H.7 Primary prevention of bacterial infections in cirrhosis and upper gastrointestinal bleeding

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
Study type	Systematic review
Number of studies (number of participants)	3 (n=532)
Countries and setting	Conducted in Spain; setting: usually hospital
Line of therapy	First line
Duration of study	Other: from 10 days to 3 weeks
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: review did not define
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients with cirrhosis and upper gastrointestinal bleeding, regardless of aetiology of cirrhosis or severity of the disease
Exclusion criteria	Not specified
Recruitment/selection of patients	Appears to be consecutive patients in 2 studies (not stated in others); Fernandez 2006: between February 2000 and April 2004; Sabat 1998: from June 1993 to 1995; Spanish Group 1998 – no further details from abstract.
Age, gender and ethnicity	Age – mean (SD): Fernandez 2006: 57(12) norfloxacin and 58(12) ceftriaxone; Sabat 1998: 65(10) norfloxacin and 61(13) norflocaxin+ceftriaxone; Spanish Group 1998 – no further details from abstract. Gender (M:F): Fernandez 2006: 85/26; Sabat 1998: 25/21; Spanish Group 1998 – no further details from abstract. Ethnicity: not reported in systematic review.

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
Further population details	1. Severity of the underlying liver disease: systematic review: mixed (Fernandez 2006: 52 CP-B, 59 CP-C; Sabat 1998: 4 CP-A, 31 CP-B, 11 CP-C; Spanish Group 1998 – not provided).
Extra comments	Aetiology of infection/treatment: Fernandez 2006: 77% portal hypertension/sclerotherapy or banding; Sabat 1998: no details/emergency sclerotherapy; Spanish Group 1998 – no further details.
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: IV: Third generation Cephalosporins (beta-lactams) – Ceftriaxone. 1 g/day for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Fernandez 2006 (n=63) Intervention 2: Oral: Quinolones – Norfloxacin. 400 mg twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Fernandez 2006 (n=42) Intervention 3: IV: Third generation Cephalosporins (beta-lactams) – Ceftriaxone. 2 g single dose after TIPS. Duration not specified. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Gulberg 1999 (n=40) Intervention 4: IV: Third generation Cephalosporins (beta-lactams) – Ceftriaxone. 1 g, single dose before TIPS. Duration not specified. Concurrent medication/care: not reported Further details: 1. Different modes of administration: IV administration Comments: Gulberg 1999 (n=21) Intervention 5: IV: Penicillin (beta-lactams) – Ampicillin/sulbactam. 1.5 g twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: IV administration Comments: Lata 2005 (n=25) Intervention 6: Oral: Quinolones – Norfloxacin. Oral or through nasogastric tube 400 mg twice daily for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: other (oral or through nasogastric tube).

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
	Comments: Lata 2005 (n=28) Intervention 7: Combinations – Ceftriaxone (IV) and norfloxacin (oral). 800 mg/day norfloxacin orally for 7 days including 2 g/day of IV ceftriaxone for the first 3 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: other (oral for full 7 days and IV for 3 of these days). Comments: Sabat 1998 (n=28) Intervention 8: Oral: Quinolones – Norfloxacin. 800 mg/day for 7 days. Duration 7 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Sabat 1998 (n=183) Intervention 9: Oral: Quinolones – Norfloxacin. 800 mg/day for 5 days. Duration 5 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Spanish Group 1998 (n=182) Intervention 10: Oral: Quinolones – Ofloxacin. 400 mg/day for 5 days. Duration 5 days. Concurrent medication/care: not reported. Further details: 1. Different modes of administration: oral Comments: Spanish Group 1998
Funding	Other (systematic review: Medica Sur Clinic & Foundation, Mexico; individual studies – Fernandez 2006: supported by grants from the Fondo de Investigacion Santaria and the Instituto de Salud Carlos III; not reported for Sabat 1998 or Spanish Group 1998.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE (1 G FOR 7 DAYS) (IV) versus NORFLOXACIN (400 MG TWICE DAILY FOR 7 DAYS) (ORAL) Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome for Fernandez 2006[39]: bacterial infection at 10 days; group 1: 6/54, group 2: 15/57; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: All-cause mortality	

Study (subsidiary papers)	Chavez-tapia 2010[23] (Chavez-tapia 2011[22], Fernandez 2006[39], Sabat 1998[114], Spanish group for the study of bacterial infections in cirrhosis 1998[135])
- Actual outcome for Fernandez 2006[39]: mortality at 10 days; group 1: 8/54, group 2: 6/57; risk of bias: very high; indirectness of outcome: serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE (2 G FOR 3 DAYS) (IV) AND NORFLOXACIN (800 MG FOR ALL 7 DAYS) (ORAL) versus NORFLOXACIN (800 MG FOR 7 DAYS) (ORAL) Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome for Sabat 1998[114]: bacterial infections at up to 3 weeks; group 1: 3/24, group 2: 4/22; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: All-cause mortality - Actual outcome for Sabat 1998[114]: mortality at up to 3 weeks; group 1: 1/24, group 2: 2/22; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 3: Length of hospital stay at end of study - Actual outcome for Sabat 1998[114]: length of hospital stay at up to 3 weeks; group 1: mean 12 days (SD 8); n=24, group 2: mean 12 days (SD 6); n=22; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORFLOXACIN (800 MG FOR 5 DAYS) (ORAL) versus OFLOXACIN (400 G FOR 5 DAYS) (ORAL) Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome for Spanish group for the study of bacterial infections in cirrhosis 1998[135]: bacterial infections at during the first 10 days of the bleeding episode; group 1: 26/183, group 2: 27/182; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life at end of study; renal failure at end of study; readmission rate at end of study, antibiotic complications at end of study

