

There have been various clinical trials in pediatric patients with CF comparing sequential ciprofloxacin therapy (intravenous followed by oral treatment) versus the standard antimicrobial combination of intravenous ceftazidime plus intravenous tobramycin [23,24]. The results of these studies suggest that the clinical response, based on clinical and pulmonary function test improvement, were similar in the two groups with one study showing a higher transient reduction in colonization with *P. aeruginosa* in the group of patients treated with ciprofloxacin versus patients treated with ceftazidime plus tobramycin (24% versus 63% respectively, $p=0$). In these trials, the percentage of drug related adverse events were similar with both regimens; additionally, close observation to cartilage toxicity in patients treated with ciprofloxacin did not show any data of toxicity and furthermore, autopsy studies from CF children that received multiple courses of ciprofloxacin failed to find quinolone related alterations in bone or joint cartilage as those seen in experimental animal models [25].

Ciprofloxacin has also been evaluated as a three month outpatient, maintenance therapy in CF children (age range 8 – 25 years) [26]. Although in this trial ciprofloxacin proved to be efficacious, safe and well tolerated, selection of ciprofloxacin resistance was observed in 23% (7/31) of *P. aeruginosa* isolates, suggesting the need to further evaluate the value of maintenance therapy versus the potential for selection of resistance.

FEBRILE NEUTROPENIA

The onset of fever in a neutropenic patient suggests a potentially serious infection and it has been estimated that approximately 50% of neutropenic patients who become febrile have an infection and that 85% of isolated microorganisms are bacterial pathogens originated, in the majority of cases, from the patient's own intestinal flora [27,28]. For more than 30 years, the management of febrile neutropenic patients was traditionally limited to urgent in-hospital treatment with combination therapy with two or more antibiotics (usually a beta-lactam plus an aminoglycoside) as well as monotherapy with extended spectrum agents (usually third generation cephalosporins, antipseudomonal penicillins or carbapenems) [29-31]. However, this practice was based on the notion that all febrile neutropenic patients have a predisposition to severe infection with high morbidity and mortality [32,33]. Over the past decade, it has become evident that neutropenic cancer patients are not a homogeneous group and that management may vary depending on their risk factor status [34,35]. Currently, febrile neutropenic patients are stratified into high-risk or low-risk groups and different treatment options have been proposed [36-38].

Low risk febrile neutropenia is defined by the National Cancer Institute criteria as those patients with less than 10-day duration of neutropenia, who are hemodynamically stable, without new pulmonary infiltrates, abdominal pain, nausea, vomiting or mental status changes [39,40]. This group of patients represents those children in whom outpatient antibiotics may be considered when they become febrile.

Initially, due to their broad antibacterial spectrum and favorable pharmacokinetic behavior, monotherapy with oral

quinolones had been considered an alternative for the treatment of febrile neutropenic patients regardless of their risk factors [41-43]. These studies with intravenous ciprofloxacin showed poor clinical response rates in patients with Gram-positive infections and an increased risk of breakthrough Gram-positive bacteremias, particularly secondary to alpha-hemolytic *Streptococcus* and coagulase negative *Staphylococcus* [44-46].

Later on, Rubenstein *et al.* randomly treated 83 episodes of low risk febrile neutropenia with combined therapy; oral ciprofloxacin plus clindamycin or intravenous aztreonam plus clindamycin [47]. Results from this trial demonstrated good clinical efficacy in both groups (88% versus 91% response rates, respectively) with no mortality.

More recently, a clinical trial in low risk febrile neutropenic children older than 2 years of age was completed [48]. The objective of this study was to compare the clinical success rates of intravenous ceftazidime (50 mg/kg/dose, every 8 hours) versus oral ciprofloxacin (12.5 mg/kg/dose, every 12 hours) used on an outpatient basis. The overall clinical success was 86% with no statistically significant differences among patients treated with oral ciprofloxacin (80%) or intravenous ceftazidime (94%) ($p=0.1$). Additionally, no significant differences were found in the duration of fever (average 2.7 days) or treatment duration (average 4.7 days) and modification of therapy was not required in most cases (77%).

Another study performed in patients 5 years to 74 years old, compared the efficacy of oral therapy with ciprofloxacin plus amoxicillin/clavulanate versus intravenous ceftazidime monotherapy for the treatment of low risk febrile neutropenic patients [49]. Even though the majority of subjects in this study were adults the results were encouraging. Clinical success without the need for modification of therapy was seen in 71% of the oral group versus 67% in the intravenous group. Duration of neutropenia was 3.4 days versus 3.8 days, respectively. The overall incidence of intolerance to oral antibiotics was 16% versus 1% in the intravenous group. In this study oral therapy with ciprofloxacin plus amoxicillin/clavulanate proved to be as effective as intravenous therapy.

Prophylaxis for bacteremia in immunosuppressed patients treated with fluoroquinolones has also been studied in several trials [50-52]. The results of these studies showed a tendency towards a marked decrease in infections caused by Gram-negative bacteria, however, Gram-positive bacterial super infections, particularly by *Streptococci viridians* and *Staphylococcus aureus* were a major concern. Because of these findings, fluoroquinolone prophylaxis is currently not routinely recommended in these patients.

The distinction of the different risk levels in febrile neutropenia has allowed the identification of a group of patients that may benefit from oral fluoroquinolone therapy. Oral therapy offers a number of advantages including total lower cost, improved quality of life and a decreased risk for nosocomial infections. Fluoroquinolones have shown efficacy and safety in the treatment of these patients when given as oral monotherapy in low risk patients or as part of combination therapy on high risk patients.

