

Changes in nature and antibiotic resistance of bacteria causing peritonitis in cirrhotic patients over a 20 year period

Catherine Dupeyron, Bernard Campillo, Nicole Mangeney, Jean-Philippe Richardet, Georges Leluan

Abstract

Aim—To assess all clinically and bacteriologically documented episodes of spontaneous bacterial peritonitis diagnosed in a single unit over a 20 year period, to identify changes in the nature and antibiotic resistance of the causative bacteria.

Setting—A specialist liver disease unit in a tertiary care centre.

Material—Cultured ascitic fluid obtained in the course of 240 consecutive episodes of clinically and bacteriologically proven spontaneous bacterial peritonitis. Patient recruitment remained stable during the 20 year period in terms of the number of cirrhotic patients admitted and the severity of their condition.

Results—78.7% of isolates were *Enterobacteriaceae* (*Escherichia coli* in 51%) and 19% were Gram positive cocci. Until 1979 all the *Enterobacteriaceae* had the wild phenotype, compared with only 50% at the end of the study period. Since 1993, 22% of *Enterobacteriaceae* have been resistant to third generation cephalosporins. Methicillin resistant staphylococci were only isolated after 1989.

Conclusions—Changes in the epidemiology and antibiotic resistance of bacteria causing spontaneous bacterial peritonitis must be monitored for optimal treatment.

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Keywords: spontaneous bacterial peritonitis; antibiotic resistance

Spontaneous bacterial peritonitis of ascitic fluid is a very serious and frequent complication in cirrhotic patients. It occurs in 8-25% of cases and is the second most common cause of death in this setting. Its frequency is linked to the severity of cirrhosis.¹⁻³

For more than 20 years, we have been working on spontaneous bacterial peritonitis in collaboration with the liver disease unit in our institution; patient recruitment remained stable during this period in terms of both the number of cirrhotic patients admitted and the severity of their condition.²

Spontaneous bacterial peritonitis usually follows translocation and haematogenous dissemination of intestinal commensals. Although it is not a nosocomial infection, it often occurs in severely ill patients who have been admitted to hospital and treated with antibiotics. The aim of this study was to assess all clinically and bacteriologically documented episodes of

Table 1 Species distribution of 240 bacterial isolates from patients with spontaneous bacterial peritonitis over a 20 year period

Species	Number	Percentage
<i>Escherichia coli</i>	104	43.3
<i>Klebsiella pneumoniae</i>	24	10
<i>Enterobacter cloacae</i>	6	2.5
<i>Serratia marcescens</i>	11	4.6
<i>Citrobacter freundii</i>	2	0.8
<i>Morganella morganii</i>	2	0.8
<i>Providencia stuartii</i>	1	0.4
<i>Pseudomonas aeruginosa</i>	3	1.3
<i>Streptococcus pyogenes</i>	2	0.8
<i>Streptococcus agalactiae</i>	2	0.8
<i>Streptococcus pneumoniae</i>	8	3.3
Group D streptococci	18	7.6
<i>Streptococcus NT*</i>	6	2.6
<i>Enterococcus avium</i>	1	0.4
<i>Enterococcus faecalis</i>	16	6.7
<i>Enterococcus faecium</i>	1	0.4
<i>Aerococcus viridans</i>	1	0.4
<i>Staphylococcus aureus</i>	11	4.6
Coagulase (-) staphylococci	7	2.9
<i>Listeria monocytogenes</i>	2	0.8
<i>Bacteroides</i>	5	2.1
<i>Fusobacterium</i>	1	0.4
<i>Clostridium</i>	4	1.7
<i>Candida albicans</i>	1	0.4
<i>Candida glabrata</i>	1	0.4

*NT, non-typable.

spontaneous bacterial peritonitis diagnosed in our unit over the last 20 years, in order to identify changes in the nature and antibiotic resistance of the causative bacteria.

Methods

MATERIAL

In a total of 240 consecutive episodes occurring between 1 April 1977 and 1 April 1997 the ascitic fluid contained at least 250 polymorphonuclear cells per mm³, a bacterial pathogen was isolated, and antibiotic treatment was prescribed.

