6):CD001176. doi: 10.1002/14651858.CD001176.pub2

25. Diverticular disease and diverticulitis. NHS choices Last updated 29/09/2014. Accessed 22/05/2015 via http://www.nhs.uk/conditions/Diverticular-disease-and-diverticulitis/Pages/Introduction.aspx

26. Papi C, Ciaco A et al. Efficacy of rifaximin on symptoms of uncomplicated diverticular disease of the colon. A pilot multicentre open trial. Italian Journal of Gastroenterology 1992; 24: 452-456.

27. Papi C, Ciaco A et al. Efficacy of rifaximin in the treatment of symptomatic diverticular disease of the colon. A multicentre double blind placebo controlled trial. Alimentary Pharmacology and Therapeutics 1995; 9: 33-39.

28. Tursi A, Brandimarte G et al. Long term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. Digestive and Liver Disease 2002; 34: 510-515.

29. Latella G, Pimpo MT et al. Rifaximin improves symptoms of acquired uncomplicated diverticular disaease of the colon. International Journal of Colorectal Disease 2003; 18: 55-62.

30. Colecchia A, Vestito A et al. Efficacy of long term cyclic administration of the poorly absorbed abtibiotic Rifaximin in symptomatic uncomplicated colonic diverticular disease. World Journal of Gastroenterology 2007; 13: 264-269.

31. Maconi G, Barbara G et al. Treatment of diverticular disease of the colon and prevention of acute diverticulitis: A systematic review. Diseases of the Colon and Rectum 2011; 54 (10): 1326-1338.

32. Pimentel M, Lembo A et al. Rifaximin therapy of patients' with irritable bowel syndrome without constipation. The New England Journal of Medicine 2011; 364: 22-32.

33. Schoenfled P, Pimentel M et al. Safety and tolerability of rifaximin for the treatment of irritable bowel syndrome without constipation: a pooled analysis of randomised double blind placebo controlled trials. Alimentary Pharmacology and Therapeutics 2014; 39:1161-1168.

34. Nelson RL, Kelsey P et al. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev 2011 Sep 7; (9): CD004610. doi: 10.1002/14651858.CD004610.pub4.

35. Neff GW, Jones M, et al. Lack of Clostridium difficile infection in patients treated with rifaximin for hepatic encephalopathy: a retrospective analysis. Journal of Clinical Gastroenterology 2013; 47: 188-92.

36. Mattila E, Arkkila P et al. Rifaximin in the treatment of recurrent Clostridium difficile infection. Alimentary Pharmacology and Therapeutics 2013; 37: 122-128.

37. Garey KW, Ghantoji SS et al. A randomised, double blind, placebo controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. Journal of Antimicrobial Chemotherapy 2011; 66: 2850-2855.

38. Chang MS, Minaya MT et al. Double blind randomised controlled trial of rifaximin for persistent symptoms in patients with coeliac disease. Digestive Diseases and Science 2011; 56: 2939-2946.

39. Singh VV, Toskes PP. Small Bowel Bacterial Overgrowth: Presentation, Diagnosis, and Treatment. Curr Treat Options Gastroenterol 2004; 7: 19-28.

40. Cheema U, Jabeen S et al. Rifaximin therapy of small intestinal bacterial overgrowth associated arthritis. American Journal of Gastroenterology 2011; 106: S253.

41. Collins BS, Lin HC. Double blind, placebo controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. Journal of Paediatric Gastroenterology and Nutrition 2011; 382-386.

42. Boltin D, Perets TT et al. Rifaximin for small intestinal bacterial overgrowth in patients without irritable bowel syndrome. Annals of Clinical Microbiology and Antimicrobials 2014; 13: 49.

43. Lauritano EC, Gabrielli M et al. Antibiotic therapy in small intestinal bacterial overgrowth: rifaximin versus metronidazole. European Review of Medical and Pharmacological Sciences 2009; 13: 111-116.

44. Scarpellini E, Gabrielli M et al. High dosage rifaximin for the treatment of bacterial overgrowth. Alimentary Pharmacology and Therapeutics 2007; 25: 781-786.

45. Shah SC, Day LW et al. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. Alimentary Pharmacology and Therapeutics 2013; 38: 925-934.

46. Sewell JL, Day LW et al. Comparative effectiveness of antibiotic therapy for small intestinal bacterial overgrowth- A systematic review. Gastroenterology 2013; 144: S533.

47. Gatta L, Scarpignato C. Rifaximin for the treatment of small intestinal bacterial overgrowth (SIBO). A systematic review and meta-analysis. Gastroenterology 2013; 144: S729.

48. Zhang Q, Mohammadi AA et al. Su1945 Comparison of different antibiotic regimens for treatment of small intestinal bacterial overgrowth syndrome. Gastroenterology 2012; 142 (5): S542-3.

49. Lauritano EC, Gabrielli M et al. Small Intestinal Bacterial Overgrowth Recurrence After Antibiotic Therapy. American Journal of Gastroenterology 2008; 103: 2031-2035.

50. Collins BS, Lin HC. Double blind placebo controlled antibiotic treatment study of small intestinal bacterial overgrowth in children with chronic abdominal pain. Journal of Pediatric Gastroenterology and Nutrition 2011; 52: 382-386.

51. Scarpellini E, Giorgio V, Gabrielli M, et al. Rifaximin treatment for small intestinal bacterial overgrowth in children with irritable bowel syndrome. Eur Rev Med Pharmacol Sci 2013; 17: 1314-20.

52. Attar A, Flourié B, Rambaud JC, et al. Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhoea: a crossover, randomized trial. Gastroenterology 1999; 117: 794-7.

