Original Article

EVALUATION OF THE APPROPRIATENESS OF INTRAVENOUS AMOXICILLIN/CLAVULANATE PRESCRIPTION IN A TEACHING HOSPITAL

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ABSTRACT

Background: Despite the implementation of strategies aiming at improving antimicrobial utilisation, inappropriate use remains an increasing problem with important consequences on both antibiotic resistance and hospital costs.

Objective: To evaluate the appropriateness of prescribing the intravenous amoxicillin/clavulanate combination (Augmentin®).

Methods: Prospective observational five-week study in a Belgian teaching hospital. Patients receiving prophylactic or therapeutic intravenous amoxicillin/clavulanate were enrolled. Data were collected by a pharmacist and the appropriateness of antibiotic treatment was analysed in collaboration with an infectious disease specialist according to local recommendations. The primary outcome measure was the appropriateness of indication, dosage, intravenous to oral switch and duration of therapy.

Results: One hundred and six patients were evaluated. The most common indications for amoxicillin/clavulanate prescriptions were: respiratory tract infections (38%), surgical/interventional prophylaxis (28%) and intra-abdominal infections (11%). Overall, 43% of intravenous amoxicillin/clavulanate prescriptions were fully appropriate. Indication for use was appropriate in 87% and dosage in 74% of cases. In contrast, the timing of intravenous to oral switch and duration of therapy were inappropriate in 64% and 53% of cases, respectively.

Conclusions: This study identified two main areas for improving amoxicillin/clavulanate prescribing: (1) the intravenous to oral switch, which is often too late or non-existent and (2) the duration of therapy, which is too long particularly in respiratory tract infections. The results have been presented to clinicians and specific interventions for optimisation are being discussed and implemented.

Key words: Anti-Bacterial Agents; Amoxicillin-Potassium Clavulanate Combination; Drug Utilization; Prospective Study; Pharmacy Service, Hospital

INTRODUCTION

Antibiotics represent an important proportion of the medications used in the acute care setting. Unfortunately, despite the development of practice guidelines, inappropriate use remains frequent and contributes to antibiotic resistance and substantial costs (1-4).

To optimise antibiotic use, several types of initiatives have been developed and promoted worldwide, including involving infectious disease (ID) specialists and antimicrobial stewardship programs. Since 2008, each Belgian hospital has had to set up a multidisciplinary antibiotic working group. Its missions are, for example, to write local recommendations on the appropriate use of antibiotics, to follow antibiotic consumption profiles and inform about the costs, to implement initiatives aiming at decreasing excessive consumption and to develop a resistance surveillance system (5).

Pharmacists also play an important role in this optimisation process. They are often involved in antibiotic working groups and share responsibilities for a number of activities. In addition, clinical pharmacists caring for individual patients can also substantially contribute to better antibiotic prescribing and to some extent to cost savings (6).

The combination of amoxicillin/clavulanate (Augmentin®) was initially developed to broaden the spectrum of amoxicillin and therefore cover β-lactamase-producing pathogens, such as *H. influenzae* or *E. coli* (7). The European guidelines for clinical practices recommend its empirical use for patients admitted to hospital with moderate to severe exacerbations of chronic obstructive pulmonary disease (COPD) or with moderate community-acquired pneumonia (CAP) (8). It is often the first choice antibiotic in the treatment of many intra-abdominal infections and sometimes in urinary tract

infections as well as skin and soft tissue infections (9). Amoxicillin/clavulanate is also indicated as a prophylactic agent for surgical site infections (10). According to the ESAC Point Prevalence Survey, a European multicentre survey of antimicrobial prescriptions in hospitals, this combination was the most commonly prescribed therapy in 2008 (11). It is also the most frequently used antibiotic in our hospital, representing about 17% of the total antibiotic consumption in 2008.

Despite its high consumption, ID specialists in our institution have no specific control over intravenous (IV) amoxicillin/clavulanate prescription (as opposed to other broad spectrum antibiotics). The present study was therefore undertaken to evaluate the appropriateness of prescribing IV amoxicillin/clavulanate. The primary objective was to evaluate the appropriateness with regard to four parameters: indication for use (prophylaxis and treatment included), dosage, timing of intravenous to oral (PO) switch and duration of therapy, according to local recommendations. The secondary objective was to calculate the potential annual savings for the hospital if this antibiotic had been correctly prescribed in three specific respiratory infections (CAP of subgroup III, bacterial bronchitis and acute exacerbation of COPD).

