Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: informahealthcare.com/journals/ijme20

A pharmacoeconomic evaluation of piperacillin/tazobactam versus meropenem in the treatment of adult febrile neutropenia

ETM Smyth, JG Barr, GM Hogg & BA Oppenheim

To cite this article: ETM Smyth, JG Barr, GM Hogg & BA Oppenheim (2002) A pharmacoeconomic evaluation of piperacillin/tazobactam versus meropenem in the treatment of adult febrile neutropenia, Journal of Medical Economics, 5:1-4, 135-145, DOI: 10.3111/200205135145

To link to this article: https://doi.org/10.3111/200205135145

Published online: 02 Dec 2008.

2002 Volume 5
Pages 135-145

A pharmacoeconomic evaluation of piperacillin/tazobactam versus meropenem in the treatment of adult febrile neutropenia

Journal of Medical Economics 2002; **5**: 135-145

A pharmacoeconomic evaluation of piperacillin/tazobactam versus meropenem in the treatment of adult febrile neutropenia

ETM Smyth[1], JG Barr[1], GM Hogg[1], BA Oppenheim[2]

Summary

A study involving 80 patients has established the safety and efficacy of piperacillin/tazobactam (PT) versus meropenem (ME) in the treatment of febrile neutropenia. The study reported here assessed 78 of 80 patients and has shown that the total antimicrobial costs of the two study arms were very similar, except for the acquisition costs of the two study drugs and the antimicrobial prescription costs in the post-study period. The total antimicrobial costs for the PT and ME arms for the prestudy, study and post-study periods, respectively, were: PT £2,052.22/ME £1,140.49, PT £28,726.57/ME £49,954.80 and PT £10,863.45/ME £3,542.27. A detailed review of these post-study antimicrobial prescriptions demonstrated that cost differences lay in the prescription of antibacterial antimicrobials. This post-study difference lay in the additional prescription of 145.15 defined daily doses of antibacterial antimicrobials in the PT arm and were ascribed, in the main, to teicoplanin, vancomycin, imipenem, metronidazole and ciprofloxacin. Forty-three percent of the total post-study antibacterial cost was due to the use of imipenem in eight patients in the PT arm.

Key words: pharmacoeconomics, piperacillin/tazobactam, meropenem, neutropenia, monotherapy

Accepted for publication: 15th November 2002

[1] Department of Bacteriology, Kelvin Laboratories, The Royal Hospitals, Belfast, Northern Ireland, UK
[2] Public Health Laboratories, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, UK

Address for correspondence: Dr ETM Smyth, Department of Bacteriology, Kelvin Laboratories, The Royal Hospitals, Belfast BT12 6BA, Northern Ireland, UK

Introduction

Infection is well recognised as a serious complication in immunocompromised patients and particularly in neutropenic patients who have undergone cytotoxic management for bone marrow or stem cell transplantation. Although traditionally empirical management of infection in these patients has been with a broad spectrum antipseudomonal penicillin and an aminoglycoside, the availability of the carbapenems has made monotherapy a possibility. Indeed carbapenems have a wide spectrum of activity against the range of pathogens associated with infection in these patients, and meropenem (ME) has been shown to be as effective as combination chemotherapy[1]. The addition of tazobactam to piperacillin (PT) has widened the spectrum of piperacillin in a manner which might be expected to render this antimicrobial a similar efficacy to ME in this patient population. A recent study by Oppenheim *et al* has established that this is indeed the case, and PT and ME have been found to have similar safety and efficacy in the treatment of febrile neutropenia[2]. In the light of this, it was considered valid to undertake a cost minimisation study of the two therapeutic arms to determine the total antimicrobial costs. This would include, in a cost assessment, the total cost of administration of other nonstudy antimicrobials prescribed throughout the trial period. This was designed to be a total antimicrobial cost assessment between two study arms of equal efficacy in the management of febrile neutropenia.

