Is there a rationale for the use of antimicrobial prophylaxis in neutropenic patients?

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Abstract. Antimicrobial prophylaxis in neutropenic patients has been practised in one form or another for several decades but the goal is no longer clear. From being initially solely an attempt at decontamination, drugs such as co-trimoxazole and later the fluoroquinolones were preferred to non-absorbable regimens because they achieve reliable protection against bacteraemia due to Gram-negative bacilli. Nevertheless, fever still invariably occurs during neutropenia leading to the initiation of traditional empirical therapy. Not only is this approach illogical but it also ignores the flexibility afforded the oral and parenteral formulations of the fluoroquinolones. Instead, it might be as effective and less costly if these agents were given orally until the end of neutropenia unless there was evidence of malabsorption or poor oral intake, in which case treatment would be continued parenterally. Should patients develop fever, an attempt would be made to complement treatment with another anti-microbial agent for microbiologically or clinically defined infection. This would be carried out at diagnosis, before any changes in the prophylactic regimen could be made. Otherwise, treatment with the prophylactic regimen would continue without modification. There is a less compelling need for prophylaxis against candidosis, herpes simplex and cytomegalovirus disease as these would be better managed pre-emptively when there is evidence of yeast carriage or re-activation of viral infection. Similarly, prophylaxis of aspergillosis is a forlorn hope and again a pre-emptive approach might serve us better once there is a screening test available and a safe and effective drug.

Keywords: prophylaxis, neutropenia, quinolone, drug availability, alternative approach.

Introduction

Since the mid-1970s, antimicrobial agents have been given to patients undergoing treatment for haematological malignancy to reduce infectious complications arising during neutropenia [1]. The rationale underpinning the approach was primarily to suppress the resident Gram-negative bacilli such as Escherichia coli and to prevent the acquisition of others such as Klebsiella pneumoniae and Pseudomonas aeruginosa in order to reduce the risk of infection and fulminant sepsis which was a major cause of death. At the time, fungi were not perceived as great a threat as now and viral infections were largely untreatable as there were no antiviral agents available. In the intervening period, the opportunity for considering prophylaxis against mycosis and viral infection presented itself as new agents became available for treating herpes simplex virus (HSV) and cytomegalovirus (CMV) infection, candidosis and also aspergillosis. However, the question of how best to employ these agents remains a thorny issue as the answer depends very largely upon whether a given infection is perceived or known to lead to unacceptably high morbidity or mortality which is considered avoidable.

Neutropenic patients do not form a homogenous group of patients and so are not at equal risk of infection nor is the infection-related morbidity and mortality always the same. A broad consensus has been reached in terms of prophylactic practices for bone-marrow transplant recipients because the principal infection risks are fairly predictable and mostly preventable. By contrast, there is no uniform approach to either the use or the nature of prophylaxis in patients who become neutropenic following remission induction and consolidation courses of chemotherapy. Therefore, an appraisal of the rationale for antimicrobial prophylaxis can only be pursued by considering the prevention of bacterial, viral and fungal infections separately.
Antibacterial prophylaxis

The aim of prophylaxis of bacterial infections was initially simply to suppress the Gram-negative bacilli such as *Escherichia coli*, *Klebsiella pneumoniae* (formerly *Klebsiella aerogenes*) and *Pseudomonas aerogenes* (also known as *Pseudomonas pyocyanea*), at source, namely, the gastrointestinal tract as it had been observed that colonization invariably preceded infection. At first, non-absorbable regimens such as gentamicin plus vancomycin plus nystatin were given in a futile attempt to sterilize the gut. Interest soon shifted to partial or selective decontamination (SDD) with framycetin (or neomycin) plus colistin (or polymyxin B) plus a polyene antifungal agent, as it had been shown in mice that preservation of the anaerobic flora was necessary to sustain colonization resistance [2]. Antifungal agents were included to prevent overgrowth of yeasts rather than candidosis. The graduation to co-trimoxazole occurred soon afterwards when it was also shown to lower the incidence of infections caused by Gram-negative bacilli while at the same time affording protection against infection from *Pneumocystis carinii*. As co-trimoxazole was given at therapeutic doses leading to both systemic and gut decontamination its use was a significant departure from the original concept that motivated prophylaxis. Meanwhile, partial antibiotic decontamination continued to have its advocates who used a regimen of nalidixic acid in addition to the non-absorbable polymyxins, aminoglycosides and a polyene or miconazole [3].

