Prospective drug utilization evaluation of three broad-spectrum antimicrobials: cefepime, piperacillin-tazobactam and meropenem

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Summary

Background: Cefepime, piperacillin-tazobactam and meropenem are among the broadest-spectrum and most expensive antimicrobials.

Aim: To evaluate guidelines for appropriate use of these drugs.

Methods: We developed guidelines for use of these antibiotics, and conducted a two-phase drug utilization evaluation. We included all patients who received one of the study drugs during two 3-month periods, with an educational intervention in the intervening period. Appropriateness was determined for initiation of treatment, and for adaptation or continuation of established treatment.

Results: Overall, 205 patients received 271 courses with one of these antibiotics, for a total of 709 defined daily doses (DDD) of cefepime, 543 of piperacillin-tazobactam, and 680 of meropenem (8.3, 6.3 and 7.9 DDD/1000 admission days, respectively). Of these 271 courses, 234 were appropriate (86%). Treatment was continued for ≥5 days in 60%, of which 88% were appropriate (NS). Of the 271 courses, 210 (77%) were empirical (83% appropriate), while 61 (23%) were based on a relevant culture result (97% appropriate) (p<0.001). Appropriateness differed significantly between departments (p<0.001), and between the two phases (p<0.001). The major difference between the two surveys was a decrease in meropenem usage (p<0.05).

Discussion: The vast majority of courses with cefepime, piperacillin-tazobactam and meropenem are empirically selected and continued, underlying the importance of an optimal initial choice. Antibiotic guidelines, in conjunction with formal infectious disease consultation, can contribute to more appropriate use of these drugs.

Introduction

The development of bacterial resistance to antibiotics has become a major problem throughout the world.1–4 Resistant organisms may emerge as a result of many factors, including widespread usage, while their spread is mainly caused by factors in the health care setting, including the health care providers’ behaviour. The broadest-spectrum antibiotics, such as fourth-generation cephalosporins, piperacillin-tazobactam and carbapenems, play an important role in the empiric therapy of serious nosocomial infections. These antimicrobials are also among the most expensive.5 Concern about escalating rates of multi-drug-resistant organisms and spiralling expenditure on broad-spectrum antimicrobials has induced most hospitals to implement a range of measures.6–16 These include supervision of their use by infectious disease consultants and/or clinical pharmacists,6,7 provision of continuing...
Another method increasingly used in this era of cost constraints and quality assurance is drug utilization evaluation (DUE). This tool was adapted by pharmacists to assess appropriateness of usage of various medications. The purpose of a DUE is generally to detect possible problems with, and improve, drug use. DUEs have traditionally focused on drugs with frequent side-effects, high price tags or complicated dosing regimens. Very few DUEs have addressed broad-spectrum antibiotics, and none has included all three last-line agents.

We developed guidelines for the use of cefepime, piperacillin-tazobactam and meropenem, and conducted a two-phase DUE using these guidelines, with an educational intervention in between, to improve use of these expensive broad-spectrum agents.

Methods

This study was done in a 550-bed university-affiliated general hospital, Jerusalem’s second largest. The hospital includes all major departments and services, including three medical and two geriatric wards, haematology and oncology; paediatrics; two surgical departments, of which one specializes in vascular surgery; gynaecology and obstetrics, heart and chest surgery, urology, orthopaedics, plastic surgery, ophthalmology, otorhinolaryngology; and several intensive care units (medical, surgical, paediatric and neonatology). Transplantations are not performed. Many patients are admitted through the emergency department, where annually about 75 000 patients are seen. The number of admissions increased from 18 783 in 1990 to 44 458 in 2004, an increase of 137%; number of admission days increased correspondingly from 111 949 to 186 213 (66%). These changes reflect the population growth in the Jerusalem area, the increase in the hospital’s services as well as the near-universal shortening of hospitalizations.