Materials and methods

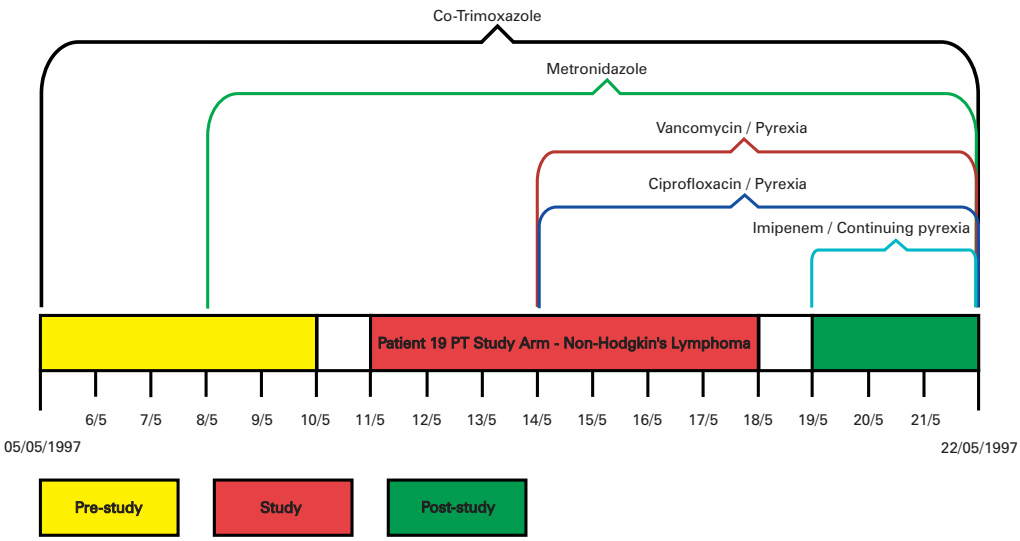
Patients

As the cost of erythromycin prescription was unavailable at the time of the study two patients who had received erythromycin therapy were excluded, therefore 78 patients were included in this pharmacoeconomic study. The study was open, randomised, prospective and single-centred. The patients were neutropenic cancer patients, and included those receiving chemotherapy for acute myeloid leukaemia (AML – PT 16, ME 19), acute lymphocytic leukaemia (ALL – PT 3, ME 3) Hodgkin's/non-Hodgkin's lymphoma (H/NH – PT 6, ME 6), multiple myeloma (PT 5, ME 7), others (PT 8, ME 5) (Table 1). The other group included mainly those with solid tumours including breast

Table 1. Diagnostic group of patients included in the study

Diagnostic group	*PT arm*	*ME arm*
Acute myeloid leukaemia	16	19
Acute lymphocytic leukaemia	3	3
Lymphoma	6	6
Multiple myeloma	5	7
Others (incl. solid tumours)	8	5
Total	38	40

Figure 1. Example of a timeline



carcinoma. For inclusion in the study, patients were also required to exhibit a single temperature of >38.5°C or 38°C on two occasions during a 12 h period.

Study design

The study agents were PT (4.5 g iv every 8 hours) and ME (1 g iv every 8 hours). The study was divided into three study periods: (a) the pre-study period — starting with the commencement of the first administration of treatment during the period covered by the study protocols and ending at the commencement of the study antibacterial antimicrobial, as recorded in the patient's clinical trial notes; (b) the study period — the time within which the study antimicrobial was administered; (c) the post-study period — the time from which the study antimicrobial was last administered to that of the last antimicrobial administration date recorded in the patient's clinical trial notes. Using this information, timelines of antimicrobial prescription, which graphically demonstrated the administration of PT, ME, imipenem, teicoplanin, vancomycin, ciprofloxacin, co-trimoxazole and metronidazole for each patient, were constructed. The timelines demonstrated the prescription of these antimicrobials over the whole study period. An example of a timeline is given in Figure 1.

Antimicrobial preparation and administration (labour) protocols

Detailed descriptions of the methods used in this pharmacoeconomic evaluation study have been published elsewhere[3,4]. These include the costs of antimicrobial acquisition, administration costs, and consumables and waste costs.

Antimicrobial costs and defined daily doses (DDDs)

Antimicrobial costs included in the calculations in this paper were based on

Table 2. WHO defined daily doses (DDDs) for antimicrobials used in the study

Antimicrobials	*DDD*	*Unit*	*Route*
Antibacterials			
Benzyl penicillin	3.6	g	P
Ceftazidime[a]	6	g	P
Ciprofloxacin	1	g	O
Ciprofloxacin[a]	800	mg	P
Clindamycin	1.8	g	P
Colistin[a]	3	mu	O
Co-trimoxazole[b]	1920	mg	O, P
Flucloxacillin	2	g	O, P
Gentamicin	240	mg	P
Imipenem	2	g	P
Meropenem[a]	3	g	P
Metronidazole	1.5	g	P
Metronidazole[b]	1.2	g	O
Netilmicin[a]	300	mg	P
Piperacillin[a]	16	g	P
Piperacillin/tazobactam[a]	13.5	g	P
Teicoplanin	400	mg	
Vancomycin	2	g	P
Antifungals/antivirals			
Amphotericin B	35	mg	P
Fluconazole	200	mg	O, P
Itraconazole	200	mg	O
Ketoconazole	200	mg	O
Aciclovir	4	g	O, P

[a] Modified WHO DDD (in line with current UK formulations and common clinical practice).