Although no single placebo-controlled trial of any regimen, whether absorbable or not, was sufficiently large to provide a conclusive answer, almost every such study showed a clear trend towards reducing infection caused by Gram-negative bacilli [4]. Several studies then followed which helped co-trimoxazole become the standard agent for many centres particularly when its lack of activity against *Staphylococcus epidermidis* could be largely compensated for by using colistin [5].

Co-trimoxazole or a fluoroquinolone?

The introduction of the fluoroquinolones in the early 1980s further expanded the range of agents with norfloxacin, ciprofloxacin, ofloxacin and pefloxacin all shown to be effective in reducing bacteraemia due to Gram-negative rods [6]. However, in common with all their predecessors, their use has little influence on fever-related and infection-related mortality. Nor do these agents possess any useful activity in vitro against Gram-positive cocci particularly the coagulase-negative staphylococci [7–9] and the viridans streptococci [10] which have become the two most common causes of bacteraemia in neutropenic patients [11]. The fluoroquinolones appear better tolerated, are much less likely to induce skin rash than co-trimoxazole and are preferred for patients receiving cytarabine which can itself cause a cutaneous drug reaction.

Problems with antibacterial prophylaxis

Despite the variety of studies undertaken, antibacterial prophylaxis has had no measurable impact on overall survival, mortality attributable to infections caused by Gram-negative bacilli, or on remission rates [1,12]. Moreover, the fall in mortality due to Gram-negative sepsis probably owes more to the prompt institution of empirical broad spectrum therapy as soon as neutropenic patients become febrile and more effective treatment of the underlying disease. Indeed, the mortality attributed to Gram-negative sepsis remains around 10–15% whether or not prophylaxis has been employed. However, only approximately 10% of patients develop this type of infection making the global mortality approximately 1–2% [13,14]. Finally, prophylaxis can actually diminish the quality of life because of side-effects and the effort often needed to comply.

Coagulase-negative staphylococci

Bacteraemia due to these bacteria is clearly related to the widespread use of intravascular catheters which become colonized, although the oral cavity and gastrointestinal tract might also be reservoirs [15]. Typically, these staphylococci are multiply resistant to sulphonamide, trimethoprim, methicillin, gentamicin and erythromycin as well as to the fluoroquinolones if one has been used for prophylaxis. A potential explanation for this has been recently suggested by the demonstration that ciprofloxacin is excreted in sweat at concentrations that correspond with those found in plasma and that *Staphylococcus epidermidis*, with the typical pattern of multiple resistance, can be detected in the axillary flora within 2 days of starting 750 mg bd. Similar strains were also found at a later stage in the nose and both these and their axillary
counterparts persisted for 3-4 weeks after stopping the drug. A similar mechanism may well apply to co-trimoxazole so it must be concluded that selection of these resistant staphylococci is an immediate and inevitable consequence of using these drugs for prophylaxis. Moreover, their evolution will increase the likelihood of their appearing sooner or later in the blood stream via either an intravascular catheter or through the oral and nasal and possibly gut lesions that result from severe mucositis.