A drug utilization evaluation (DUE) program was carried out over two 3-month periods: January–March and August–October 2001. It included all 16 departments in which the study drugs (cefepime, piperacillin-tazobactam and meropenem) were in use, and all patients who were treated with at least one of these three antibiotics. Patients receiving a study drug were identified by daily review of the patients’ drug records in each of the participating departments. Patients were followed from initiation until discontinuation of treatment.

Drug treatment was divided into two periods: the initial period (≤ 5 days, i.e. the time interval during which relevant culture results might become available and hence influence subsequent change or continuation of drug therapy); and the often more protracted period of definite treatment, influenced by culture results or empirically continued. The appropriateness of drug treatment was assessed for the initial period in both phases of the study, and for the definite period in phase 1 only.

Appropriateness was determined using a predefined, two-page guideline (Appendix A), prepared as part of the study. It was based upon the following underlying principles: (i) accordance with the hospital’s protocols, summarized in the guideline; (ii) treatment targeted according to susceptibility data of an organism from a relevant clinical specimen; and (iii) drug therapy as recommended by an infectious disease consultation. All files were reviewed between two investigators, one of whom was an infectious disease consultant: post factum agreement with prescribed treatment was considered to indicate appropriate treatment, even if this deviated from the guideline. However, this ‘over-rule’ was applied only in a few cases of uncertainty, e.g. when relevant data were not available or had not been recorded, as these sessions were not held in real time, and with the patients’ charts at hand only. The hospital’s protocols for antibiotic usage for common clinical situations consists of a 100-page booklet, which has been distributed to all physicians since the early 1990s, and is periodically updated. These protocols, in turn, were based on the literature, local susceptibility patterns, and available antimicrobial agents.

Antibiotic use was expressed according to the internationally accepted defined daily dose (DDD) system. According to this method, the usual daily dose of a drug, prescribed to an adult patient without renal or liver impairment, is 1 DDD. Adoption and implementation of this method allows hospitals to compare their overall as well as particular drug use with that reported and published by other medical centres.

Demographic and clinical data were retrieved from the relevant patients’ files. Data gathered included: demographic information; blood urea nitrogen and creatinine levels; indication for initiation of treatment; therapy with other broad spectrum antibiotics during the present hospitalization; source of infection (nosocomial or community-acquired);
involvement of an infectious disease consultant (prescription of the three study drugs requires prior authorization by an infectious disease consultant); results from the microbiology laboratory regarding a pertinent clinical specimen, including bacterial identification and susceptibilities. Results of the first survey were analysed, and subsequently an educational campaign was mounted based on the findings of that survey. The campaign consisted of a written distribution to all the medical centre’s physicians of the results of the initial survey, accompanied by the practice guideline. In addition, oral presentations were made during departmental staff meetings, stressing the study’s major findings and discussing the hospital’s guidelines for use of the study antibiotics. Several months later, a second survey, identical to the first, was conducted. During the course of data collection, the investigators refrained from influencing clinical decisions by clinicians. No attempt was made to verify the infectious diseases diagnosis for which the broad-spectrum antimicrobial had been selected. Infections were classified as community- or hospital-acquired according to standard definitions: basically, if an infection was acquired >72 h after admission, it was considered nosocomial.

Collecting data were entered into the Epi info 6.04d computer program (CDC), which was also used for data analysis. Proportions were compared using the χ² or Fisher’s exact test, where appropriate. Continuous variables were compared by the Student’s t-test. All p values were two-tailed, and p<0.05 was considered statistically significant.

