

Original article

OUTPATIENT AND HOME PARENTERAL ANTIBIOTIC THERAPY (OHPAT) IN LOW-RISK FEBRILE NEUTROPENIA: CONSENSUS STATEMENT OF A BELGIAN PANEL

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Keywords: Outpatient intravenous antibiotics, febrile neutropenia, low-risk

ABSTRACT

Febrile neutropenia requires adequate antibiotic treatment. A subgroup of patients are only at low risk for complications and could be treated at home/as outpatients (OHPAT) after a short initial admission for work up. This position paper by a Belgian panel of experts presents criteria defining low-risk in febrile neutropenia, gives an overview of the existing experience and examines the present obstacles to a more widespread use of OHPAT in this country.

INTRODUCTION

A panel of Belgian experts, has examined the feasibility of OHPAT in febrile neutropenia in this country. An introductory document, reviewing the history of and summarizing the available clinical experience with ambulatory antibiotic administration in febrile neutropenia and other indications was prepared by an independent copy-writer. Panel participants reviewed this text and three meetings were subsequently held (April 19th 1999, October 18th 1999 and April 3rd 2000), during which the various aspects of the subject were extensively discussed. Audio tapes served as a basis for the minutes and additional literature references were gathered. Thereafter, a draft manuscript was prepared, and reviewed several times by all participants independently, under the guidance of one of the authors (Y.B.). The project was supported by Aventis Pharma. The present document summarizes the pro's and con's of this approach, and examines the various problems in the present situation, from an organizational, legal and financial point of view.

Over 30 years ago, Bodey (1) recognized that most neutropenic patients experience febrile episodes during anticancer chemotherapy, especially for those having prolonged and/or pronounced neutropenia (WBC count < 500/mm³). Clinical signs alone, however, do not always enable us to distinguish between life-threatening bacteremic episodes and other less severe infections, or even non-infectious conditions (2). Since mortality is increased when antibiotic treatment is delayed (3) - death rate reaching 80% in Gram-negative sepsis, for instance - it has become common practice to start broad spectrum antibiotics empirically at the onset of fever, mostly as an association of several parenteral compounds but

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also as broad-spectrum monotherapy.

In many western countries, budgetary restrictions impose severe cuts on health expenditures, and one is looking for safe but less expensive approaches to the treatment of many medical problems. Hospital admission as such represents a major burden to the financial envelope. Since twenty years, parenteral antibiotics have occasionally been administered on an outpatient basis. The very first reference to this method has been published in 1974 (4) in cystic fibrosis pediatric patients, whereas the first mention in adults dates back to 1978 (5). Nowadays, OHPAT represents 250,000 patients per year in the US (6).

OHPAT has been widely used to treat bacterial endocarditis (7). These patients mostly need a lengthy hospital stay and clearly benefit from this approach. Their often precarious clinical condition somehow limits the feasibility of this method and most series report the percentage of OHPAT in this disease to be around 5% (8). As far as glycopeptides are concerned, some experience has been gained with a thrice-a-week or even twice-a-week administration of teicoplanin on an outpatient basis (9). OHPAT offers many advantages in the case of bacterial osteomyelitis or arthritis. Most patients do not require hospitalization because of their general condition, and the prolonged stay is the result of the need for parenteral antibiotics only. A recently published document (10) gives an overview of this topic. Besides these two main indications, OHPAT has been used in the management of community-acquired lower respiratory infections and in cystic fibrosis (11), in the therapy of skin and soft tissue infections (12), in central nervous system infections (13) and in the HIV arena (14).

Oral antibiotherapy has been compared to intravenous antibiotherapy in neutropenic patients receiving anticancer chemotherapy (15,16), but some experience has been gained with OHPAT as well in febrile neutropenia. In 1994, a pilot study on 30 patients concluded that early discharge of low-risk patients on OHPAT is feasible, well received and cost-saving (17). In 1996 and again in 1999 (18,19), Rolston stated that OHPAT of low-risk patients resulted in a reduction of cost of therapy, better resource utilization and enhanced quality of life. In the pediatric setting, terminally ill patients with malignancies have been treated with OHPAT during febrile episodes (20).