MATERIALS AND METHODS

Setting and design

This prospective, observational study was conducted at Mont-Godinne teaching hospital (a 450-bed institution) in Belgium, over a five-week period (March 23, 2009 – April 24, 2009). The protocol was previously approved by the local Ethics Committee.

Local recommendations for the management of the most common infectious diseases are available to all hospital physicians through the intranet. They have been elaborated by the infectious disease specialists and the microbiologist of the institution in collaboration with pharmacists. Physicians from each medical/surgical specialty were consulted and the antibiotic working group finally approved them. They provide information on the choice and dosage of antibiotics as well as duration of therapy. No specific recommendations are made on the timing to switch to oral therapy except in the general introduction.

Study population

All hospitalised patients receiving IV amoxicillin/clavulanate 1 g/200 mg or 2 g/200 mg during the study period in the selected care units were included. The participating units were: pneumology, digestive surgery, gastroenterology, haematology, oncology, ear-nose-throat ward, internal medicine, geriatrics, urology, neurology-neurosurgery, cardiology, orthopaedic surgery, thoracic/cardiovascular surgery, psychiatry and the rehabilitation ward. Exclusion criteria included patients admitted in the paediatric department (use of IV amoxicillin/clavulanate 500 mg/50 mg), patients in intensive care unit (ICU) due to organisational limitations and patients receiving IV amoxicillin/clavulanate for allergy testing (usefulness of this group probably very limited).

Data collection

Each morning, a clinical pharmacist (CA) identified the hospitalised patients receiving IV amoxicillin/clavulanate through the prescription orders. Then, the clinical pharmacist collected relevant data from computerised patient's file and from the patient's drug record on the ward. All data were entered on a patient-specific form. Data collected included: age, sex, body weight, height, care unit, responsible doctor's name, date and number of admission, duration of hospital stay, baseline serum creatinine, use of antibiotics over the preceding month, indication for which IV amoxicillin/clavulanate was prescribed, dose and interval, microbiological data and modifications in antimicrobial management (if applicable). In addition, the clinical pharmacist followed on a daily basis the parameters used for evaluating the opportunity for IV to PO switch (temperature, C-reactive protein and leukocytes, oxygen pressure, blood pressure, other oral medications taken, impairment of gastrointestinal absorption). The pharmacist also visited patients to evaluate their clinical status and check whether they were able to take oral medications. If the pharmacist was uncertain about the patient's ability to take oral medications, the patient's nurse was consulted. The computerised medical record and the interaction with the staff allowed the investigators to obtain all requested information. Each patient was followed until prescription of amoxicillin/clavulanate was discontinued.

Primary outcome measures

The appropriateness of amoxicillin/clavulanate prescriptions was evaluated at a weekly meeting with an ID specialist. Each parameter (indication for use, dosage, timing of IV to PO switch and duration of therapy) was rated as appropriate/inappropriate/debatable (i.e. subject to discussion, for example in case of an infection not well-defined clinically but with other inflammatory parameters, or in specific situations not addressed in the local recommendations)/not applicable (e.g. the timing of IV to PO switch was rated as not applicable if only a single dose was needed) or not defined (e.g. if some information as dosage or duration of treatment were lacking). The ratings of appropriateness regarding indications for use, dosages and durations of therapy were evaluated according to local hospital antibiotic guidelines. As for the IV to PO switch, the criteria were drawn from the literature. Inclusion criteria encompassed: evidence of clinical improvement, temperature $< 38°C$ for at least 24h, C-Reactive Protein and white blood cell count normalised or decreasing, no signs of malabsorption, oral fluid/food tolerance and ability to take oral medication. Exclusion criteria were severe sepsis, vomiting, severe diarrhea, presence of a swallowing disorder or infection requiring IV administration (e.g. osteomyelitis, deep abscess) (12-14). Table 1 describes local guidelines for the main indications of amoxicillin/clavulanate.

Secondary outcome measures

The unnecessary/excessive intravenous and oral treatments over the five-week period were estimated for three respiratory tract infections. Only those infections for which the use of (IV) amoxicillin/clavulanate was appropriate were considered. The three respiratory tract infections chosen were: CAP of subgroup III (= hospitalised patient but not in ICU), bacterial bronchitis and acute exacerbation of COPD. These infections were selected because they represented the majority of evaluated infections. When not clearly mentioned in the local guidelines, the timing of IV to PO switch and duration of therapy were decided by consensus among the investigators based on existing literature.