## Results

During the first survey, conducted in all departments where cefepime, piperacillin-tazobactam and meropenem were prescribed, 102 patients received 143 courses with at least one of these three antibiotics. During the second survey, 103 patients received 128 courses with at least one of these antibiotics. Table 1 shows drug and pharmaceutical data of the study drugs during the two phases of the survey, including number of courses given with each antibiotic, duration of treatment and dosing. Notably, meropenem use decreased from 44% of all broad-spectrum therapy in the first period to 22% in the second (p<0.05). An opposite trend was seen in cefepime use, which increased from 22% to 44% of all broad-spectrum treatment in the first period to 44% in the second (p<0.05). Analysis of individual antibiotic use for separate indications revealed that for nosocomial pneumonia in phase 1 of the study, 44% of broad-spectrum courses were with meropenem; this percentage decreased to 18% in phase 2 (p<0.05). Not surprisingly, the opposite happened with cefepime: in phase 1, 17% of courses for nosocomial pneumonia were with cefepime, increasing to 36% in phase 2 (p<0.05). There was a similar, although statistically insignificant, shift for the treatment of sepsis.

Table 2 shows data regarding appropriateness of antibiotic use in both study phases. Overall, initiation of treatment was justified in 234/271 (86%) cases: 122/143 (85%) instances in phase 1 and 112/128 (87%) in phase 2 (NS). The rate of

### Table 1: Pharmaceutical data of drugs used in both phases of the survey

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cefepime</th>
<th>Piperacillin-tazobactam</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total courses</td>
<td>88</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>Phase 1 (n=143)</td>
<td>32 (22%)</td>
<td>48 (34%)</td>
<td>63 (44%)</td>
</tr>
<tr>
<td>Phase 2 (n=128)</td>
<td>56 (44%)</td>
<td>44 (34%)</td>
<td>28 (22%)</td>
</tr>
<tr>
<td>Antimicrobial duration (days)</td>
<td>6.6 ± 3.6</td>
<td>6.8 ± 3.7</td>
<td>9.6 ± 6.6</td>
</tr>
<tr>
<td>Daily dose (g±SD)</td>
<td>8.9 ± 6.2</td>
<td>7.5 ± 4.2</td>
<td>10.8 ± 10</td>
</tr>
<tr>
<td>Duration of treatment (days±SD)</td>
<td>2.0 ± 0.5</td>
<td>11.6 ± 2.8</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Total dose/course (g)</td>
<td>7.7 ± 4.9</td>
<td>7.1 ± 3.9</td>
<td>10.2 ± 8.3</td>
</tr>
<tr>
<td>Total use in study periods</td>
<td>15.4</td>
<td>82.4</td>
<td>15.3</td>
</tr>
<tr>
<td>DDD (defined daily doses)</td>
<td>709</td>
<td>543</td>
<td>680</td>
</tr>
<tr>
<td>DDD/1000 admission days</td>
<td>8.3</td>
<td>6.3</td>
<td>7.9</td>
</tr>
<tr>
<td>DDD/1000 patients</td>
<td>38.8</td>
<td>29.7</td>
<td>37.3</td>
</tr>
</tbody>
</table>

*The number of cefepime courses increased significantly (p<0.05), while the number of meropenem courses decreased significantly (p<0.05) from phase 1 to phase 2. *b*Total duration of antimicrobial treatment, in days (mean±SD).
appropriateness of treatment for sepsis in phase 2 was significantly lower than for other indications ($p<0.05$). In addition, the overall rate of appropriateness of empirical treatment (175/210, 83%) was significantly less appropriate than treatment based on relevant culture results (59/61, 97%) ($p<0.001$). Finally, the rate of appropriateness of treatment differed significantly between the departments ($p<0.001$), both overall and in each of the two phases ($p<0.001$).

Figure 1 shows the characteristics of drug therapy in the two study phases. In phase 1, 77% of all newly instituted treatment was empirical, compared to 78% in the second phase (NS). Accordingly, only 23% and 22%, respectively, of treatment was initiated based on the results of a relevant culture. The appropriateness rate of the latter, i.e. treatment started according to a relevant positive culture, was 97% in phase 1, and 96% in phase 2 (NS). On the other hand, the rates of appropriateness of empirically initiated treatment were 82% and 85%, respectively (NS). Not unexpectedly, the appropriateness rate of empirically chosen treatment was significantly lower than that of treatment selected according to a positive relevant culture ($p<0.001$). Data collected from the first phase of the survey showed that only 60% of initiated treatment was continued beyond 5 days, of which 88% appeared appropriate.