53. Tahan S, Melli LC, Mello CS, et al. Effectiveness of trimethoprim-sulfamethoxazole and metronidazole in the treatment of small intestinal bacterial overgrowth in children living in a slum. J Pediatr Gastroenterol Nutr 2013; 57: 316-318.

54. Majewski M, Reddymasu SC et al. Efficacy of rifaximin, a non-absorbed oral antibiotic in the treatment of small intestinal bacterial overgrowth. American Journal of the Medical Sciences 2007; 333 (5): 266-270.

55. Yang J, Lee HR, Low K, et al. Rifaximin versus other antibiotics in the primary treatment and retreatment of bacterial overgrowth in IBS. Dig Dis Sci 2008; 53:169-174.

56. Minero J. Re-treatment with rifaximin in patients with small bowel bacterial overgrowth-preliminary study. Journal of Gastroenterology and Hepatology 2013; 28 (Suppl 3): 35.

57. Pimentel M, Morales W, Chua K, et al. Effects of rifaximin treatment and retreatment in non-constipated IBS subjects. Digestive Diseases & Sciences 2011; 56: 2067-72.

58. Lo, Wai-Kit. Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: A meta-analysis. Gastroenterology 2013; 144: S53

59. Compare D, Pica L, Rocco A, et al. Effects of long-term PPI treatment on producing bowel symptoms and SIBO. Eur J Clin Invest 2011; 41: 380-6.

60. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clin Gastroenterol Hepatol 2010; 8: 504-8.

61. Law D, Pimentel M. Proton pump inhibitor therapy does not affect hydrogen production on

lactulose breath test in subjects with IBS. Dig Dis Sci 2010; 55: 2302-8.

62. Hutchinson S, Logan R. The effect of long-term omeprazole on the glucose-hydrogen breath test in elderly patients. Age Ageing 1997; 26:87-89.
63. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. Gut 1996; 39: 54-59.
64. Fried M, Siegrist H, Frei R, et al. Duodenal bacterial overgrowth during treatment in outpatients with omeprazole. Gut 1994; 35: 23-26.
65. Ratuapli SK, Ellington TG, O'Neill MT, et al. Proton pump inhibitor therapy use does not predispose to small intestinal bacterial overgrowth. Am J Gastroenterol 2012; 107: 730-5.
66. Medicines and Healthcare Products Regulatory Agency (MHRA). Public assessment report for rifaximin, decentralised procedure. UK/H/4662/001/DC. Accessed 08/01/2015 via http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con249660.pdf
67. Baxter K, editor. Stockley's Drug Interactions. Accessed 02/01/2015 via www.medicinescomplete.com
68. Reference costs 2013-2014. Department of Health. November 2014. Accessed 22/01/2015 via https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014
69. Economou M, Zambeli et al. Incidence and prevalence of Crohn's disease and its etiological influences. Annals of Gastroenterology 2009; 22: 158-167.
70. Scottish Medicines Consortium. SMC Advice regarding Targaxan (rifaximin), September 2013. Accessed 02/01/2015 via http://www.scottishmedicines.org.uk/SMC_Advice/Advice/893_13_rifaximin_Targaxan/rifaximin_Targaxan
71. All Wales Medicines Strategy group (AWMSG). Rifaximin Appraisal exclusion Reference No 1068. Published 12/11/2012, accessed 02/01/2015 via http://www.awmsg.org/awmsgonline/app/appraisalinfo/1058

Assessment against ethical and commissioning principles

Treatment assessed (May 2015)	Rifaximin (Targaxan®) for gastrointestinal disorders such as Crohn's disease, Ulcerative Colitis, Diverticular disease, Irritable bowel syndrome.
East of England Priorities Advisory Committee Recommendation	NOT RECOMMENDED
1. Clinical effectiveness	There is currently very limited evidence which has failed to show any significant benefit of rifaximin treatment over existing therapies for these indications. Good quality randomised controlled trials (RCTs) are lacking. All the available trials are either small, short term uncontrolled and/or retrospective in design. There is very little long term data and there is not enough data to determine the effect, if any, of long term rifaximin use on bacterial resistance rates particularly to rifamycin type antibitoics which are a mainstay in the treatment of Tuberculosis (TB).
2. Cost effectiveness	Not available
3. Equity	No issues identified.
4. Needs of the community	It is difficult to assess the overall impact on 100,000 population. The overall incidence of IBD ranges from 7.8 to 8.6 to cases per 100,000, therefore the cost burden to the local health community can be high. The numbers of patients who would require treatment with rifaximin is unknown. The impact of long term rifaximin treatment on bacterial resistance to rifamycin type antibiotics is unknown. See below for further discussion.
5. Need for healthcare (incorporates patient choice and exceptional need)	Patients with IBD and diverticular disease exacerbations are frequently admitted to hospital for acute treatment. From 2013-2014 reference costs, the average cost of a non-elective inpatient stay is £1531. However there is no data to confirm the overall effect, if any of rifaximin treatment for these patients on hospitalisation rates. It is unclear if rifaximin treatment, would affect bacterial resistance rates to rifamycin type antibiotics although this seems unlikely due to the poor systemic bioavailability of rifaximin but could affect gut flora, particularly Enterococci and Streptococci species. The overall safety impact of long term treatment to both the individual and wider community, particularly in areas with a high incidence of TB, from this theoretical risk, is not currently known.
6. Policy drivers	None.
7. Disinvestment	None identified. It is likely that this treatment (if approved) would be used in addition to current treatments.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

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