The study period was divided into five 4 year periods: period I (01/04/77 to 01/04/81), period II (01/04/81 to 01/04/85), period III (01/04/85 to 01/04/89), period IV (01/04/89 to 01/04/93), and period V (01/04/93 to 01/04/97).

TECHNIQUES

Cytological studies of ascitic fluid were based on conventional microscopy, with percentage counts of the different cell types. Microbiological diagnosis was based on aerobic and anaerobic blood cultures in nutrient broth; this method was adopted in our laboratory in 1977¹⁻² and has since been widely validated.⁴

Isolates were identified by means of conventional biochemical methods and *Enterobacteriaceae* by API 20 E system (bioMérieux SA,

Hôpital Albert Chenevier, Créteil, France:

Laboratoire de Bactériologie
C Dupeyron
N Mangeney
G Leluan

Service d'Hépatogastro-entérologie
B Campillo
J-P Richardet

Correspondence to:
Catherine Dupeyron,
Laboratoire de Bactériologie,
Hôpital Albert Chenevier, 40
rue de Mesly, 94000 Créteil,
France.

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Table 2 Bacterial isolates from ascitic fluid over two decades, in four year periods

Species	Period									
	I		II		III		IV		V	
	n	%	n	%	n	%	n	%	n	%
<i>E coli</i>	24	51	20	37	27	53	11	31.4	22	44.5
<i>K pneumoniae</i>	11	23	4	7.5	2	3.9	3	8.6	4	7.6
<i>E cloacae</i>	0	0	2	3.7	0	0	2	5.7	2	3.8
<i>S marcescens</i>	2	4.3	5	9.3	0	0	2	5.7	2	3.8
<i>C freundii</i>	0	0	0	0	1	2	0	0	1	1.9
<i>M morgani</i>	0	0	0	0	1	2	0	0	1	1.2
<i>P stuartii</i>	0	0	1	1.8	0	0	0	0	0	0
All Enterobacteriaceae	37	78.7	32	59.2	31	60.7	18	51.4	32	60.3
<i>P aeruginosa</i>	1	2.2	0	0	0	0	0	0	2	3.8
<i>Streptococcus pyogenes</i>	0	0	2	3.7	0	0	0	0	0	0
<i>Streptococcus agalactiae</i>	1	2.2	0	0	1	2	0	0	0	0
<i>Streptococcus pneumoniae</i>	3	6.5	1	1.8	3	5.8	1	2.9	0	0
Group D streptococci	2	4.3	4	7.5	6	11.6	3	8.6	3	5.7
<i>Streptococcus NT</i>	2	4.3	1	1.8	0	0	0	0	3	5.7
<i>Enterococcus avium</i>	0	0	0	0	0	0	0	0	1	1.9
<i>Enterococcus faecalis</i>	1	2.2	7	13	4	7.8	3	8.6	1	1.9
<i>Enterococcus faecium</i>	0	0	0	0	0	0	0	0	1	1.9
<i>Aerococcus viridans</i>	0	0	0	0	0	0	0	0	1	1.9
<i>Staphylococcus aureus MS</i>	0	0	3	5.6	1	2	0	0	1	1.9
<i>Staphylococcus aureus MR</i>	0	0	0	0	0	0	5	14.2	1	1.9
coagulase (-) staphylococcus, MS	0	0	1	1.8	0	0	1	2.8	1	1.9
coagulase (-) staphylococcus, MR	0	0	0	0	0	0	3	8.6	1	1.9
All Gram + cocci	9	19	19	35	15	29	16	46	14	26
<i>Listeria monocytogenes</i>	0	0	0	0	2	3.9	0	0	0	0
Bacteroides	0	0	2	3.7	1	2	0	0	2	3.8
Fusobacterium	0	0	0	0	1	2	0	0	0	0
Clostridium	0	0	1	1.8	1	2	0	0	2	3.8
<i>Candida albicans</i>	0	0	0	0	0	0	1	2.9	0	0
<i>Candida glabrata</i>	0	0	0	0	0	0	0	0	1	1.9
All isolates	47		54		51		35		53	

MR, methicillin resistant; MS, methicillin sensitive; n, number of isolates; NT, non-typable.