Sub-analyses revealed that of 90 appropriately initiated, empirically-chosen antibiotic courses in phase 1 of the study, 54 (60%) were continued: 7 (13%) according to culture results, of which 5 (71%) were deemed appropriate. The remaining 47 (87%) were continued empirically (of which 100% were deemed appropriate). On the other hand, of 20 inappropriately initiated, empirically-chosen antibiotic courses in phase 1 of the study, 12 (60%) were continued, all empirically: of these, only one (8%) was deemed appropriate. Therefore, the rate of appropriateness of definite therapy was considerably higher for those courses whose initiation was considered appropriate vs. those whose initiation was considered inappropriate ($p<0.001$).

The patients’ records were also reviewed for documentation of an infectious disease consultation. The hospital’s guidelines regarding restricted antimicrobials, which include cefepime, piperacillin-tazobactam and meropenem, require an infectious disease consultation prior to initiation of these drugs. Such a consultation may take place

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Overall appropriateness of treatment, with comparison of the two phases</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>76/88 (86%)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>83/92 (90%)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>75/91 (82%)</td>
</tr>
<tr>
<td>Indication for treatment</td>
<td></td>
</tr>
<tr>
<td>Sepsis (nosocomial)</td>
<td>86/100 (86%)</td>
</tr>
<tr>
<td>Pneumonia (nosocomial)</td>
<td>84/96 (87%)</td>
</tr>
<tr>
<td>Other</td>
<td>68/75 (91%)</td>
</tr>
<tr>
<td>Initiationa</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>234/271 (86%)</td>
</tr>
<tr>
<td>Empirical</td>
<td>175/210 (83%)</td>
</tr>
<tr>
<td>Based on a relevant culture result</td>
<td>59/61 (97%)</td>
</tr>
<tr>
<td>Initiation by departmentb</td>
<td></td>
</tr>
<tr>
<td>Intensive care</td>
<td>53/56 (95%)</td>
</tr>
<tr>
<td>Medical departments</td>
<td>109/118 (92%)</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>12/26 (46%)</td>
</tr>
<tr>
<td>Other</td>
<td>60/71 (84%)</td>
</tr>
</tbody>
</table>

Data are numbers of appropriate treatments/total treatments (percentage). In phase 1, 44% of broad-spectrum courses for nosocomial pneumonia were with meropenem; this percentage decreased to 18% in phase 2 ($p<0.05$). The opposite happened with cefepime: in phase 1, 17% of courses for nosocomial pneumonia were with cefepime, which increased to 36% in phase 2 ($p<0.05$). A similar, although less pronounced shift, occurred for the treatment of sepsis (NS). In phase 2, the appropriateness level was significantly lower for patients with sepsis than for other indications ($p<0.05$). The appropriateness level was significantly lower for patients with sepsis than for other indications ($p<0.05$).
at the bedside (preferable), and is therefore recorded by the consultant in the patient’s record, or alternatively, via telephone, in which case the consulting physician is required to document the results of the consultation in the patient’s record. The rate of documentation was low: only 33% and 39% of antibiotic courses in phase 1 and phase 2, respectively (NS). However, the rate of consultation could conceivably have been much higher than the rate of documentation. The education effort in between the phases evidently did not affect a substantial improvement.

Expenditure on cefepime, piperacillin-tazobactam and meropenem constitutes 40% of the hospital’s outlay on antimicrobial agents. Of 709 defined daily doses (DDDs) of cefepime, 99 (14%) were considered inappropriate; for piperacillin-tazobactam, 54/543 (10%) were deemed inappropriate; and for meropenem, 122/680 (18%) were considered inappropriate. These amount to inappropriately spent sums of £3498 on cefepime, £2832 on piperacillin-tazobactam and £7049 on meropenem, totalling £13 379 over the 6 months of the study. Only part of this sum could have been saved, as more appropriate therapy with alternative agents would have been less costly but certainly not negligible. However, as fewer courses of these broad-spectrum agents are prescribed, selective pressure may be less severe, possibly with slower emergence of drug-resistant organisms.