Even though some clinical studies indicate successful outcome with OHPAT, they are either retrospective or of limited size when prospective. Although some studies use a reliable scoring system to assess the real

risk (17), this approach is unfortunately not widespread. Yet, it might otherwise allow treatment of a larger proportion of patients, when a subgroup with predictable low-risk becomes clearly defined.

ADVANTAGES AND DRAW-BACKS OF OHPAT

For the present time, most neutropenic patients with a febrile episode are treated in the hospital setting. This provides opportunities for close monitoring in a safe environment, easy access to intravenous treatment, and fast intervention in case of unforeseen complications. On the other hand, cost of treatment is high and the quality of life is largely impaired. OHPAT offers many advantages, as reported in the prospective studies by Malik. (21,22).

a) Advantages of OHPAT

Financial savings

Nowadays, cost-benefit analyses are a difficult endeavor as they should take into account direct cost savings (hospital stay, physician visits, drugs and supplies, childcare, housekeeping, transportation ...) as well as indirect benefits (lost wages, both for patient and family members) (23). In a cohort of 30 patients, attending the day ward of a large London hospital because of chemotherapy courses through central lines, savings up to 3,000 £ per individual have been found in patients switched to OHPAT in combination with an oral fluoroquinolone, as compared to intravenous hospital treatment with a β -lactam and aminoglycoside combination (24). In another study (25), 5.2% of patients or 11% of those receiving antibiotics in a 54 beds unit could benefit from OHPAT. The total cost of intravenous drugs in the classical in-hospital treatment was cheaper by 44 £ overall, as compared to the ambulatory treatment. But, and this more than compensates for the cost of drugs, 532 hospital days were saved during the study period. Williams (26) showed clear evidence for the cost effectiveness of OHPAT programs.

Decreased prevalence of nosocomial infections

Keeping patients out of hospital should reduce the prevalence of hospital-acquired infections. Indeed, it has been shown that nosocomial infections affect 5% of

hospitalized patients, and increase with every day of stay (27,28). They are a particular threat to granulocytopenic patients. However, this theoretical advantage has not been substantiated yet in patients with neutropenia of short duration.

Improved quality of life (QOL)

The psychosocial benefit of staying at home is difficult to quantitate. The ability to attend school for children and to resume work for employed adults has been described to be as high as 96% and 90%, respectively, in one study (29). In the pediatric setting, incentives for keeping children or even infants out of hospital are even stronger (parental occupations, psychological traumatism, school attendance ...). The Parker study (25) also identifies facts perceived as advantages or disadvantages for OHPAT by general practitioners and patients in the United Kingdom (Table 1). Not all of these may apply to the Belgian situation.

b) Adverse effects of OHPAT

In 1999, a group from Pennsylvania reviewed the medical records of 269 patients (291 courses of treatment) receiving home parenteral antimicrobial therapy (30), scrutinizing the adverse effects. HIV-patients were excluded from the analysis, and the reason for OHPAT

was osteomyelitis in 59% of cases. Taking the different characteristics of this population into account, one notes that the most common side effect of OHPAT was a depression of the WBC count (both leucopenia and neutropenia) and of the platelet count, mostly linked to long-term use of β -lactams. Further, nephrotoxicity (8%), diarrhea (7%) and rash (4%) were noted. Line complications occurred in 11% of central catheters and 9% of the peripheral lines. Overall, admission was needed in 8% of the patients. Obviously the risks for the patients also depended on the type of complications for which antibiotics were given and not only on line- or drug-related events. The authors concluded that complications are roughly the same as those expected with inpatients. We are not aware of any such study specifically addressing neutropenic patients.

PROGNOSTIC FACTORS OF INFECTION OUTCOME

For the above-mentioned reasons, one would like to be able to discharge patients early, after a short admission for work-up and for initiating antimicrobial treatment. One should clearly delineate a "low-risk" group of patients, with criteria easy to apply in daily medical practice.