Table 1: Local guidelines for the main indications of amoxicillin/clavulanate in the study

Type of infection	Local recommendations[a]		
	Antibiotic(s) and dosage(s)[b]	IV to PO switch	Duration
Community-acquired pneumonia (CAP) subgroup III (hospitalised patient)	**amoxicillin/clavulanate** IV 2gm q8h or cefuroxime IV 1.5gm q8h *IgE mediated allergy to penicillins*: moxifloxacin IV or PO 400 mg q24h	IV to PO switch as soon as clinical status and fever improve	7 days
Acute bacterial bronchitis	Antibiotics not systematically indicated[c]. If needed[d], see below.	NA	5 days
Exacerbation of COPD	**amoxicillin/clavulanate** PO 500-875 mg q8h or 2gm (sustained release) q12h *Non IgE mediated allergy to penicillins*: cefuroxime axetil PO 500 mg q8h *IgE mediated allergy to penicillins*: moxifloxacin PO 400 mg q24h or TMP-SMX PO 160-800 mg q12h	No particular recommendation	5-7 days
Community-acquired angiocholitis	**amoxicillin/clavulanate** IV 2gm q8h or cefuroxime IV 1.5gm q8h + metronidazole IV 1.5gm q24h (+ aminoglycosides) *IgE mediated allergy to penicillins*: ciprofloxacin IV 400 mg q12h + metronidazole IV 1.5gm q24h	No particular recommendation	7 days if bacteriemia, max 24h if drainage
Community-acquired diverticulitis or cholecystitis	**amoxicillin/clavulanate** IV 2gm q8h or cefuroxime IV 1.5gm q8h + metronidazole IV 1.5gm q24h *IgE mediated allergy to penicillins*: ciprofloxacin IV 400 mg q12h + metronidazole IV 1.5gm q24h	No particular recommendation	7-10 days in patients conservatively treated After surgery: 24h without perforation, 3-5 days with perforation
Prophylaxis, ENT surgery (extensive surgery with incision of oral, pharyngeal mucosa)	**amoxicillin/clavulanate** IV 2gm or cefazolin IV 2gm *IgE mediated allergy to penicillins*: clindamycin IV 600 mg	NA	1 initial dose (if necessary, 1 dose IV 8h and 16h after initial dose)
Prophylaxis, digestive surgery (biliary/lower gastrointestinal surgery)	**amoxicillin/clavulanate** IV 2gm *IgE mediated allergy to penicillins*: ciprofloxacin IV 400 mg + metronidazole IV 1.5gm	NA	1 initial dose (if necessary, 1 dose IV 8h and 16h after initial dose)

COPD = Chronic Obstructive Pulmonary Disease; TMP-SMX = Trimethoprim-sulfamethoxazole; NA = not applicable; ENT = ear-nose-throat.
[a] The major sources of these recommendations were *The Sanford Guide to Antimicrobial Therapy,* recent international literature and local epidemiologic data.
[b] Dosage of amoxicillin/clavulanate refers to amoxicillin.
[c] No indication of antibiotic treatment in immunocompetent adults without complicating comorbid conditions.
[d] e.g.: in case of postoperative bronchial obstruction.

The potential savings for the hospital were evaluated. Cost savings were calculated as the difference between the cost of the prescribed treatment and the cost if the recommendations had been applied. For CAP of subgroup III, the savings were calculated assuming that the best (and maximal) treatment was 3 days by intravenous route and 4 days by oral route (15, 16). For exacerbation of COPD, intravenous antibiotic was allowed for 2 days, followed by 3 days of oral antibiotics. For the treatment of bacterial bronchitis, intravenous route being unnecessary, the cost of the recommended treatment corresponded to an oral treatment of 5 days of amoxicillin/clavulanate. The Belgian official hospital costs were used: IV amoxicillin/clavulanate 1 g/200 mg= 3.01€; IV amoxicillin/clavulanate 2 g/200 mg = 4.06€; amoxicillin/clavulanate tablet 500 mg/125 mg = 0.26€; amoxicillin/clavulanate tablet 875 mg/125 mg = 0.70€; amoxicillin/clavulanate tablet 1 g/62.5 mg = 0.37€. Annual (52-week) savings were finally extrapolated from the 5-week calculated savings.