[b] In-house DDD (no WHO value).

O, oral; P, parenteral; g, gram; mg, milligram; mu, million units.

British National Formulary prices and were those pertaining in September 2000. DDDs for each antimicrobial were obtained from the WHO DDD tables or from in-house modifications[5]. The basis of these modifications was either the absence of a WHO DDD value, or because a different dosage regimen was normally adopted in the UK. Table 2 shows the DDD values used, including the in-house modifications.

Due to incomplete therapeutic details for some patients in the post-study period, DDDs were calculated on the basis of the last recorded antimicrobial date in the post-period, according to the patients' clinical trial notes.

Results

Length of pre-study, study and post-study periods

In the PT arm, the mean length (median and range) of the pre-study, study and post-study periods were 6.5 (6.5, 0-18), 8.6 (8, 3-19), 3 (0.5, 0-18) days, respectively. In the ME arm, these values were 6.5 (6, 0-18), 9.6 (8, 1-26), 2 (1, 0-10) days, respectively.

Prescription of additional antibacterial, antifungal and antiviral antimicrobials during the pre-study, study and post-study periods

In some cases more than one antimicrobial was prescribed for individual patients: this has resulted in the total number of prescriptions exceeding the number of study patients.

Prescription of additional antibacterial antimicrobials

The prescription of antibacterial antimicrobials during the different periods is shown in Table 3. The Table includes, for

Table 3. Antibacterial prescription and total costs (£ Sterling)

Additional antibacterials	*PT DDDs*	*Patients*	*PT costs*	*ME DDDs*	*Patients*	*ME costs*
Pre-study period						
Ciprofloxacin po	26.00	4	87.36	13.25	3	44.52
Co-trimoxazole po	65.60	14	77.93	73.50	9	87.32
Flucloxacillin po	0.00	0	0.00	6.00	1	12.20
Metronidazole po	34.00	10	66.59	44.00	11	86.18
Netilmicin iv	0.51	1	8.50	0.00	0	0.00
Teicoplanin iv	0.00	0	0.00	1.00	1	50.66
Vancomycin iv	4.00	1	198.53	0.00	0	0.00
Total	130.11		438.91	137.75		280.88
Study period						
Benzyl penicillin iv	31.98	2	593.68	2.66	1	49.38
Ceftazidime iv	8.00	1	519.00	0.00	0	0.00
Ciprofloxacin iv	17.50	4	950.07	13.00	4	705.77
Ciprofloxacin po	31.50	6	105.84	8.50	3	28.56
Clindamycin iv	22.70	1	777.78	0.00	0	0.00
Colistin po	9.00	1	29.40	6.00	1	19.60
Co-trimoxazole po	47.56	14	56.50	20.00	7	23.76
Flucloxacillin iv	0.00	0	0.00	18.00	2	336.42
Flucloxacillin po	48.00	3	97.63	1.50	1	3.05
Metronidazole iv	30.99	6	445.39	12.00	2	172.47
Metronidazole po	113.00	17	221.32	109.00	20	213.48
Netilmicin iv	28.96	5	482.76	24.50	5	408.41
Teicoplanin iv	22.50	10	1,138.88	52.51	13	2,660.23
Vancomycin iv	82.25	19	4,082.18	107.00	16	5,310.56
Total	493.94		9,500.43	374.67		9,931.69
Post-study period						
Ciprofloxacin iv	28.00	4	1,520.11	7.50	2	407.17
Ciprofloxacin po	36.00	4	120.96	18.40	2	61.82
Clindamycin iv	2.27	1	77.78	0.00	0	0.00
Co-trimoxazole po	20.06	11	23.81	6.50	5	7.72
Flucloxacillin iv	0.00	0	0.00	25.00	1	467.25
Flucloxacillin po	2.00	1	4.07	1.50	2	3.05
Gentamicin iv	7.50	1	100.24	0.00	0	0.00
Imipenem iv	64.00	8	4,365.12	0.00	0	0.00
Metronidazole iv	13.99	5	201.07	0.00	0	0.00