Table 1: Advantages and disadvantages of OHPAT, as evaluated in the United Kingdom (adapted from (25))

	ADVANTAGES	DISADVANTAGES
TO GENERAL PRACTITIONER	<ul style="list-style-type: none"> • saves hospital admissions • maintains GP responsibility • makes home management possible • reduces hospital billing to GP • speeds up access to hospital 	<ul style="list-style-type: none"> • increased work-load • concern about safety at home • costs to GP budget • distance from hospital • some loss of responsibility
TO PATIENT	<ul style="list-style-type: none"> • own environment • no travel for relatives • quicker improvement • better contact with GP • less stress • happier relatives 	<ul style="list-style-type: none"> • distance from hospital • lack of nursing care • worries of relatives • ill patients should be in hospital • lack of compliance • anxiety • possibility of worse outcome • infection risk of the IV site

a) Features of the patient in general

Over the last few years, various sets of guidelines have been proposed on both sides of the Atlantic, to try to determine in advance which patients could be considered low-risk for complications (17, 31-37). The following criteria seem very important:

- depth of neutropenia: a nadir of neutrophils below 500/ μ L, and even more so below 100/ mm^3 , is associated with a much increased risk for severe pneumonia and sepsis
- duration of neutropenia: expected duration of 7 to 10 days is often used as cut-off point.
- low monocyte count: monocyte count < 100/ μ L
- hospitalization for other underlying medical problems
- uncontrolled cancer
- type of cancer: solid tumors have a more favorable course than acute leukemias
- type of treatment: maintenance therapy is more favorable than induction chemotherapy. Stem cell or bone marrow transplantation also carries a higher risk. However, Herrmann (38) recently showed that a group of 51 Hodgkin's and non-Hodgkin's lymphoma patients (including high dose chemotherapy and autologous peripheral stem cell transplantation) could effectively be managed at home, and compared well with a group of 88 patients receiving similar treatment in a hospital setting.
- serious comorbidity (heart failure, chronic obstructive pulmonary disease, diabetes, recent surgery) worsens the prognosis
- clinical signs: following signs carry a poor prognosis: hypotension, neurologic changes and alteration of consciousness, dyspnea, abdominal pain, dehydration, bleeding, heart failure or arrhythmias, hepatic or renal failure, extensive cellulitis

b) Characteristics of the infectious process

After wide clinical use of the first β -lactams, Gram-negative organisms became the first cause of sepsis in neutropenics during the sixties and the seventies. After the introduction of broad spectrum compounds and widespread quinolone prophylaxis, at the turn of the eighties, Gram-positive cocci became more and more important.

At the present time, Gram-positive micro-organisms cause some 60% of all bacteremias in the neutropenic (39). This might be due to the widespread use of tunneled central venous catheters, fluoroquinolone prophylaxis and to the mucositis accompanying intensive chemo-

therapy. This, together with the rise of some fungi (*Candida* spp. and *Aspergillus fumigatus*), has had an impact on the empiric choices.

A high number of febrile episodes remains without known cause, even after extensive work-up: 66% of fevers remain unexplained according to the American National Cancer Institute and the EORTC (2). Fever of unknown origin conveys a worse prognosis in non-neutropenic patients, but this does not seem to be true in febrile neutropenia. (31). However, unspecified infections will often require many changes in antibiotic treatment, in itself a risk factor. Amongst specific infections, uncomplicated urinary tract infections and catheter exit infections have a better prognosis than extensive pneumonia or than infection of the subcutaneous catheter tunnel. The virulence of the micro-organism determines the outcome. For instance, catheter-related bacteremia caused by coagulase-negative staphylococci has a better prognosis than Gram-negative sepsis.

DEFINITION OF LOW-RISK NEUTROPENIA

In Talcott's paper (32), the risk groups were defined as follows:

- group 1: inpatients at the time of fever appearance
- group 2: outpatients with concurrent comorbidity
- group 3: same as 2 but uncontrolled cancer
- group 4: neutropenic outpatients with fever but without risk factors. The latter was considered "low-risk".

Taking into account the experience detailed above, particularly that of the EORTC and of Talcott, the Multinational Association for Supportive Care in Cancer developed an internationally validated scoring system (36). We summarize here the factors contributing to the risk index in that document:

- absence of symptoms or mild symptoms (5 points) or moderate symptoms (3 points)
- absence of hypotension (5 points)
- absence of chronic pulmonary obstructive disease (4 points)
- solid tumor or absence of previous fungal infection in hematologic patients (4 points)
- absence of dehydration (3 points)
- outpatient status (3 points)
- age younger than 60 years (2 points)

A risk-index score ≥ 21 identified low-risk patients with a specificity of 91%.