RESULTS

During the study period, IV amoxicillin/clavulanate was prescribed in 13 care units (there was no prescription from psychiatric and rehabilitation wards). A total of 158 patients were identified, but 20 were excluded (based on exclusion criteria) and an additional 32 could not be evaluated (because of lack of information or still in progress when the study stopped). The mean age of the 106 remaining patients was 65 years (range 6-88 years). The most frequent indications were respiratory tract infections (38%), surgical/interventional prophylaxis (28%) and intra-abdominal infections (11%). Details are provided in Table 2.

The evaluation of prescribing shows that 43.3% (n = 46) of prescriptions had appropriate ratings for the four criteria (indication for use, dosage, timing of IV to PO switch and duration of therapy). Looking at each criterion separately, inappropriateness was more frequent for both the duration and IV to PO switch (Table 3).

Table 2: Indications for prescribing intravenous amoxicillin/clavulanate

Indication	n (%)
Respiratory tract infections	40 (37.7)
– Community-acquired pneumonia	23 (21.7)
– Bronchitis	9 (8.5)
– Exacerbation of COPD	6 (5.7)
– Pulmonary abscess	2 (1.9)
Prophylaxis (surgical/interventional)	30 (28.3)
Intra-abdominal infections[a]	12 (11.3)
Urinary tract infections	5 (4.7)
Soft tissue infections	2 (1.9)
Unclear infections[b]	6 (5.7)
Others[c]	11 (10.4)
TOTAL	**106 (100)**

COPD = Chronic Obstructive Pulmonary Disease.
[a] Intra-abdominal infections included different types of infections such as diverticulitis, peritonitis, appendicitis, angiocholitis, cholecystitis, abscess or infected cyst.
[b] Unclear infections encompassed unknown indications (therefore inappropriate or debatable).
[c] Others: septicemia, septic shock, pleural effusion, febrile neutropenia, complicated arytenoidectomy, infection of unknown/respiratory origin, unconfirmed infection.

Seventy-two percent (n = 76) of prescriptions were for treatment and 28% (n = 30) for prophylaxis. The prescriptions were fully appropriate for 37% and 60% of therapeutic and prophylactic cases, respectively.

The rates of appropriateness varied substantially depending on the care units in which patients were treated and per type of indication. In pneumology and oncology wards, where respiratory tract infections were the main reason for antibiotic therapy, the prescriptions were fully appropriate in only 18% and 36% of cases, respectively. As shown in Table 4, respiratory tract infections were also the most frequent infections inadequately treated by amoxicillin/clavulanate in the whole hospital. Regarding the duration, the treatment of CAP (subgroup III) lasted on average 10 days instead of the recommended 7 days. For exacerbations of COPD, the oral switch was usually performed after five days of parenteral therapy (instead of 2 days). As for surgical prophylaxis, the lowest percentage of fully appropriate prescriptions (0%) was seen in the ear-nose-throat ward (e.g. mean duration of 6 days instead of the recommended single dose and inappropriate IV to oral switch). In contrast, amoxicillin/clavulanate was adequately prescribed in the majority of other surgical wards (mainly in digestive surgery).

Among the 38 patients receiving amoxicillin/clavulanate for CAP, bacterial bronchitis and exacerbation of COPD, dosage and/or IV treatment and/or duration was excessive in 24 cases (63%). This represented a mean of 36.1€ lost per patient (difference between the cost of the treatment given and the cost if the recommendations had been applied). The treatments prescribed were on average twice as expensive as the recommended treatments. When these data were extrapolated on an annual basis, we found that the hospital could save around 9,000 Euro annually if the use of amoxicillin/clavulanate for respiratory tract infections was appropriate in terms of dosage, IV to PO switch and duration of therapy.

DISCUSSION

The present study shows that the indication for IV amoxicillin/clavulanate was appropriate in 87% of cases, and that the dosage was correct in 74% of cases. This contrasts with the results of appropriateness with regard to the timing of IV to PO switch and duration of therapy, as the prescriptions

Table 3: Appropriateness of prescribing intravenous amoxicillin/clavulanate (n = 106)

Criteria	Evaluation of appropriateness			
	Appropriate n (%)	Inappropriate n (%)	Debatable n (%)	NA or ND n (%)
Indication	85 (80.2)	14 (13.2)	7 (6.6)	0 (0)
Dosage	74 (69.8)	28 (26.4)	1 (0.9)	3 (2.8)
IV/PO switch (timing)	19 (17.9)	38 (35.8)	2 (1.9)	47 (44.3)
Duration of therapy	38 (35.8)	46 (43.4)	3 (2.8)	19 (17.9)

NA = not applicable; ND = not defined.