Continued

Table 3. Antibacterial prescription and total costs (£ Sterling). Continued

Additional antibacterials	*PT DDDs*	*Patients*	*PT costs*	*ME DDDs*	*Patients*	*ME costs*
Metronidazole po	29.00	8	56.80	30.00	8	58.76
Netilmicin iv	3.11	2	51.83	16.13	4	268.82
Piperacillin iv	2.00	1	115.10	8.00	2	460.43
Teicoplanin iv	34.00	8	1,722.49	17.00	5	861.24
Vancomycin iv	36.25	6	1,799.14	3.00	1	148.89
Total	278.18		10,158.52	133.03		2,745.15

each antimicrobial by each utilised route of administration, the total patient DDDs prescribed, the total number of patients who received that antimicrobial, and the total costs of that antimicrobial for each of the study arms.

It was noted that in the pre-study period, the total DDDs prescribed in the two arms was similar (PT 130.11: ME 137.75). Although there was a substantial difference in total costs in the two arms, this was mainly due to prescription of four DDDs of vancomycin in one patient in the PT arm.

Table 4. Antifungal prescription and total costs (£ Sterling)

Additional antibacterials	*PT DDDs*	*Patients*	*PT costs*	*ME DDDs*	*Patients*	*ME costs*
Pre-study period						
Amphotericin B iv	2.56	2	14.52	0.00	0	0.00
Fluconazole iv	15.00	3	339.60	0.00	0	0.00
Fluconazole po	39.50	8	385.07	32.50	8	316.83
Ketoconazole po	270.00	18	211.41	322.00	22	251.16
Total	327.06		950.60	354.50		567.99
Study period						
Amphotericin B iv	85.11	11	482.72	103.88	15	589.18
Fluconazole iv	8.50	2	262.42	0.00	0	0.00
Fluconazole po	24.50	10	238.84	31.50	9	307.08
Itraconazole po	12.60	2	39.31	40.00	2	124.80
Ketoconazole po	262.00	16	205.15	376.00	22	293.28
Total	392.71		1,228.44	551.38		1,314.34
Post-study period						
Amphotericin B iv	16.86	6	95.62	52.46	2	297.54
Fluconazole po	17.50	4	170.60	7.50	4	73.11
Itraconazole po	42.00	2	131.04	2.00	1	6.24
Ketoconazole po	114.00	8	89.26	94.00	8	73.60
Total	190.36		486.52	155.96		450.49

In the study period, although the total costs of antimicrobials was similar in the two study arms (PT £9,500.43: ME £9,931.69), there were notable differences in the prescription of some antibacterials in one or other of the two arms.

In the post-study period, there were substantial differences in the number of DDDs prescribed in the two arms (PT 278.18 : ME 133.03). This equated to a very substantial difference in costs in the two arms (PT £10,158.52; ME £ 2,745.15). These differences resided largely in additional prescription in the PT arm of imipenem iv, vancomycin iv, teicoplanin iv, metronidazole iv , ciprofloxacin iv and by mouth. In particular, the cost differences in the two arms was due to vancomycin iv, teicoplanin iv, imipenem iv and ciprofloxacin iv.

Prescription of additional antiviral and antifungal antimicrobials

In comparison with the differences in costs in the two arms of additional antibacterial antimicrobials, the additional cost of antiviral and antifungal prescription was small, and little difference was noted between the two arms (Tables 4 and 5).

Summary of total antimicrobial prescription costs

Table 6 summarises the prescription of antibacterial, antiviral, antifungal antimicobials and study drug costs in the prestudy, study and post-study period. This clearly demonstrates that, apart from differences in costs of the study antibacterials themselves, the main differences lay in the prescription of antibacterial antimicrobials in the two arms, and most particularly during the post-study period.

