H.9 Primary prevention of spontaneous bacterial peritonitis (SBP) in people with cirrhosis and ascites

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
Study type	Systematic review
Number of studies (number of participants)	5 (n=404)
Countries and setting	Conducted in Argentina, France, Spain; setting: usually hospital
Line of therapy	First line
Duration of study	Other: from 6 months to 1 year treatment period (and up to 32 months follow-up)
Method of assessment of guideline condition	Systematic review: method of assessment mixed: all studies used a combination of clinical, laboratory, and ultrasonographic data or histology to confirm cirrhosis (method not described in Soriano 1991)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with ascites (diagnosed with any method) due to cirrhosis and without overt signs of bacterial infections in any setting, regardless of the aetiology of cirrhosis or severity of disease
Exclusion criteria	Not reported in systematic review. Fernandez 2007 – previous norfloxacin prophylaxis, quinolone allergy, HCC, organic renal failure (ultrasonography showing obstructure uropathy/parenchymal renal disease/haematuria and/or proteinuria), HIV infection; Grange 1998 – active GI bleeding, HCC, other life-threatening disease; Rolachon 1995 – quinolone allergy, recent GI bleeding, hepatic encephalopathy grade II-III, renal failure, HCC; Soriano 1991 – community-acquired infection, active GI bleeding at admission and those undergoing antibiotic therapy in the week before admission; Terg 2008 – active bleeding in previous 30 days, pregnancy, active GI bleeding, encephalopathy >grade 2, HCC, quinolone allergy, creatinine >3 mg/dl, bilirubin >3.2 mg/dl, platelet <98,000, bacterial infection
Recruitment/selection of patients	Fernandez 2007: September 2000 to June 2004, Grange 1998: February 1991 to February 1993 (consecutive), Rolachon 1995: November 1991 to August 1993, Terg 2008: March 2000 to December 2005 (no further details; no details for Soriano 1991).
Age, gender and ethnicity	Age –mean (SD): Fernandez 2007: 62(11) versus 61(12), Grange 1998: 55 (35–70) versus 55 (31–70), Rolachon 1995: 57 (9.6) versus 55 (9.4), Soriano 1991: 62 (11) versus 61 (11), Terg 2008: 56 (10) versus 58 (11). Gender (M:F): Fernandez 2007: 22/13 versus 23/10, Grange 1998: 36/17 versus 32/21, Rolachon 1995: 15/13 versus versus/15, Soriano 1991: 18/14 versus 20/11, Terg 2008: not reported. Ethnicity: not explicitly reported.
Further population details	1. Risk of SBP: systematic review: mixed (ascitic level in Fernandez 2007: <15 g/L or impaired renal function were inclusion criteria (mean 9[4] versus 9[3]), Grange 1998: <15 g/L (mean 10.4 versus 9.3 g/l), Rolachon 1995: <15 g/L, Soriano 1991: <15 g/L, Terg 2008: <1.5 g/dl (0.84 [0.31] versus 0.85 [0.36]). 2. Severity of the underlying liver disease: systematic review: mixed (Fernandez 2007: Child Pugh=/>9 only, Grange 1998: not specified [but most advanced with