Table 4: Appropriateness of prescribing IV amoxicillin/clavulanate for the five most frequent indications

Indications (n patients)	Evaluation of appropriateness		
	All criteria appropriate, n (%)[a]	One inappropriate criterion, n (%)	≥ 2 inappropriate criteria, n (%)
Surgical prophylaxis (30)	18 (60)	7 (23)	5 (17)
Community-acquired pneumonia (23)	5 (22)	6 (26)	12 (52)
Bronchitis (9)	2 (22)	3 (33)	4 (44)
Exacerbation of COPD (6)	1 (17)	1 (17)	4 (67)
Urinary tract infections (5)	2 (40)	2 (40)	1 (20)

COPD = Chronic Obstructive Pulmonary Disease.
[a] The ratings "debatable", "not applicable" and "not defined" were considered as being "appropriate".

were appropriate in only 36% and 47% of cases, respectively.

There were three main situations of inappropriate indication. Firstly, patients who had already received oral amoxicillin/clavulanate or a broader spectrum antibiotic for several days just before admission should have received an antibiotic with broader spectrum. Secondly, patients with risk factors (e.g. known colonisation, multiple antibiotherapies within the 3 months, chronic corticosteroid therapy) for infections due to *Pseudomonas aeruginosa* (or other more resistant Gram-negative bacteria) should have received an anti-pseudomonas antibiotic instead of amoxicillin/clavulanate. These two situations, despite being clearly explained in the local recommendations, are relevant findings given that inadequate treatments contribute to poor patient outcomes. The third situation involved patients with no/unclear indications for antibiotic therapy.

The main reason for inappropriateness of dosage was the lack of adjustment to renal function in older patients. However, the local guidelines recommend that the daily dosage of amoxicillin/clavulanate must be adjusted in patients with moderate (creatinine clearance 10-50 ml/min) and severe (creatinine clearance < 10 ml/min) renal dysfunction.

In the vast majority of cases where applicable, the IV to PO switch was made too late and was sometimes nonexistent. This may be due to the assumption that the intravenous route is more effective, despite the lack of evidence to support this idea (specific situations excluded), or perhaps to the higher convenience of the intravenous administration in some cases. The fact that there are no written guidelines on this topic in the local recommendations could also be an explanation for the low rate of appropriate switch.

As for the total duration of treatment, this was often found to be too long, exposing the patient to adverse drug reactions, resistant pathogens and increased costs.

The figure of potential annual savings for the hospital is probably underestimated since the study was not conducted during the peak incidence period of respiratory tract infections. In addition, administration costs (material and excess workload), costs related to prolonged length of stay and to the treatment of adverse drug events (e.g. IV-line infections, hepatic dysfunction) were not included in these costs. Whatever, substantial savings could already be realised if clinicians would give oral antibiotics at an earlier stage in the patient's treatment, avoid unnecessary prolonged antimicrobial therapies and adjust dosage to the patient's renal function.

The literature is replete with studies evaluating the appropriateness of prescribing antibiotics in hospitals (2, 17, 18). Hogerzeil reported rates of inappropriate antibiotic use as high as 41% to 91% in teaching hospitals (19). A recent study found that 57% of the prescriptions were inappropriate regarding the choice of antibiotic, the indication for use, the route of administration and the duration of treatment (20). In addition, a retrospective analysis of 108 IV amoxicillin/clavulanate prescriptions in another Belgian hospital found rates of inappropriateness very similar to the rates reported in the present study (A. Libois personal communication). In that study, there was indeed at least one inappropriate rating (with regard to indication, intravenous duration and total duration) in 51% of prescriptions. Total duration was too long in 42% of cases and doses were inappropriate in 11% of cases.