On the other hand, many factors may also prevent discharge:

- allergy to the drugs contemplated for OHPAT
- microbial resistance to contemplated antibiotics
- need for hospitalization for concomitant medical conditions: renal failure, hepatic failure, shock, respiratory failure, bleeding, cardiac failure or arrhythmias, extensive mucositis or cellulitis ...
- need for other IV lines (rehydration, other drugs ...)
- inability to ensure proper hydration and/or to take oral medications
- inadequate reliability and psychosocial environment
- central nervous system infections
- allogeneic stem cell transplantation
- induction chemotherapy

PRACTICAL CONSIDERATIONS

a) Short admission to hospital for work-up

Most authors will agree that a short admission (48 hours) is necessary for work-up in neutropenic patients with unexplained fever. It will also enable the physicians to obtain the results of at least some laboratory tests (e.g. blood cultures, expectorations, urine culture) and to initiate antibiotic treatment adequately. During that period, it will be critical to determine the risk category of the patient and to document the origin of infection. Every effort will be made to localize the origin of the fever, all necessary samples will be sent to the microbiology laboratory and antibiotic treatment will be started, largely on an empiric basis. A review from the Infectious Diseases Society of America (35) describes the available options: [1] combination therapy with an aminoglycoside plus either an antipseudomonal penicillin, a 3rd or 4th generation cephalosporin, or a carbapenem; [2] if the use of vancomycin is justified, choose a combination of vancomycin and either an antipseudomonal penicillin, cefepime, ceftazidime or a carbapenem, with or without an aminoglycoside. The attitude will be reassessed if fever persists after 36-72 hours. After that initial work-up phase, low risk patients will possibly be discharged. Some low risk patients may be eligible for oral antibiotics, but this is beyond the scope of this paper.

b) Antibiotics and supportive care

Broad-spectrum antibiotics suitable for once-a-day intravenous administration belong to three categories:

- aminoglycosides (all the molecules available in Belgium)
- cephalosporins (ceftriaxone in particular)
- glycopeptides (teicoplanin in particular).

As an alternative, molecules with a shorter half-life can be chosen, making use of slow infusion devices. Detailed reviews on the pharmacokinetics of antimicrobial drugs and on infusion devices available for outpatient use have been published (40,41). Most of the times, ceftriaxone will be the treatment of choice. For documented or probable infections with Gram positive cocci, teicoplanin will be the treatment of choice. Duration of treatment will be guided by clinical judgment and recovery from neutropenia, and will usually range from 5 to 8 days.

According to ASCO recommendations (42), there is strong evidence that colony-stimulating factors (CSF) cannot be recommended as routine adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows : fever < 10 days in duration ; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction or invasive fungal infections ; and no uncontrolled malignancies. All trials have consistently shown a decrease in the duration of neutropenia < 500/ μ l, but clinical benefit has not consistently accompanied the decreased duration of neutropenia.

c) Potential alternatives for the IV administration

In any case, the patients and their family will be given a list of useful telephone numbers, and the address of the emergency ward of the hospital in charge, in case of unforeseen complications. These facilities should be accessible 24 hours a day. A new admission will be contemplated in case of reappearance of fever. However, this eventuality seems rather infrequent. Two alternatives are possible for antibiotic administration. General organizational aspects of these alternatives in neutropenic and non-neutropenic patients have been reviewed (43).

On a day clinic basis

Where no financial intervention from Social Security is available, patients attend the day clinic, on a daily or thrice-a-week basis (9). The nursing team administers the parenteral injection and the physician takes advantage of the patient's presence to check the vital signs and the clinical evolution. In our country, some teams

occasionally treat individual adult patients with OHPAT (personal communication, Dr. D. Vogelaers, Infectious Disease specialist, University Hospital Ghent and Dr. D. Selleslag, oncologist, AZ St Jan, Brugge). To illustrate this point, we mention the following case report (courtesy of Dr. Selleslag).