Regarding the three components of drug costing – the drug aqusition cost, the administration/labour costs and consumables/waste cost — the major influence on drug costs is the drug

Table 5. Antiviral prescription and total costs (£ Sterling)

Antivirals	*PT DDDs*	*Patients*	*PT costs*	*ME DDDs*	*Patients*	*ME costs*
Pre-study period						
Aciclovir iv	1.54	2	261.28	0.00	0	0.00
Aciclovir po	27.60	18	401.43	20.50	10	291.62
Total	29.14		662.71	20.50		291.62
Study period						
Aciclovir iv	4.86	3	824.55	4.27	4	724.45
Aciclovir po	35.90	17	522.15	48.70	14	708.32
Total	40.76		1,346.70	52.97		1,432.77
Post-study period						
Aciclovir iv	0.19	1	32.24	0.50	1	84.83
Aciclovir po	12.80	8	186.17	18.00	6	261.80
Total	12.99		218.41	18.50		346.63

Table 6. Summary of total anti-microbial prescribing costs including study drugs (£ Sterling)

Antimicrobials	*PT DDDs*	*PT costs*	*ME DDDs*	*ME costs*
Antibacterials				
Pre-study	130.11	438.91	137.75	280.88
Study excl. PT & ME	493.94	9,500.43	374.67	9,931.69
Study PT & ME	325.00	16,651.00	371.00	37,276.00
Post-study	278.18	10,158.52	133.03	2,745.15
Total	1,227.23	3,6748.86	1,016.45	50,233.72
Antifungals				
Pre-study	327.06	950.60	354.50	567.99
Study	392.71	1,228.44	551.38	1,314.34
Post-study	190.36	486.52	155.96	450.49
Total	910.13	2,665.56	1,061.84	2,332.82
Antivirals				
Pre-study	29.14	662.71	20.50	291.62
Study	40.76	1,346.70	52.97	1,432.77
Post-study	12.99	218.41	18.50	346.63
Total	82.89	2,227.82	91.97	2,071.02
Overall study costs		41,642.24		54,637.56

aquisition cost. Consequently, changes in the drug aquisition costs will have the most impact on the total prescription costs in both study arms, e.g. the aquisition cost for PT and ME are 85% and 93% respectively of the total presciption costs.

Evaluation of post-study antibacterial prescription in the two study arms

Post-study prescription of vancomycin iv

Vancomycin was prescribed in the post-study period in seven patients — AML (2), myeloma (2), ALL (1), H/NH (1) and others (1) — in the PT arm, and in one patient only — others (1) — in the ME arm. In seven of the eight patients in which vancomycin was added, the patients were still neutropenic at the time of addition: in only two of eight was the treatment a continuation from the study period. Six of eight patients had continuing pyrexia in the post-study period, while five of eight had recorded Hickman-line associated infections.

Post-study prescription of teicoplanin iv

Teicoplanin was prescribed in the post-study period in eight patients — AML (3), myeloma (1), H/NH (1) and others (3) — in the PT arm, and in five patients — AML (2), myeloma (1), H/NH (1) and others (1) — in the ME arm. In 12 of the 13 patients in which teicoplanin was added, the patients were still neutropenic: in eight of the 13 the treatment was a continuation from the study period. Four of eight patients in the PT arm had continuing

pyrexia in the post-study period, while seven of 13 had recorded Hickman-line associated infections.

Post-study prescription of metronidazole iv

Metronidazole was prescribed in the post-study period in 12 patients — AML (4), ALL (1) myeloma (5), H/NH (1) and others (1) — in the PT arm, and in nine patients — AML (2), ALL (2), myeloma (1), H/NH (2) and others (2) — in the ME arm. In 19 of the 21 patients in which metronidazole was added, the patients were still neutropenic: in 18 of the 21, the treatment was a continuation from the study period. In six of 12 patients in the PT arm, a continuing pyrexia in the post-study period was recorded. Seven of nine patients in the ME arm and only two of 12 in the PT arm had recorded mucositis.

Post-study prescription of imipenem iv

Imipenem was prescribed in the post-study period in the PT arm in a total of eight patients: AML (3), myeloma (1), ALL (1), H/NH (1) and others (2). Seven of the eight patients were still neutropenic and all patients had continuing pyrexia. In no case was imipenem a continuation treatment from the study period.

Post-study prescription of ciprofloxacin iv

Ciprofloxacin was prescribed in the post-study period in seven patients — AML (4), H/NH (1) and others (2) — in the PT arm, and in three patients — AML (2), and others (1) — in the ME arm. In six of the seven patients in the PT arm, the patients were still neutropenic compared with none of three in the ME arm. In five out of seven in the PT arm, this was continuation therapy compared with none of three in the ME arm. Four out of seven patients in the PT arm had continuing pyrexia in the post-study period.