Several strategies have been described to optimise antibiotic use. Multifaceted interventions seem to be more effective than single interventions (21). Therefore, after providing feedback of the present study to all prescribers, the following approaches for optimisation are being successively implemented and/or discussed: (a) distribution of the local guidelines in booklet form to improve availability of information; (b) addition of a checklist of criteria for switching from intravenous to oral antibiotics; (c) face-to-face meetings or creating a newsletter reminding clinicians of the recommendations for dosage adjustments of IV amoxicillin/clavulanate; (d) proactive decision support system through computerised prescribing order entry (e.g. warnings concerning dosage and duration of therapy, proposition of IV to PO switch); (e) closer collaboration between clinical pharmacists and ID specialists; and, (f) regular audit and feedback. All these interventions have already demonstrated effectiveness in improving antibiotic use (22-28). However a follow-up evaluation, similar in design to this study, should ideally be conducted to assess the impact of these initiatives.

The present study has several limitations. The number of patients included was small and the study took place in a single centre over a short period compared to other observational studies (29, 30). Despite this, our results compare very well with the results of another Belgian study. Intensive care and paediatric units were not included, but the prescriptions of IV amoxicillin/clavulanate on these wards represented only 10% of prescriptions (n = 16). Importantly, the impact of (in) appropriateness on clinical outcomes, such as number of therapeutic failures/cures, rate of adverse drug events, duration of hospital stay, readmission or mortality, was not evaluated. It is probable that the study would have been insufficiently powered to demonstrate significant differences.

Despite these limitations, this study has several strengths. Firstly, it was a prospective cohort, and this design is more robust than retrospective or cross-sectional studies that are frequently conducted on that topic (31, 32). Secondly, detailed and in-depth evaluations were performed. Four criteria of appropriateness were evaluated, while the majority of studies usually assessed only two or three criteria or do not give the results regarding each criterion (20, 23, 33). In addition, many different biochemical/clinical parameters were followed on a daily basis and the pharmacist had contact with the patients to assess their current clinical status and collect some information that could not be found in the patient's files. It is unlikely that the presence of the clinical pharmacist on the ward would have been a significant confounding factor since her presence was very limited, discrete and without any intervention. Thirdly, both therapeutic and prophylactic prescriptions were evaluated. Finally, to maximise the validity of ratings of appropriateness, the clinical pharmacist closely collaborated with the ID specialists, and, if necessary, with nurses and clinicians caring for the patient.

In conclusion, there is room for improvement in the prescription of amoxicillin/clavulanate in our institution. The IV to PO switch and duration of treatment appear to be the parameters that need more specific attention. Multifaceted interventions focusing on these issues could potentially reduce the incidence of antimicrobial resistant pathogens, generate substantial savings and contribute to improvements in patient safety. An evaluation study will be conducted in the

near future to assess the impact of the aforementioned actions.