A 60-year-old AML patient in remission was on outpatient maintenance therapy with monthly cycles of low dose cytarabine. He developed fever of 39°C when the neutrophil count was 300/μl. There was no sign of infection on clinical examination and blood pressure was normal. Chest X-ray was normal. He was admitted for work-up and was started on empiric antibiotic treatment (ceftazidim and amikacin). After 48 hours, all blood cultures became positive for *Staphylococcus epidermidis*, susceptible to glycopeptides only. The bacteremia presumably originated from a double lumen Hickman line, although no sign of exit site or tunnel infection was present. The Hickman line was kept in place because of peripheral venous access problems. Treatment was switched to teicoplanin 800 mg IV/day, making use of another lumen of the catheter every day. The patient became afebrile 72 hours after admission. As he fulfilled the criteria for low-risk neutropenia, he completed treatment for another 7 days at the day clinics. More than 2 months after the last chemotherapy, the Hickman line is still in place, without recurrence of bacteremia. This case report illustrates the feasibility of outpatient treatment with once-a-day antibiotics for coagulase negative *Staphylococcus* catheter-related bacteremia in patients with low risk neutropenia.

As home treatment

Practice guidelines for community-based parenteral antibiotherapy have been published (44). In the Netherlands, some teams have accumulated experience with home parenteral antibiotics (45-47). The hospital pharmacy delivers all the needed material (drugs, IV lines, syringes, dressings ...), a financial agreement is reached with Social Security or, alternatively, sponsoring is organized with private funding. In some instances, nurses have been especially trained to educate the patients and perform the first administration at home. In order to be able to achieve home parenteral antibiotics, some practical problems need to be tackled:

- budgetary issues: parenteral antibiotics often cannot claim reimbursement on an out-of-hospital basis, medical advice from the oncologist in charge is often not paid for, community pharmacies are not always

able to charge for the necessities.

- organizational issues: the relay between hospital and home care is less than perfect, as far as exchange of medical information is concerned (link between general practitioner and hospital oncologist), but also concerning nursing needs (private home nursing systems or free-lance nursing personnel). Moreover, some drugs or technical devices may not be available for out-of-hospital use.
- qualification issues: the private nurses are not always acquainted with the type of care needed and the general practitioners may be reluctant to take full responsibility for cancer patients, especially acute leukemias. At this point, one must emphasize the importance of trained nurses, able to interact with the hospital and the community health care providers (city nurses, general practitioners, family ...).

EXPERIENCE IN GHENT: THE “KOESTER PROJECT”

The Koester project (for “Kinder Oncologische Eenheid voor Specifieke Thuiszorg En Rehabilitatie”) started in 1990 at the Akademisch Ziekenhuis Ghent under the guidance of Prof. Y Benoit (Pediatric onco-hematologic department) and Dr. G Laureys (Department of Pediatrics). After initial work-up during a short hospital stay for providing precise diagnosis, taking all necessary samples and initiating treatment, most febrile neutropenic patients come into consideration for further home treatment. Of these, a selected (see table 2 for criteria) subgroup is discharged on parenteral antibiotics – either a once-a-day third generation cephalosporin and an aminoglycoside in case of susceptible Gram-negative infection, or a once-a-day glycopeptide for Gram-positive infections, mostly due to methicillin-resistant staphylococci.

The team consists of permanent collaborators available in the hospital and, for home interventions, of pediatricians, oncologists, psychotherapists and 3 specially trained nurses who interact with the home care (physician, community nurses, patient's close relatives). They are reachable 24 hours a day and make very precise instructions available, together with a list of useful telephone numbers (pediatrician in charge, emergency ward of the teaching hospital, general practitioners on call ...). The medicines, as well as all the necessary accessories, such as perfusion kits, needles, dressings are dispatched through the hospital pharmacy. Financial support is provided in part by the association

Table 2 : Selection criteria for home treatment in children (Koester project)

- age older than 1 year
- solid tumor or acute lymphoblastic leukemia in first remission
- availability of an indwelling central catheter (Hickmann)
- afebrile period of at least 24 hours prior to discharge
- favorable clinical evolution and improvement of the inflammatory tests
- adequate psycho-social environment

“Kinderkankerfonds, vzw”. A prospective study is still ongoing concerning various aspects of this project.

CONCLUSION

Febrile neutropenia has undergone profound changes over the last decade. A subgroup of low-risk patients can be delineated that is amenable to out-of-hospital treatment. OHPAT is widely used in other severe infectious conditions (such as endocarditis, osteomyelitis, HIV infection ...) and is already common practice in the pediatric setting of febrile neutropenia in our country. A few limiting factors, mostly of financial and organizing nature, prevent the spread of home parenteral antibiotherapy to adult cancer patients at large. However, OHPAT can widely be provided in the outpatient clinics.

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