**Oral viridans streptococci**

Bacteraemia caused by the oral viridans streptococci has also increased in frequency and was first noted after prophylaxis co-trimoxazole [16-19]. The fluoroquinolones also appear to predispose certain patients to streptococcal bacteraemia by giving the bacteria a selective advantage [20]. Exposure to ciprofloxacin is more likely to predispose to bacteraemia caused by these streptococci than is found for co-trimoxazole when low doses of cytarabine are used [21]. By contrast, the nature of cytostatic chemotherapy appears a more important risk factor than does antimicrobial prophylaxis when high doses of cytarabine are used for chemotherapy. This is almost certainly due to the degree and severity of mucositis induced by chemotherapy as *Streptococcus oralis* and *Streptococcus mitis* are the two most common isolates from blood cultures and both are normal microbial residents of the oral cavity. They also exhibit median MICs of 2-4 mg/L ciprofloxacin [22] which straddles the peak serum levels of the drug following a 500 mg oral dose in neutropenic patients [23].

**Selection of other natively resistant bacteria**

The application of selective pressure on natively resistant bacteria is one of the inevitable consequences of employing any antimicrobial agent for prophylaxis for decontaminating body sites and providing adequate systemic concentrations. Thus, apart from oral 'viridans' streptococci and coagulase-negative staphylococci, *Stomatococcus mucilaginosus, Bacillus* spp, lactobacilli, and enterococci are easily selected by exposure to fluoroquinolones because of their marginal susceptibility. The same is true for Gram-negative bacteria such as *Stenotrophomonas (Xanthomonas) maltophilia*. Prophylaxis therefore alters the epidemiology of infection, sometimes in an unpredictable way but more often in directions that can be anticipated by knowledge of the dominant flora of the neutropenic population. It is therefore unwise for any particular centre to adopt antimicrobial prophylaxis without first understanding its own infectious epidemiology and attempting to forecast the likely benefits and disadvantages of employing any particular regimen.

**Selection of resistant Gram-negative bacilli**

Almost as soon as co-trimoxazole was adopted for prophylaxis, there were reports of emergent resistance [24]. Bacteraemia due to fluoroquinolone resistant *Escherichia coli* has also occurred in neutropenic patients following treatment with ofloxacin [25], pefloxacin [26], and norfloxacin [27] and it is probably only a matter of time before similar cases are reported following ciprofloxacin. This is a matter of concern and should encourage regular surveillance of the oral cavity and bowel as the resistant bacteria can be detected in the faeces before the onset of fever [28].

**Impact of cytoreductive chemotherapy on drug availability**

The protection afforded by fluoroquinolones and, to a lesser extent, co-trimoxazole is not confined to decontamination but is also provided systemically as these drugs are given at therapeutic doses most of which is absorbed and therefore available to the tissues. However, the pharmacokinetics of ciprofloxacin have been shown to alter following treatment with chemotherapy with peak concentrations being about half those expected 13-15 days after starting treatment [23]. This has been attributed to reduced absorption owing to the toxicity induced by chemotherapy [23,29]. This has also been confirmed for ofloxacin. The International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer has also noted that serum levels of pefloxacin were lower in patients who became febrile than in patients who did not [30] as were those of trimethoprim [31]. Drug levels are therefore at their lowest at the onset of profound neutropenia and fever and infection. Mucositis also occurs around this time suggesting that drug levels drop as the chemotherapy begins to exert its toxic effects on the mucosa and bone marrow namely, mucositis and neutropenia. The absorption of xylose is also reduced
following treatment with cytarabine [32] and gut permeability markedly increases following conditioning therapy for bone-marrow transplant [33]. Moreover, this is also about the same time that patients suffer most from nausea and vomiting so even if absorption is not impaired, compliance is likely to be poor. Lower drug levels may well allow less susceptible bacteria, such as the viridans streptococci, to survive in the bloodstream after invasion from damaged oral mucosa. Invasion may also emanate from the bowel if it becomes colonized as a result of reduced gastric acidity induced by H₂ antagonists which may present a risk factor for the sepsis syndromes such as adult respiratory distress syndrome (ARDS) are associated with bacteraemia caused by Streptococcus mitis [18].

Why does antibacterial prophylaxis fail?