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REFERENCES

1. Goossens H. Antibiotic consumption and link to resistance. *Clin Microbiol Infect* 2009; 15 Suppl 3: 12-15.
2. van der Meer JW, Gyssens IC. Quality of antimicrobial drug prescription in hospital. *Clin Microbiol Infect* 2001; 7 Suppl 6: 12-15.
3. Paladino JA, Adelman MH, Schentag JJ, Iannini PB. Direct costs in patients hospitalised with community-acquired pneumonia after non-response to outpatient treatment with macrolide antibacterials in the US. *Pharmacoeconomics* 2007; 25: 677-683.
4. Gutierrez Zufiaurre MN, Garcia-Rodriguez JA. National multicenter survey: the use of intravenous antimicrobial agents. *Rev Esp Quimioter* 2006; 19: 349-356.
5. *Royal Decree of February 12, 2008 laying down the standards which a hospital pharmacy must meet in order to be approved.* Available at: http://www.ejustice.just.fgov.be/cgi/api2.pl?lg = fr&pd = 2008-03-28&numac = 2008024120 (accessed 15 December 2010).
6. von Gunten V, Reymond JP, Beney J. Clinical and economic outcomes of pharmaceutical services related to antibiotic use: a literature review. *Pharm World Sci* 2007; 29: 146-163.
7. Todd PA, Benfield P. Amoxicillin/clavulanic acid. An update of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1990; 39: 264-307.
8. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138-1180.
9. Sanford JP, Gilbert DN, Moellering RC, Sande MA, Eliopoulos GM. *The Sanford Guide to Antimicrobial Therapy.* Sperryville: Antimicrobial Therapy Inc. 2009: 2-78.
10. Wilson AP, Shrimpton S, Jaderberg M. A meta-analysis of the use of amoxycillin-clavulanic acid in surgical prophylaxis. *J Hosp Infect* 1992; 22 Suppl A: 9-21.
11. Zarb P, Amadeo B, Muller A, et al. Identification of targets for quality improvement in antimicrobial prescribing: the web-based ESAC Point Prevalence Survey 2009. *J Antimicrob Chemother* 2010.
12. McLaughlin CM, Bodasing N, Boyter AC, Fenelon C, Fox JG, Seaton RA. Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: an intervention study. *QJM* 2005; 98: 745-752.
13. Sevinc F, Prins JM, Koopmans RP, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. *J Antimicrob Chemother* 1999; 43: 601-606.
14. *Guideline for the intravenous to oral switch of antibiotic therapy.* Available at: http://www.nuh.nhs.uk/nch/antibiotics/Full%20Guidelines/iv%20switch%20policyupdate%20dec08_final.pdf (accessed 6 December 2008).
15. Athanassa Z, Makris G, Dimopoulos G, Falagas ME. Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. *Drugs* 2008; 68: 2469-2481.
16. Oosterheert JJ, Bonten MJ, Schneider MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ* 2006; 333: 1193.
17. Seaton RA, Nathwani D, Burton P, et al. Point prevalence survey of antibiotic use in Scottish hospitals utilising the Glasgow Antimicrobial Audit Tool (GAAT). *Int J Antimicrob Agents* 2007; 29: 693-699.
18. Redding PJ, Taylor A, Smith AM. Audit on the use of prophylactic parenteral antimicrobial agents and the use of co-amoxiclav and metronidazole. *Health Bull (Edinb)* 1996; 54: 499-504.
19. Hogerzeil HV. Promoting rational prescribing: an international perspective. *Br J Clin Pharmacol* 1995; 39: 1-6.
20. Kisuule F, Wright S, Barreto J, Zenilman J. Improving antibiotic utilization among hospitalists: a pilot academic detailing project with a public health approach. *J Hosp Med* 2008; 3: 64-70.
21. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group. *BMJ* 1998; 317: 465-468.
22. Briquet C, D'Hoore W, Bisot-Locard S, Simon A, Tilleul P. Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: a prospective study in a teaching hospital. Presented at ISPOR 11th Annual european congress in Athens (Greece), 8-11 November 2008.
23. Vogtlander NP, Van Kasteren ME, Natsch S, Kullberg BJ, Hekster YA, Van Der Meer JW. Improving the process of antibiotic therapy in daily practice: interventions to optimize timing, dosage adjustment to renal function, and switch therapy. *Arch Intern Med* 2004; 164: 1206-1212.
24. Thursky K. Use of computerized decision support systems to improve antibiotic prescribing. *Expert Rev Anti Infect Ther* 2006; 4: 491-507.
25. Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis* 2001; 33: 289-295.
26. Weller TM, Jamieson CE. The expanding role of the antibiotic pharmacist. *J Antimicrob Chemother* 2004; 54: 295-298.
27. Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2005; 4: CD003543.
28. Deuster S, Roten I, Muehlebach S. Implementation of treatment guidelines to support judicious use of antibiotic therapy. *J Clin Pharm Ther* 2010; 35, 71-78.
29. Raveh D, Levy Y, Schlesinger Y, Greenberg A, Rudensky B, Yinnon AM. Longitudinal surveillance of antibiotic use in the hospital. *QJM* 2001; 94: 141-152.
30. Parret T, Schneider R, Rime B, Saghafi L, Pannatier A, Francioli P. Evaluation of antibiotic use: a prospective study in a university hospital center. *Schweiz Med Wochenschr* 1993; 123: 403-413.
31. Tobia CC, Aspinall SL, Good CB, Fine MJ, Hanlon JT. Appropriateness of antibiotic prescribing in veterans with community-acquired pneumonia, sinusitis, or acute exacerbations of chronic bronchitis: a cross-sectional study. *Clin Ther* 2008; 30: 1135-1144.
32. Hadi U, Duerink DO, Lestari ES, et al. Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia. *Clin Microbiol Infect* 2008; 14: 698-707.
33. Vlahovic-Palcevski V, Dumpis U, Mitt P, et al. Benchmarking antimicrobial drug use at university hospitals in five European countries. *Clin Microbiol Infect* 2007; 13: 277-283.