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	history of complications], Rolachon 1995: A/B/C - 0/17/11 versus 1/18/13, Soriano 1991: A/B/C - 2/13/17 versus 1/14/16, Terg 2008: mean 8.5 [1.5] versus 8.3 [1.3]).
Extra comments	Inclusion criteria: Fernandez 2007 – protein <15 g/L, impaired renal function (serum creatinine level =/>1.2 mg/dl, BUN =/>25 mg/dl or serum Na+=/< 130 mEq/l) or severe liver failure (CP score =/>9 with serum bilirubin =/>3 mg/dl); Grange 1998 – low protein ascites (<15 g/l), negative ascitic cultures, <250 neutrophils/ul; Soriano 1991 – total ascitic protein <1.5 g/dl; Terg 2008 – low ascitic total protein concentration (1.5 g/dl)
Indirectness of population	No indirectness: Rolachon 1995 and Soriano 1991 had small proportions of patients with prior SBP (11% and 6% respectively).
Interventions	(n=38) Intervention 1: oral: quinolones – norfloxacin. 400 mg/day tablet (identical tablets prepared by Madaus S.A., Barcelona, Spain). Duration: 1 year. Concurrent medication/care: SBP was treated with ceftriaxone and received intravenous albumin to prevent HRS. Norfloxacin 400 mg/12 hours for 7 days was given to patients who developed upper GI haemorrhage to prevent bacterial infections (HRS was not treated with vasoconstrictors as there were very few data on this treatment at the time of protocol approval). Further details: 1. Antibiotic class: quinolones (norfloxacin). Comments: Fernandez 2007 (n=36) Intervention 2: placebo. One tablet (identical tablets prepared by Madaus S.A., Barcelona, Spain). Duration: 1 year. Concurrent medication/care: SBP was treated with ceftriaxone and received intravenous albumin to prevent HRS. Norfloxacin 400 mg/12 hours for 7 days was given to patients who developed upper GI haemorrhage to prevent bacterial infections (HRS was not treated with vasoconstrictors as there were very few data on this treatment at the time of protocol approval). Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Fernandez 2007 (n=53) Intervention 3: oral: quinolones – norfloxacin. 400 mg/day every 24 hours (Noroxine, Merck Sharp and Dohme, Paris, France). Treatment was discontinued if SBP occurred but continued if GI haemorrhage, HCC or hepatic encephalopathy occurred). Duration: 6 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: quinolones Comments: Grange 1998 (n=54) Intervention 4: placebo. Daily oral tablet (identical to active tablets; prepared by Merck Sharp and Dohme, Paris, France). Treatment was discontinued if SBP occurred but continued if GI haemorrhage, HCC or hepatic encephalopathy occurred). Duration: 6 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: not applicable/not stated/unclear

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	Comments: Grange 1998 (n=50) Intervention 5: oral: quinolones – ciprofloxacin. 500 mg/d (Ciriax, Laboratorios Roemmers, Buenos Aires, Argentina). Study medication withdrawn if SBP occurred and transitorily if patients had other complications like GI bleeding or encephalopathy (patients were withdrawn from the study if they were off study medications for more than 2 weeks). Duration: 12 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: quinolones Comments: Terg 2008 (n=50) Intervention 6: placebo. No details provided. Study medication withdrawn if SBP occurred and transitorily if patients had other complications like GI bleeding or encephalopathy (patients were withdrawn from the study if they were off study medications for more than 2 weeks). Duration: 12 months. Concurrent medication/care: no further details. Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Terg 2008 (n=28) Intervention 7: oral: quinolones – ciprofloxacin. 750 mg/week (Bayer Pharma, Germany). Duration: 6 months. Concurrent medication/care: 6 patients were also receiving diuretics and were transitorily free of ascites so the diuretics were withdrawn in these patients and recommenced when ascites recurred (none of these patients had SBP). Further details: 1. Antibiotic class: quinolones Comments: Rolachon 1995 (n=32) Intervention 8: placebo. Identical pills prepared by Bayer Pharma (Germany). Duration: 6 months. Concurrent medication/care: 9 patients were also receiving diuretics and were transitorily free of ascites so the diuretics were withdrawn in these patients and recommenced when ascites recurred (none of these patients had SBP). Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Rolachon 1995 (n=32) Intervention 9: oral: quinolones – norfloxacin. 400 mg/day started in the first 8 hours of hospitalisation and for the length of hospitalisation. Duration: mean 27 (SD 15) versus 24 (SD 13) days. Concurrent medication/care: 23 were treated with diuretics during hospitalisation. Further details: 1. Antibiotic class: quinolones Comments: Soriano 1991