These observations beg the question of whether prophylaxis fails because of intrinsic inactivity of the drug or because less of the drug is available? This is important because prophylaxis is considered to have failed and is invariably stopped as soon as fever develops and is replaced by an empirical regimen of a β-lactam with or without an aminoglycoside which affords essentially the same spectrum of activity against Gram-negative bacilli. This is because it is assumed that any pathogen involved in the putative infectious process must be resistant to prophylaxis. However, such pathogens are usually coagulase-negative staphylococci and viridans streptococci rather than Gram-negative bacilli, and typical empirical regimens are not considered optimal without the early addition of a glycopeptide [9,34–36]. The switch from oral prophylaxis to broad-spectrum parenteral therapy maintains the protection against Gram-negative bacillary infection albeit with different compounds but the automatic progression from prophylaxis to empirical therapy when fever occurs is not entirely logical.

Prophylaxis against candidosis

Candida spp. particularly Candida albicans are common residents of the oral cavity and alimentary tract and, occasionally, the skin and are classical opportunists causing diseases that range from superficial mucosal infections to deep-seated candidosis. However, apart from Candida tropicalis which has a relatively high likelihood of proceeding from colonization to infection [37,38], there are no features that mark out the potential pathogens from harmless commensal species.

The polyenes, amphotericin B and nystatin are highly active in vitro against Candida spp. and have been employed to suppress the overgrowth of candida that tends to accompany treatment with antibacterial agents [39,40] and hence lessen the risk of infection which is invariably preceded by colonization and mostly occurs in carriers [37,38]. However, at least 4.5 MU of nystatin must be given every day before there is any significant impact on candida colonization in either the oral cavity or gut. This is difficult to achieve as the drug is unpalatable and infections can still occur despite as much as 30 MU/day [39,41,42]. Amphotericin B is more effective in suppressing colonization provided at least 1.5–2 g/day is given [43] and the patient is willing to tolerate another unpleasant drug suspension. Also, amphotericin B was never licensed in the USA for oral administration which may partly explain the complete lack of placebo-controlled trials of sufficient numbers of patients to show a significant difference with a power of at least 80%.

The early azoles clotrimazole and miconazole have not fared much better even though both appear to prevent oral candidosis without having any marked effect on colonization [44]. Once again there have been no adequate controlled trials of either of these agents. Moreover, neither these agents nor the polyenes, provide systemic levels when given orally.

When first introduced, ketoconazole seemed to offer the ideal characteristics for an antifungal agent against candidosis, being active in vitro and able to deliver effective concentrations both systemically and locally. After many prophylactic studies of this drug [45] it was only found to be effective against mucocutaneous candidosis of the oral cavity oesophagus at doses of 400–600 mg/day which were higher than anticipated or considered desirable. Moreover, absorption is variable and is impaired by H₂ receptor antagonists and, while treatment with ketoconazole reduces colonization with Candida albicans there is an increase in faecal overgrowth with Candida glabrata [45,46]. The drug also interacts with P₄₅₀ cytochrome oxidase enzymes causing cyclosporin to be released with the consequent risk of nephrotoxicity to transplant recipients. Compliance is better than that obtained with polyenes but the drug failed to find a place in the prevention of candidosis. It was only
when the triazole fluconazole was introduced that the issue of prophylaxis against candidosis could be properly assessed. Fluconazole offers flexible dosing with bioequivalence of oral and parenteral administration and is effective at 50 mg/day in both treating and preventing oral candidosis [47]. A placebo-controlled study in adult bone-marrow transplant recipients and another in patients undergoing chemotherapy for acute leukaemia showed the benefit of 400 mg/day fluconazole in reducing both superficial and systemic candidosis. A rapid reduction in colonization of the alimentary tract with Candida albicans but not Candida krusei was also achieved [48,49]. Other investigators achieved similar results with 150 mg/day calling into question the need for 400 mg/day fluconazole [50]. In any case, since candidosis is almost always preceded by mucosal colonization, it is surprising that there has been no attempt to look at the potential benefit of antifungal prophylaxis only in patients who actually carry Candida spp. on their mucosal surfaces.

