RESEARCH NOTE

Differences in the proportions of fluoroquinolone-resistant Gram-negative bacteria isolated from bacteraemic children with cancer in two Italian centres

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ABSTRACT

The proportion of ciprofloxacin-resistant Gram-negative bacteria isolated from the blood of children with cancer (not receiving prophylaxis) was 10% in a paediatric hospital (Genoa) where the use of quinolones was highly restricted, compared with 41% in a department of haematology (Rome) where leukaemic adults, who received fluoroquinolone prophylaxis, were also treated ($p < 0.0001$). Moreover, simultaneous resistance to ciprofloxacin and ceftazidime, amikacin or imipenem–cilastatin was 11% in Genoa compared with 37% in Rome ($p < 0.001$). Ciprofloxacin resistance was more frequent in children who shared an environment with adults who were receiving ciprofloxacin prophylaxis.

Keywords Cancer patients, children, ciprofloxacin, fluoroquinolone resistance, prophylaxis, resistance

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Antibacterial prophylaxis with fluoroquinolones is a common practice in adults with cancer. The practice decreases the incidence of infections caused by Gram-negative bacteria, but does not have a significant impact on other clinical parameters such as use of empirical antibiotics and infection-related mortality [1,2]. However, prophylaxis has been associated with the emergence of resistant Gram-negative bacteria [3–6], which sometimes also show cross-resistance to β-lactams and aminoglycosides [7,8], following modification of the microbial flora colonising the patients [4–6].

The use of fluoroquinolones is generally contraindicated in children and adolescents aged <18 years, as these agents have been shown to cause cartilage damage in every juvenile animal model tested at doses similar to those required for therapeutic purposes [9]. Possible exceptions to this rule are infections caused by multiresistant Gram-negative bacteria, exacerbation of cystic fibrosis, and Gram-negative bacterial infections in immunocompromised hosts when prolonged oral therapy is desired [9]. However, in practice, fluoroquinolones have been used widely for therapy (targeted or empirical) or prophylaxis of bacterial infections in neutropenic children with cancer [10,11], despite the lack of documented efficacy for the latter population [1,2].

The present study evaluated retrospectively the proportion of ciprofloxacin-resistant Gram-negative bacteria isolated from blood cultures in two Italian paediatric cancer units with different environments during the period 1994–1999. The first centre was at G. Gaslini Children's Hospital (Genoa), where widespread use of fluoroquinolones was restricted, while the second was in the Department of Cellular Biotechnologies and Hematology, University 'La Sapienza' (Rome), where leukaemic children and adults are both treated and fluoroquinolone prophylaxis was given routinely to adults [12]. Anti-neoplastic treatment protocols in use at both centres during the study period were those adopted by the Italian Association of Pediatric Hematology and Oncology. In both units, paediatric patients were admitted to single rooms with procedures of reverse isolation, and did not receive antibacterial prophylaxis, and febrile neutropenia was treated initially with the combination of a third-generation cephalosporin and an aminoglycoside [13].

Susceptibility of bacterial isolates to ciprofloxacin was evaluated by means of the Kirby–Bauer

method, with results recorded as either susceptible or resistant [14]. Data on resistance to ceftazidime, amikacin and imipenem–cilastatin for Gram-negative bacteria, and to oxacillin for *Staphylococcus aureus* and coagulase-negative staphylococci, were also collected. In total, 434 bacterial isolates from blood cultures, comprising 260 Gram-negative isolates (54 *Pseudomonas aeruginosa*, 32 other Pseudomonadaceae, 62 *Escherichia coli*, 63 members of the *Klebsiella–Enterobacter–Serratia* group, 49 other Gram-negative bacilli) and 174 staphylococci (39 *S. aureus* and 135 coagulase-negative staphylococci), were evaluated. Since sensitivity to ciprofloxacin, amikacin, ceftazidime and imipenem–cilastatin was not always tested for all isolates, the number of isolates tested was slightly different for each antibiotic.