Study	Kim 2011[68]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in South Korea
Line of therapy	First line
Duration of study	Intervention time: 7 days

Study	Kim 2011[68]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: cirrhosis diagnosis based on clinical, laboratory and ultrasonographic data or histological assessment
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients between 18 and 80 years old, had active gastrointestinal haemorrhage (haematemesis [vomiting of blood] and/or melena [black or tarry faeces]) within 24 hours prior to inclusion, had decompensated liver cirrhosis as defined by the Child-Turcotte-Pugh score of 7 or greater.
Exclusion criteria	Allergy to cephalosporins or quinolones, presence of any of the following signs of infection (fever >37.5 degrees celsius, white blood count >15 000/mm^3, immature neutrophils >500/mm^3, polymorphonuclear cell count in ascitic fluid >250/mm^3, 15 or more leuckocytes/field in the fresh urine sediment, or data compatible with pneumonia on the chest X-ray), treatment of antibiotics within 2 weeks before haemorrhage, previously diagnosed advanced hepatocellular carcinoma (one nodule greater than 5 cm, 3 nodules with one greater than 3 cm, or more than 3 nodules), and HIV infection.
Recruitment/selection of patients	From 172 patients admitted to 3 Korean hospitals for the treatment of gastrointestinal haemorrhage between May 2007 and April 2009
Age, gender and ethnicity	Age – mean (SD): 53.9 (9.7). Gender (M:F): 93/20. Ethnicity: not explicitly reported.
Further population details	1. Severity of the underlying liver disease: Child-Pugh mixed categories (study inclusion of decompensated liver cirrhosis only and defined this as Child-Pugh 7 or greater; 77% had grade B and 23% grade C)
Extra comments	58.4% had cirrhosis due to alcoholism (but other causes included HBV and HCV and cryptogenic cirrhosis), mean Child-Turcotte-Pugh score: 8.6 (SD1.7), mean MELD score 14.8 (SD 5.7), 77% had ascites and 24% had hepatic encephalopathy, 6% had hepatocellular carcinoma. Authors state that there may be some resistance of certain bacteria to quinolones in Korea and that this may affect the performance of ciprofloxacin, making it appear worse than it may be in areas with less resistance.
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Oral: Quinolones – Ciprofloxacin. 500 mg every 12 hours for 7 days, initiated immediately after enrolment and within first 6 hours after admission to hospital. Duration 7 days. Concurrent medication/care: gastrointestinal haemorrhage treatment included emergency endoscopy & endoscopic treatment (variceal ligation and/or N-butyl-2-cyanoacrylate injection or haemoclipping and/or injection haemostasis with hypertonic saline-epinephrine) within 24 hours of bleed onset; terlipressin given if oesophageal or gastric varices bleeding or portal hypertensive gastropathy; proton pump inhibitors (PPI) if form peptic ulcer; blood transfusions to maintain haematocrit levels 25–30%.

Study	Kim 2011[68]
	Further details: 1. Different modes of administration: not applicable/not stated/unclear (no details given). (n=66) Intervention 2: IV: Third generation Cephalosporins (beta-lactams) – Ceftriaxone. 2 g per day for 7 days, initiated immediately after enrolment and within first 6 hours after admission to hospital. Duration 7 days. Concurrent medication/care: gastrointestinal haemorrhage treatment included emergency endoscopy & endoscopic treatment (variceal ligation and/or N-butyl-2-cyanoacrylate injection or haemoclipping and/or injection haemostasis with hypertonic saline-epinephrine) within 24 hours of bleed onset; terlipressin given if oesophageal or gastric varices bleeding or portal hypertensive gastropathy; PPI if from peptic ulcer; blood transfusions to maintain haematocrit levels 25–30%. Further details: 1. Different modes of administration: IV administration.
Funding	Academic or government funding (Korea Association of Study for Liver Disease)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CIPROFLOXACIN versus CEFTRIAXONE Protocol outcome 1: Occurrence of bacterial infections at end of study - Actual outcome: Occurrence of bacterial infections at 7 days; group 1: 13/57, group 2: 2/66; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	All-cause mortality; quality of life at end of study; renal failure at end of study; length of hospital stay at end of study; readmission rate at end of study; antibiotic complications at end of study