Apart from selecting natively resistant non-albicans Candida, including Candida glabrata and Candida krusei, prophylaxis with fluconazole might also lead to the development of superinfection by Aspergillus fumigatus [51]. There is also anxiety that resistance might emerge among Candida albicans as has been observed in patients with AIDS as a result of long-term treatment for oral candidosis [52]. However, neutropenic patients are very unlikely to require prolonged treatment and do not generally have persistent or recurring oral candidosis.

Prophylaxis against aspergillosis

Aspergillus spp. are opportunistic pathogens of the airways and only disseminate at a terminal stage. The spores are airborne and ubiquitous and colonize the nasal cavity, sinuses or bronchi before invading the tissues and causing disease. Not surprisingly there have been several attempts at interrupting spore transmission by using aerosols of 10–20 mg amphotericin B daily with variable success. Many of these trials were initiated in response to a sudden sharp rise in the incidence of invasive aspergillosis and none were randomized. Therefore, any reduction in infection rates might have been due simply to the seasonal variation in airborne spore burden or a cessation of building activities which are associated with high spore counts. Indeed, an interim analysis of randomized trials is still ongoing, but has failed thus far to show a significant reduction in the incidence of invasive pulmonary aspergillosis [53].

Giving amphotericin B prophylactically has also been tried in bone-marrow transplant recipients but in a placebo-controlled trial of 0.1 mg/kg/day amphotericin B (known affectionately as Amphot-Lite) failed to offer any benefit to those who received the drug [54]. The costs and infusion-related complications were not favourable and the nephrotoxic potential of amphotericin B also precludes its use when cyclosporin is being given to prevent graft-versus-host disease in allogeneic bone-marrow transplantation. Amphotericin B given intravenously at 0.5 mg/kg three times a week did not offer any advantage over 400 mg/day fluconazole to neutropenic patients [55].

Unlike fluconazole, itraconazole, another triazole, is active against aspergillus and is therefore a potential candidate for prophylaxis against both candidosis and aspergillosis. Unfortunately, only oral preparations of the drug have been available for study and absorption appears to be erratic, especially during neutropenia [56]. Indeed, a recent double-blind trial of 400 mg/day together with oral amphotericin B failed to show any benefit against candidosis or aspergillosis [57]. Itraconazole might offer some protection to bone-marrow transplant recipients [44] although interactions with cyclosporin have occurred with 200 mg/day [58].

Interactions of azoles and other drugs

Co-administered antacids lower the plasma concentrations of ketoconazole and itraconazole by decreasing absorption and both H₂-receptor antagonists and sucralfate impair the uptake of ketoconazole. Drugs such as rifampicin and phenytoin increase the metabolism of ketoconazole, itraconazole and fluconazole whereas the ketoconazole and itraconazole both increase the plasma concentrations of cyclosporin, phenytoin, tolbutamide, midazolam, triazolam, astemizole as well as the vinca alkaloids vincristine and vinblastine by inhibiting their metabolism [59].

Is there actually a need for prophylaxis against candidosis and aspergillosis?

Although there is considerable concern that systemic mycosis is increasing, there are few reliable data on
the actual prevalence, partly because diagnosis is usually made post-mortem [60] and autopsy rates are low, particularly in Europe [44]. The incidence of disseminated candidosis have to be gleaned from prophylactic studies mentioned earlier and suggest a prevalence of <10% despite prophylaxis and approximately twice this figure when none is used. Therefore, the case for giving fluconazole prophylactically is not very compelling and it may be better to restrict prophylaxis to those most at risk of candidosis, namely, carriers of Candida albicans who are colonized at one or more sites [38,61] or who have in excess of 400 cfu/mL saliva [62].