Table 3 shows the use of the three study drugs, in addition to intravenous ciprofloxacin and ceftazidime, during the study periods, as well during comparable periods in the year before and the year following the present study. There has been a decrease in use of ciprofloxacin over these years, as a result of diminishing susceptibility of Enterobacteriaceae and particularly Pseudomonas to this agent.9,25,26 Ceftazidime has been removed from the hospital’s formulary during 2002, on account of its potential for induction of extended spectrum beta-lactamases in Enterobacteriaceae. As a result, there has been a significant increase in cefepime use. Nonetheless, there appears to have been a modest reduction in overall use of broad-spectrum agents, expressed in DDDs per 1000 hospitalization days and per 1000 admissions.

Table 4 shows the susceptibility rates of all strains of Enterobacteriaceae and Pseudomonas isolated during the study phases and comparable periods in the years before and after the study. The number of depicted isolates increased artificially between 2000 and 2002: in 2000 only blood culture results were computerized, while during the subsequent years results from other culture specimens were increasingly computerized as well. There appears

Figure 1. Distribution of drug therapy between the two study phases. *The difference between the two phases was not significant for all parameters. **The difference between empirical treatment and treatment based on culture results was significant in both phases (p<0.001). ***This aspect was not examined in phase 2.
to be a slow decline in susceptibility rates of Enterobacteriaceae to ceftazidime and cefepime, and a similar decline in Pseudomonas susceptibility to ciprofloxacin, although not to advanced generation cephalosporins.

**Discussion**

This study was conducted in order to evaluate and improve the rate of appropriate use of cefepime, piperacillin-tazobactam and meropenem, three of the broadest-spectrum antibiotics. Together, these agents consume a significant proportion of most hospitals’ outlay on antimicrobial agents, although they constitute only a small percentage of drug use in terms of defined daily doses. Our methods consisted of the development and modification of practice guidelines, based on relevant literature and susceptibility data from organisms isolated from various clinical settings to guide physicians regarding optimal use of these antibiotics, and the conduct of two 3-month drug utilization surveys, with an educational effort in between.

The principal findings of our study were as follows. First, the appropriateness rates for cefepime, piperacillin-tazobactam and meropenem were...
relatively high (86%). Treatment was continued for \(\geq 5\) days in 60% of cases, of which the majority was deemed appropriate. Second, most antibiotic courses were empirical and only a minority (22%) were based on a relevant culture result; the rate of appropriateness of empiric treatment was significantly lower than that of treatment based on a relevant culture results. Third, the rate of appropriate treatment differed significantly among the departments and between the two phases. The major difference between the two surveys was a decrease in meropenem usage, while an opposite trend occurred with cefepime use. Over the years subsequent to the study, the use of meropenem and piperacillin-tazobactam has decreased, while that of cefepime has increased; part of this increase can be explained by the concomitant decrease in ciprofloxacin use as well as phasing out of ceftazidime (Table 3). Finally, an infectious disease consultation was recorded in about one third of the cases only; this is remarkable, because use of these drugs in our institution, like in most others, requires prior approval by an infectious disease consultant. Some of these prior authorizations may have not been recorded in the patients’ files. However, it appears that a sizeable percentage of use of these agents bypasses the formal route. Only a system of unit dosing (supplying every single dose of antibiotics directly from the pharmacy to the patient’s floor) would solve this issue, although requiring presence of pharmacists around the clock.