Period I, 01/04/77 to 01/04/81; period II, 01/04/81 to 01/04/85; period III, 01/04/85 to 01/04/89; period IV, 01/04/89 to 01/04/93; period V, 01/04/93 to 01/04/97.

Marcy l'Etoile, France) over the whole study. Antibiotic susceptibility was established by the disk diffusion method (Diagnostics Pasteur, Marnes la Coquette, France) as recommended by the French Comité de l'Antibiogramme. Antibiotics tested were ampicillin, gentamicin, tobramycin, amikacin, doxycycline, minocycline, nalidixic acid, and cotrimoxazole for Gram negative microorganisms, and penicillin, oxacillin, gentamicin, kanamycin, tobramycin, erythromycin, lincomycin, pristinamycin, nitrofurantoin, vancomycin, and fosfomycin for Gram positive organisms. From period II, third generation cephalosporins and fluoroquinolones were also tested.

Results

The number and species distribution of the isolated are given in tables 1 and 2. The number of isolates did not change over the five periods. Most infections were caused by *Enterobacteriaceae* and their percentage did not change significantly (χ^2 test, NS).

The main species was *Escherichia coli* throughout the study period. All strains of *E coli* had the wild phenotype until 1980, after which cases of resistance to ampicillin started to emerge. The percentage of wild strains then remained relatively stable—about 60%—during the ensuing periods. However, during period V we isolated two strains of *E coli* (9%) resistant to third generation cephalosporins and showing high level cephalosporinase production, and two other strains (9%) resistant to β lactamase inhibitors with the IRT phenotype. As regards the other *Enterobacteriaceae*, we iso-

lated one *Citrobacter freundii*, three *Enterobacter cloacae*, and one *Serratia marcescens* with the high level cephalosporinase phenotype, bringing to 22% the percentage of *Enterobacteriaceae* resistant to third generation cephalosporins during period V. One *Pseudomonas aeruginosa* isolate resistant to penicillin- β lactamase inhibitor combinations and to imipenem was also isolated during the same period.

While the percentage of Gram positive cocci did not vary significantly in the course of the study, qualitative changes did occur: thus no staphylococci were isolated during period I; methicillin sensitive *Staphylococcus aureus* strains were isolated during periods II, III, and V; methicillin resistant *Staphylococcus aureus* and methicillin resistant coagulase negative staphylococci were isolated in periods IV and V; and one *Enterococcus avium* and one *Enterococcus faecium* isolate resistant to amoxicillin were found during period V.

Discussion

The changes observed during this 20 year period reflect modifications of the hospital bacterial ecology under the pressure of antibiotic selection, with the release of new compounds. First treated with β lactam-aminoglycoside combinations, infections in cirrhotic patients were subsequently treated with third generation cephalosporins or penicillin- β lactamase inhibitor combinations, sometimes together with fluoroquinolones.⁵

Period IV in our study corresponds to the introduction of spontaneous bacterial peritonitis prophylaxis with norfloxacin in liver units.⁶⁻⁹

Since 1990 a large proportion (40%) of cirrhotic patients referred to our unit are already receiving this preventive treatment (norfloxacin 400 mg/d) on arrival, and we have continued it. This considerably reduces the number of intestinal *Enterobacteriaceae* and hence the frequency of Gram negative spontaneous bacterial peritonitis. During this period we have observed fewer Gram negative infections, as have others.⁶⁻⁹ At the same time the profile of the infections has changed, and severe infections caused by resistant Gram positive species have started to emerge (table 2). We showed that this type of prevention led to the emergence of multidrug resistant bacteria in the stools of approximately half our patients.¹⁰ Following this study, and after four fatal cases of spontaneous bacterial peritonitis caused by methicillin resistant staphylococci (two *Staphylococcus aureus*, two coagulase negative staphylococci) in patients treated with norfloxacin, we decided in April 1993 to limit norfloxacin prevention to selected cases.

Our observations confirm that bacterial isolates from spontaneous bacterial peritonitis have shown an increasing level of resistance to standard antibacterial agents over the last eight years. This phenomenon must be watched closely and taken into account in empirical antibiotic treatment, especially for patients with a history of infections. Treatment should

be adapted rapidly to bacteriological findings, and its duration should be limited to minimise the emergence of resistant strains.

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