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
	(n=31) Intervention 10: placebo. No details provided except that it was started within the first 8 hours of hospitalisation and provided for the length of hospitalisation. Duration: mean 27 (SD 15) versus 24 (SD 13) days. Concurrent medication/care: 22 were treated with diuretics during hospitalisation. Further details: 1. Antibiotic class: not applicable/not stated/unclear Comments: Soriano 1991
Funding	Funding for systematic review: not stated (Individual papers: Fernandez 2007 had grants from Fondo de Investigacion Sanitaria and Instituto de Salud Carlos III; Grange 1998 was supported from a grant from Merck Sharp and Dohme, Paris, France; Terg 2008 study was supported from a grant from the Consejo de Investigacion en Salud del Gobierno de la Ciudad de Buenos Aires; no details of funding for Rolachon 1995 or Soriano 1991).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400 MG/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Fernandez 2007[38]: occurrence of SBP at 12 months; group 1: 2/35, group 2: 10/33; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Fernandez 2007[38]: mortality (dichotomous) at 12 months; group 1: 10/35, group 2: 13/33; risk of bias: high; indirectness of outcome: serious indirectness
- Actual outcome for Fernandez 2007[38]: mortality (time-to-event) at 12 months; HR 0.44 (95%CI 0.19 to 1) calculated from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Fernandez 2007[38]: incidence of SBP caused by quinolone-resistant bacteria at 12 months; group 1: 0/2, group 2: 0/10; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: renal failure at end of study
- Actual outcome for Fernandez 2007[38]: renal failure at 12 months; group 1: 7/35, group 2: 16/33; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 5: liver failure at end of study
- Actual outcome for Fernandez 2007[38]: liver failure leading to death at 12 months; group 1: 4/35, group 2: 1/33; risk of bias: high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400 MG/DAY) versus PLACEBO

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Grange 1998[56]: occurrence of SBP at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) days for placebo; group 1: 0/53, group 2: 5/54; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Grange 1998[56]: mortality (dichotomous) at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) days for placebo; group 1: 8/53, group 2: 10/54; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Grange 1998[56]: incidence of resistant organisms not present at baseline at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) days for placebo; group 1: 10/24, group 2: 3/22; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: liver failure at end of study
- Actual outcome for Grange 1998[56]: liver failure leading to death at mean 128 (SD 71) days for norfloxacin versus 136 (SD 69) days for placebo; group 1: 4/53, group 2: 1/54; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN (500 MG/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Terg 2008[147]: occurrence of SBP at 12 months; group 1: 2/50, group 2: 7/50; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Terg 2008[147]: mortality (dichotomous) at 12 months; group 1: 6/50, group 2: 14/50; risk of bias: very high; indirectness of outcome: serious indirectness
- Actual outcome for Terg 2008[147]: mortality (time-to-event) at 12 months; HR 0.37 (95% CI 0.14 to 0.96) calculated –from logrank P-value; risk of bias: low; indirectness of outcome: no indirectness

Protocol outcome 3: renal failure at end of study
- Actual outcome for Terg 2008[147]: renal failure at 12 months; group 1: 7/50, group 2: 9/50; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: liver failure at end of study
- Actual outcome for Terg 2008[147]: liver failure leading to death at 12 months; group 1: 2/50, group 2: 2/50; risk of bias: high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN (750 MG/WEEK) versus PLACEBO

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Rolachon 1995[108]: occurrence of SBP at 6 months; group 1: 1/28, group 2: 7/32; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Rolachon 1995[108]: mortality (dichotomous) at 6 months; group 1: 4/28, group 2: 6/32; risk of bias: very high; indirectness of outcome: serious indirectness

Protocol outcome 3: incidence of resistant organisms at end of study
- Actual outcome for Rolachon 1995[108]: incidence of acquired resistance to ciprofloxacin or modifications of faecal flora gram-positive cocci at 6 months; group 1: 0/28, group 2: 0/32; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 4: liver failure at end of study
- Actual outcome for Rolachon 1995[108]: liver failure leading to death at 6 months; group 1: 2/28, group 2: 4/32; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 5: length of hospital stay at end of study
- Actual outcome for Rolachon 1995[108]: length of hospital stay; group 1: mean 9.3 length of hospital stay (SD 4.5); n=28, group 2: mean 17.6 length of hospital stay (SD 6.2); n=32; risk of bias: high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (400 MG/DAY) versus PLACEBO

Protocol outcome 1: occurrence of SBP at end of study
- Actual outcome for Soriano 1991[134]: occurrence of SBP at mean 27 (SD 15) versus 24 (SD 13) days; group 1: 0/32, group 2: 7/31; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: all-cause mortality
- Actual outcome for Soriano 1991[134]: mortality (dichotomous) at mean 27 (SD 15) versus 24 (SD 13) days; group 1: 2/32, group 2: 5/31; risk of bias: high; indirectness of outcome: serious indirectness