Discussion

The percentage of total antimicrobial costs attributable to antiviral or antifungal prescription in either of the pre-study, study or post-study periods was small. No substantial differences were noted in the prescription of these antimicrobials during any of the study periods, although it was noted that a trend of ketoconazole prophylaxis was established across the prestudy, study and post-study periods (Tables 4 and 5).

With respect to antibacterial antimicrobials, little difference in total DDDs prescribed, or their costs, was noted in either arm of the pre-study period. During the study period, however, 119.27 DDDs of additional nonstudy antibacterials were employed in the PT arm, but this was not reflected in any substantial overall additional cost in nonstudy antibacterials. However, substantial differences in costs were noted between the two study arms, which reflect only the much higher acquisition costs of ME, and not any major differences in drug administration or consumables/waste and disposal costs of the study drugs.

The post-study period was very interesting in that substantially greater costs and higher DDDs were prescribed in the PT

arm compared to the ME arm. In the PT arm, this equated to 278.18 DDDs, equivalent to a cost of £10,158.52, while in the ME arm there were only 133.03 DDDs prescribed at a cost of £2,745.15. We identified this greater total DDD prescription and cost to be attributable particularly to vancomycin iv, teicoplanin iv, imipenem iv, ciprofloxacin iv and metronidazole iv.

Forty-three percent of the total post-study antibacterial costs were due to the use of imipenem in eight patients in the PT arm.

With respect to glycopeptide administration in this period, prescription was usually initiated while the patient was still neutropenic, and in 10 of 21 patients this represented continuation therapy. The prescription of glycopeptide antimicrobials seems largely to be justified on the basis of continuing pyrexia, neutropenia and recorded Hickman-line associated infections. No major differences were noted with respect to patients with different specific underlying disease.

Regarding ciprofloxacin, most prescription in the PT arm was initiated in neutropenic patients within the study period, while the contrary was the case in the ME arm. A local protocol recommended the initiation of ciprofloxacin treatment when screening rectal swabs yielded growth of *Pseudomonas* spp, and this may have contributed to this drug prescription. In the case of imipenem, the initiation of all prescription was in the post-study period in patients with continuing neutropenia and pyrexia in the PT arm. This was clearly a natural progression in patients with continuing neutropenia and unresolving pyrexia. Clearly this opportunity was not available in the ME arm, where a change from ME to imipenem would not be logical. This post-study period of antimicrobial management was striking by the absence of substantial aminoglycoside or antifungal antimicrobial prescription in those patients with continuing neutropenia and pyrexia.

It remains clear, however, as shown in Table 6, that a substantially lower total cost for all prescribed antimicrobials was recorded in the PT arm. The difference between this cost (£41,642.24) and the total costs in the ME arm (£54,637.56) largely reflected a very substantial difference in total costs of the two study drugs PT (£16,651.00) and ME (£37,276.00). This means that the potential cost saving of £21,056.26 in the total antibacterial antimicrobial costs during the study period of the PT arm has been diminished by £7,413.37 (35%) due to the costs of additional prescribed antibacterial antimicrobials in the post-study period.

The use of timelines of prescription of antimicrobials over a prolonged period in these study patients provided a very useful method for collating prescription in the individual patient, and in comparisons between patients in different arms of the study, or different patient groups within the study arms. Utilisation of timelines may find useful employment in other studies of this nature and may also have a valuable role in teaching and audit.

Acknowledgements

The authors wish to thank Wyeth Laboratories (UK) for their financial support of this study.

References

1. Cometta A, Calandra T, Gaya H *et al*. Monotherapy with Meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrobial Agents and Chemotherapy* 1996; **40**: 1108-1115.
2. Oppenheim BA, Morgenstern GR, Chang J *et al*. Safety and efficacy of piperacillin/tazobactam versus meropenem in the treatment of febrile neutropenia. Proceedings of 7th Conference of the Federation of Infection Societies 2000, P67, 52.
3. Smyth ETM, Barr JG, O'Neill CA, Hogg GM. An assessment of the hidden and total antibiotic costs of four parenteral cephalosporins. *PharmacoEconomics* 1995; **8**: 540-550.
4. Smyth ETM, Barr JG, Hogg GM. An assessment of hidden costs on total prescribing costs of courses of meropenem and imipenem/cilastatin. *British Journal of Medical Economics* 1996; **10**: 325-340.
5. Anatomical, Therapeutic, Chemical (ATC) Classification Index including Defined Daily Doses (DDD). WHO Collaborating Centre for Drug Statistical Methodology, 2000.