The prevalence of invasive pulmonary aspergillosis is even more difficult to ascertain as it depends upon local factors including seasonal variation and hospital building activity [63]. Furthermore, removing spores physically from the air using HEPA filters is not very compelling and it may be better to restrict prophylaxis to those most at risk of candidosis, namely, carriers of Candida albicans who are colonized at one or more sites [38,61] or who have in excess of 400 cfu/mL saliva [62].

The prevalence of invasive pulmonary aspergillosis is even more difficult to ascertain as it depends upon local factors including seasonal variation and hospital building activity [63]. Furthermore, removing spores physically from the air using HEPA filters is much more likely to reduce exposure and hence the risk of infection. Therefore, there is no convincing case for prophylaxis against aspergillosis although itraconazole does confer benefit for maintaining protection against relapse or reinfection once the disease has essentially been cured [44].

**Antiviral prophylaxis**

In the early 1980s it was established that acyclovir could protect neutropenic patients from mucocutaneous HSV infection [64–66] its use as prophylaxis quickly became standard practice for bone-marrow transplant recipients but not for those undergoing chemotherapy for acute leukaemia. Acyclovir can also afford protection against infectious diseases caused by varicella-zoster virus following bone-marrow transplantation but it is not considered cost-effective to maintain prophylaxis for more than 3 months post-transplant [67]. Acyclovir has no reliable influence on infections caused by CMV. The morbidity and mortality attributed to HSV infection is considered by some to be insufficient to warrant routine prophylaxis [68]. Moreover, there is usually a period after transplant when swallowing becomes difficult and many patients then receive the drug parenterally causing a considerable increase in costs. Unfortunately, there has been no pharmaco-economic assessment of prophylaxis but given the ability to detect HSV rapidly it might be more cost-effective to treat pre-emptively when there is evidence of reactivation rather than continue universal prophylaxis. By contrast, a pre-emptive approach to managing CMV infective disease has more or less become established practice and involves treatment with ganciclovir only when there is evidence of active CMV infection before disease becomes manifest [69].

**An alternative approach to prophylaxis**

For antimicrobial prophylaxis to continue to form part of the routine supportive care of neutropenic patients, its nature and goals must be radically reappraised. The primary goal of prophylaxis in neutropenic patients remains the prevention of Gram-negative infection which can be achieved by using the fluoroquinolones [70–72]. However, we have not made the best use of these drugs which are available in both an oral and parenteral formulation and therefore afford flexibility which has been foregone unwittingly because of the essentially artificial distinction between prophylaxis and therapy. As mentioned earlier, it would actually be much more rational to switch from oral to intravenous administration when a patient becomes febrile to maintain suppression of Gram-negative bacilli rather than changing to the more traditional empirical regimens which essentially provide the same spectrum of activity.

The use of oral ciprofloxacin for prophylaxis has been recently shown to reduce the need for parenteral therapy [73]. The drug was given to 53 adults undergoing cytotoxic treatment of haematological malignancy for 60 episodes of neutropenia and was complemented with ceftazidime and vancomycin in 55 episodes because of fever. Ceftazidime was discontinued after 24–48 h in 40 (91%) of 44 episodes because there was no evidence of Gram-negative bacillary infection and both vancomycin and oral prophylaxis were continued. Treatment was further complemented with metronidazole, rifampin or fluconazole in 18 of these episodes. The approach only failed in four episodes, one of which involved bacteremia caused by Pseudomonas aeruginosa. Thus, continuing prophylaxis with a fluoroquinolone to maintain protection against Gram-negative bacillary infection until bone-marrow recovery and complementing the regimen with specific agents only when the need arises seems a viable alternative to conventional practice (Fig. 1). Better results might also be obtained if the drug was administered parenterally when malabsorption is likely to occur, or the patient is...
Fig. 1 A typical neutropenic episode is depicted in the figure. Prophylaxis with a fluoroquinolone is started orally before chemotherapy is begun and continued until bone-marrow recovery. The drug is administered intravenously when malabsorption is likely to occur, or the patient is unable to tolerate oral medication, or drug levels are low. Should fever develop, every attempt would be made to identify the cause before altering treatment as prophylaxis should protect against rapid deterioration owing to Gram-negative bacillary infection. The prophylactic regimen would then only need to be complemented with a specific agent when a microbiologically defined infection is identified or with another agent determined by the nature of a clinically defined infection, e.g. amphotericin B for a pulmonary infiltrate or sinusitis. Fluconazole would be started pre-emptively if carriage of Candida spp. is identified or for oral candidosis and acyclovir would be given when herpes simplex virus is reactivated. Prophylaxis would be stopped prematurely if there was a Gram-negative bacillary infection, deterioration of vital signs associated with organ failure or shock or because of intolerance or a potentially harmful drug interaction. A wait-and-see approach would be adopted for persistent unexplained fever.