Protocol outcome 3: length of hospital stay at end of study
- Actual outcome for Soriano 1991[134]: length of hospital stay; group 1: mean 27 length of hospital stay (SD 15); n=32, group 2: mean 24 length of hospital stay (SD 13); n=31; risk of bias: high; indirectness of outcome: no indirectness

Study (subsidiary papers)	Cohen 2009[27] (Terg 2008,[147] Fernandez 2007,[38] Grange 1998,[56] Rolachon 1995,[108] Soriano 1991[134])
Protocol outcomes not reported by the study	Quality of life at end of study; readmission rate at end of study

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[146]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=95)
Countries and setting	Conducted in Mexico
Line of therapy	First line
Duration of study	Intervention + follow up: 4-week treatment + 6 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Included were patients aged from 19 to 79 years, who were able to give written informed consent and who had cirrhosis of the liver and ascites.
Exclusion criteria	Patients were excluded if cirrhosis was due to autoimmune disease, history of SBP, active gastrointestinal bleeding, total protein in ascitic fluid <1.5g/dL, use of antibiotics within the last 30 days, pregnancy, encephalopathy ≥grade 2, immune-related comorbidities, immunosuppressive therapy, hepatocarcinoma or other malignancies, allergy to fluoroquinolones, and bacterial infection at the time of enrolment.
Recruitment/selection of patients	Diagnosis of cirrhosis was supported by means of clinical (jaundice, ascites, hepatic encephalopathy, evidence of portal hypertension, variceal haemorrhage), laboratory (abnormal liver function test as decreased serum albumin, elevated serum bilirubin, elevated serum aminotransferases), ultrasound (hyperechoic hepatic parenchyma, heterogeneous liver, nodularity of the liver surface, and selective enlargement of the caudate lobe) and/or histologic data (diffuse involvement of the liver with progressive fibrosis with nodule formation and distortion of the hepatic architecture). Upon enrolment, physical examination and laboratory tests (liver and renal function tests, red and white cell counts, platelet count, and pro-thrombin time) were performed.
Age, gender and ethnicity	Age – mean (SD): intervention: 56.7 (13.2); placebo: 56.3 (11.7). Gender (M:F): not reported. Ethnicity: unknown (presumed Mexican)
Further population details	1. Risk of SBP: low risk total protein in ascitic fluid ≥1.5g/dL. 2. Severity of the underlying liver disease: Child-Pugh A 14/95, Child-Pugh B 62/95, Child-Pugh C 19/95.
Extra comments	The same (as baseline) assessment was repeated 4, 6, 12, 18, and 24 weeks afterwards, or whenever a primary end

Study	Primary prophylaxis with ciprofloxacin trial: Tellez-Avila 2013[146]
	point occurred. Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Patients taking the study medication for less than 2 weeks were considered as non-compliers and were withdrawn from the per-protocol analysis.
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Oral: Quinolones – Ciprofloxacin. Oral ciprofloxacin 500 mg/day (Ciproflox, Laboratorios Senosiain, S.A. de C.V., Mexico). Duration 4 week intervention + 6 month follow-up. Concurrent medication/care: Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Further details: 1. Antibiotic class: quinolones (n=46) Intervention 2: Placebo. 500 mg/day of an equally appearing placebo. Duration: 4 week intervention + 6 month follow-up. Concurrent medication/care: Enrolled patients continued with their regular baseline medications during the 6 month follow-up of the trial. Further details: 1. Antibiotic class: N/A
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN versus PLACEBO Protocol outcome 1: Occurrence of SBP at end of study - Actual outcome: Incidence of SBP at follow-up (6 months); Group 1: 2/49, Group 2: 0/46; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: all-cause mortality - Actual outcome: Mortality (time-to-event) at 6 months; HR 0.34 (95% CI 0.05 to 2.41) was estimated from the P value; total number of deaths during study period: ciprofloxacin 1/49; placebo 3/46. Risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; incidence of resistant organisms at end of study; renal failure at end of study; liver failure at end of study; length of hospital stay at end of study; readmission rate at end of study