The problem of resistance to antibiotics is worldwide, but should be addressed locally in every medical centre.\(^6\)–\(^{17}\) Resistance is foremost a function of the extent of use: for most antimicrobials, the more they are prescribed, the higher the resistance rates.\(^30\) Generally, some 15–40% of antimicrobial drug use is inappropriate.\(^8\)–\(^9\),\(^31\) Although the key to appropriate use consists of education, most medical centres have instituted certain administrative measures with the dual purpose of cost control and reducing the rate of emergence of resistant organisms.\(^10\),\(^17\) These measures range from the simple (the requirement to obtain infectious disease approval prior to initiation or continuation of certain drugs) to the sophisticated (interactive computer programs for ordering these drugs, offering advice at various stages of the process).\(^15\),\(^32\) Appropriate selection of antibiotic treatment requires a thorough knowledge of various issues, including the most likely pathogens causing the patient’s infection (taking into account individual host factors), local susceptible patterns of these pathogens (which change over time), pharmacokinetic and pharmacodynamic properties of the relevant antimicrobials, possible drug interactions, hypersensitivity and adverse effects. Since this study, our hospital has introduced such a computer system, but it is abundantly clear that the input of infectious disease physicians, a clinical pharmacist and/or clinical microbiologist remains essential.

The majority (77%) of our broadest-spectrum antibiotic treatment was initiated empirically. As expected, the rate of appropriateness was significantly lower for empirically selected treatment than for that tailored according to relevant microbiology results. Importantly, the rate of continuation of drug treatment beyond 5 days, during which time laboratory results may be expected that often lead to adaptation of treatment, was similar for appropriately and inappropriately initiated courses (60%). Therefore, the rate of appropriateness of definite therapy (after 5 days) was considerably higher for those courses whose initiation was considered appropriate than for those whose initiation was considered inappropriate. Our data, although limited in scope, support the crucial role of the infectious disease consultant\(^13\),\(^34\) when antibiotic therapy is selected or adapted empirically, which is evidently the situation in the vast majority of the cases. If the selected spectrum of treatment is too narrow, complications may ensue, or worse. If treatment is too broad-spectrum, improving patients usually remain on the chosen regimen; if they do not respond, this may well lead to change to even broader spectrum agents. Both situations, with heavy use of broad-spectrum agents, will lead to emergence of multi-drug-resistant organisms, as well as significant expenses.

Our study has several limitations. The first concerns the guidelines for appropriate use of the broad-spectrum antimicrobials. Other teams of infectious disease physicians, pharmacists and/or clinical microbiologists would quite likely define appropriate use of these agents in similar, but not necessarily identical ways. Nonetheless, we believe that the basic approach to developing guidelines for appropriate use of these broadest-spectrum agents will be comparable with that elsewhere. Second, appropriateness was evaluated as adherence with these guidelines, rather than as an objective fact. This, however, is the case with most drug utilization evaluations. Third, in our drug utilization evaluation, we compared pre-intervention with post-intervention results, rather than with those of a simultaneous control group. Consequently, unvalueated confounding factors may have influenced the study results. However, long-term follow-up of these agents has shown an overall stability or even modest decrease in their use. Indeed, since publication of another study on antimicrobial usage in our hospital,\(^29\) we have recorded a modest but persistent
decrease in defined daily doses, both per 1000 admissions and per 1000 hospitalization days, as well as a modest decrease in expenditure on antimicrobials. This is particularly remarkable since the patient population in most hospitals and in ours as well, continues to increase in age and disease complexity. These patients often suffer from infections acquired in nursing homes or the hospital itself, secondary to multi-drug-resistant organisms, mandating use of broad-spectrum antimicrobials. We believe that an actively involved infectious disease team, ongoing educative efforts and up-to-date microbiology and pharmacy databases are at least partially responsible for these improvements.

In conclusion, we developed guidelines for use of three of the broadest-spectrum antimicrobial agents and conducted a drug utilization evaluation before and after an educational intervention. We believe that the presence of such guidelines, their widespread publication, ongoing education of hospital staff regarding their use, and continued need to obtain approval prior to prescribing these agents, are all necessary components in the effort to control spiralling expenditure on such agents, and the emergence of multi-drug-resistant organisms. We believe that infectious disease consultation should be mandatory prior to prescription of these broad-spectrum agents, as well as 3–5 days subsequently, when laboratory results and clinical changes could influence a change in antibiotic management.