If patients do develop fever, rather than automatically switching to empirical therapy, every attempt would be made to identify the cause before altering treatment. Prophylaxis would thus protect against rapid deterioration owing to Gram-negative bacillary infection thereby allowing time to attempt to diagnose the cause of fever. The prophylactic regimen would then only need to be complemented with a specific agent when a microbiologically defined infection is identified or with another agent determined by the nature of a clinically defined infection, e.g. amphotericin B for a pulmonary infiltrate or sinusitis, metronidazole for a potentially anaerobic infection of the oral cavity of gut, fluconazole for oral candidosis or acyclovir for HSV infection. In the unlikely event of a Gram-negative bacillary infection, treatment would have to be changed altogether to a more appropriate regimen. A wait-and-see approach could be adopted for fever that persists but remains unexplained.

Clearly, the details and nature of complementary therapy would have to be tailored to the needs of the patient unable to tolerate oral medication. This manoeuvre alone might prevent bacteraemia caused by viridans streptococci and other Gram-positive cocci while maintaining cover against Gram-negative bacillary infection.
individual patients in any particular institution. Nevertheless, the experience of two large studies of empirical therapy for fever in neutropenic patients show that the reasons for complementing initial treatment are limited and that glycopeptides and amphotericin B are the most common drugs given [13,14]. The optimum dose of drug for prophylaxis would have to be determined for maintaining serum levels throughout neutropenia using an oral dose that achieves 70–80% of the bioavailability provided by the parenteral route. For ciprofloxacin this would be an oral dose of 750 mg b.d. and a parental dose of 400 mg t.d.s. [74]. There would also have to be adequate safeguards such as regular surveillance for resistant Gram-negative bacilli in oral and faecal samples as well as in blood cultures and a readiness to obtain appropriate specimens for establishing a diagnosis of oral, cutaneous and lung infections.

As for candidosis, HSV and CMV infection, a preemptive approach appears more logical and may prove more cost-effective as treatment would only be initiated with fluconazole for carriers of Candida spp. and with acyclovir and ganciclovir, respectively when HSV and CMV re-activate.

**Conclusion**

Such a strategy would have to be formerly tested against the more conventional approach to prophylaxis leading to empirical therapy and should be subjected to a thorough pharmaco-economic analysis with all that that entails. At the moment there is probably insufficient interest in re-evaluating the role of fluoroquinolones in managing infectious complications during neutropenia even though there is a scientific need to do so and financial constraints demand better husbanding of scarce healthcare resources. Clearly, there would need to be a commitment to continuous microbiological surveillance of important body sites as well as the patient’s environment in order to recognize colonization with potential pathogens, detect disease activity and maintain detailed monitoring of resistance. But if this approach to prophylaxis were to prove cost-effective, the savings could be diverted to improving diagnosis while giving the clinician enough confidence to stay his hand and wait rather than treat empirically and the microbiologist the opportunity of having a more direct and immediate input in patient care.

**References**


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