Overall, resistance to ciprofloxacin was 10% in Genoa and 41% in Rome ($p < 0.0001$; Chi-square test) (Table 1). Variations in the proportions of ciprofloxacin-resistant Gram-negative isolates were observed throughout the years of the study (Fig. 1). This phenomenon was evaluated by inserting the year of observation as a continuous variable in a logistic regression model [15]. A slight, but not significant, decreasing trend in the proportion of resistant isolates was present in both centres (p 0.310 in Genoa; p 0.343 in Rome; likelihood ratio test), but adjusting for time trend in a multivariate model did not influence the differences observed between the two centres during the period of the study. The differences in the overall proportions of Gram-negative bacteria resistant to the other antibiotics were significant for amikacin (p 0.005) and imipenem–cilastin (p 0.004), but not for ceftazidime (p 0.6) (Table 1). The proportions of isolates with resistance to ciprofloxacin and at least one of the other antibiotics (ceftazidime, amikacin or imipenem–cilastatin) were 10% (9/86) in Genoa and 37% (43/115) in Rome ($p < 0.001$; Chi-square test). Oxacillin resistance among staphylococci was 37% in Genoa and 52% in Rome (p 0.069; Chi-square test), but the proportions of oxacillin-resistant coagulase-negative staphylococci were very similar (49% in Genoa and 56% in Rome). The proportions of oxacillin-resistant isolates of *S. aureus* were 4% in Genoa and 27% in Rome (p 0.06; Chi-square test), although this apparent difference may have been caused by the low number of isolates (Table 1).

Table 1. Cumulative proportions of bacterial isolates resistant to different antibiotics from blood cultures in two Italian paediatric cancer centres

		Percentage of resistant strains (no. resistant/no. tested)		
Organism	**Antibacterial agent**	**Genoa**	**Rome**	**p value**
Gram-negative bacteria	Ciprofloxacin	10 (9/86)	45 (69/155)	< 0.0001
	Ceftazidime	25 (25/100)	29 (20/69)	0.6
	Amikacin	15 (16/105)	31 (46/149)	0.005
	Imipenem	7 (7/96)	24 (17/72)	0.004
CNS	Oxacillin	49 (36/73)	56 (35/62)	0.69
Staphylococcus aureus	Oxacillin	4 (1/28)	27 (3/11)	0.06

CNS, coagulase-negative staphylococci.

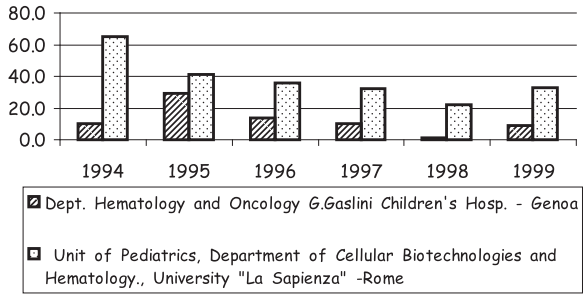

Fig. 1. Annual proportions of ciprofloxacin-resistant Gram-negative bacteria isolated from blood cultures in two Italian paediatric centres.

The risk of development of ciprofloxacin resistance in cancer centres using ciprofloxacin prophylaxis has been associated with changes in the microbial flora colonising the patients [4–6], and has sometimes been associated with cross-resistance to antimicrobial agents belonging to other classes [7,8]. The data in the present study confirm these observations, but also indicate an important role for the hospital environment. Although paediatric cancer patients in both centres did not receive ciprofloxacin prophylaxis, children treated in Rome had a higher proportion of bacteraemias caused by ciprofloxacin-resistant bacteria, often associated with resistance to amikacin and imipenem–cilastatin in Gram-negative bacteria, but not to oxacillin resistance in Gram-positive bacteria. Since supportive care for children was similar in both centres, it is likely that the differences in the Gram-negative resistance patterns are attributable to the local environment, and probably to the widespread use of quinolone prophylaxis in adults treated in Rome, although other local factors cannot be excluded completely.

In conclusion, the present study emphasises the crucial importance of a policy for the use

of antimicrobial agents in determining the epidemiology of severe infectious complications caused by antibiotic-resistant pathogens in cancer hospitals. There is an overall need for more judicious use of fluoroquinolones, as these agents may be important for empirical therapy (both oral and parenteral) of febrile neutropenia, especially in the presence of β-lactam allergy, or for the treatment of severe documented infections caused by multiresistant Gram-negative bacteria.

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RESEARCH NOTE

Elevated serum alanine aminotransferase (ALT) levels in patients with serologically verified *Mycoplasma pneumoniae* pneumonia

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ABSTRACT

The possibility of liver involvement in *Mycoplasma pneumoniae* pneumonia is still controversial. This study investigated 33 adult patients with serologically confirmed *M. pneumoniae* community-acquired pneumonia (CAP) (median age 31 years) and 38 patients with bacteraemic *Streptococcus pneumoniae* CAP (median age 54 years), all without pre-existing liver disease. Serum alanine aminotransferase (ALT) levels were elevated in 12 (36.4%) patients with *M. pneumoniae* CAP (median 53.5 U/L), and in four (10.5%) patients with *S. pneumoniae* CAP (median 61 U/L) (p 0.025). In most patients with *M. pneumoniae* CAP, the elevated ALT levels decreased during

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