Acknowledgements

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References

Appendix A: Guidelines for appropriateness of therapy with cefepime, piperacillin-tazobactam and meropenem

I. Initiation of treatment, based upon culture result

Treatment was initiated based upon susceptibility results of an organism isolated from a clinically relevant specimen. If so, check the following:

1. The organism was susceptible to cefepime, piperacillin-tazobactam or meropenem, but not to a narrower-spectrum antimicrobial.
2. The organism was not susceptible to an aminoglycoside, or, if susceptible to an aminoglycoside, either the creatinine clearance (CrCl) was ≤ 30 ml/min, or the CrCl was >30 ml/min but the associated infection was purulent, e.g. pneumonia or intra-abdominal.
3. The organism was isolated from a clinically relevant specimen, including:
   a. Blood or cerebrospinal fluid.
   b. If isolated from synovial, pleural or peritoneal fluid, or from a removed foreign body (e.g. heart valve, joint, goretex graft), there has to be clinical evidence of infection that cannot be easily ascribed to another source.
   c. If isolated from sputum, a Gram stain has to show a paucity of epithelial cells (<10 per HPF), an abundance of leukocytes (>20 per HPF) and there has to be clinical evidence of infection, e.g. pneumonia by chest radiogram.
   d. If isolated from the tip of a removed intravascular device, rolled on an agar plate, there have to be more than 15 CFUs and there has to be clinical evidence of infection that cannot be ascribed easily to another source.
   e. If isolated from a urine culture, the urinalysis shows > 2 + leukocytes and/or > nitrates and/or there is clinical evidence of an urinary tract infection that cannot be ascribed easily o another source.
4. An infectious disease consultant recommended the particular agent, even if the patient’s condition deviated from the abovementioned definitions.

Treatment is considered justified if the following criteria were met: 1 AND 2 AND at least one parameter of 3(a–e); OR 4.

II. Initiation of empirically selected treatment

1. Infection was acquired in the hospital.
2. The CrCl was ≤ 30 ml/min OR the CrCl was >30 ml/min (in which case treatment should include an aminoglycoside), but the associated infection was purulent, e.g. pneumonia or intra-abdominal.
3. Patient was previously treated with ciprofloxacin or ceftazidime without clinical response, or there was substantial reason to believe that the causative organism would be resistant to the latter agents.

4. In case of empirical meropenem treatment: considered appropriate only in intensive care units or equivalent patients in regular wards, i.e., immuno-compromised patients, patients on ventilators, etc.

5. An infectious disease consultant recommended the particular agent, even if the patient’s condition deviated from the abovementioned definitions.

Treatment is considered justified if the following criteria were met: 1 AND 2 AND 3 AND 4 (in case of meropenem treatment); OR 5.

III. Continuation of treatment ≥ 5 days, based upon a culture result

As section I.

IV. Continuation of empirically selected treatment ≥ 5 days

1–4. As section II.

5. There was significant clinical improvement according to the patient’s physician, defined as improvement of at least two of the following parameters:

a. Successful reduction in dosage of vaso-pressor drugs.

b. Improvement in arterial blood gases, or successful partial-complete weaning from a respirator.

c. A decrease of at least 1°C if there had been fever, or an increase of at least 1°C if there had been hypothermia.

d. A decrease of >15% if there had been leukocytosis or increase of 15% if there had been leukopenia.

e. Improvement of blood acid-base abnormalities.

f. Improvement of renal abnormalities, such as uraemia or decreased urine output.

g. Improvement of a lung infiltrate on the chest radiogram.

6. An infectious disease consultant recommended the particular agent, even if the patient’s condition deviated from the above-mentioned definitions.

Treatment is considered justified if the following criteria were met: 1 AND 2 AND 3, AND 4 (in case of meropenem treatment), AND at least two parameters from 5(a–g); OR 6.