Quality of antimicrobial drug prescription in hospital

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There is worldwide concern about the development of antimicrobial resistance [1]. Selective pressure by antimicrobial drugs is by far the most important driving force for the development of resistance. Antimicrobial drugs are among the most commonly prescribed drugs in hospitals. In developed countries, some 30% of the hospitalized patients will be treated with these drugs. It is generally accepted that antimicrobial prescribing is often suboptimal, even in a country like the Netherlands, where both antibiotic consumption and microbial resistance rates are low [2,3]. The major problem with inappropriate prescribing is because of insufficient education in infectious diseases and antimicrobial therapy. Often, the prescription of these drugs with little toxicity is unjustified because of insecurity about the diagnosis of the clinician; 'drugs of fear' [4]. In our surveys, some 15% of the antibiotic prescriptions in surgical and internal medicine wards were considered unjustified [5,6]. Many prescribers are not yet fully aware that their justified or unjustified prescription adds to the resistance problem. In this paper, aspects of the quality of antimicrobial prescribing in the hospital setting will be discussed.

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ASSESSMENT OF THE QUALITY OF ANTIMICROBIAL PRESCRIBING

For proper antimicrobial prescribing, ideally, the clinician should try to define the type of infection and the presumable causative micro-organism [4]. From surveys investigating antimicrobial prescribing, we know that clinicians rarely have a clear hypothesis on the causative microbe. In our experience with an antibiotic order form, which required the mentioning of a pathogen, the answer was left blank in 147 out of 550 cases (26.7%) [7]. Some years ago, we developed a flow chart to evaluate the quality of antimicrobial prescribing (Figure 1) [8]. This flow chart, which was adapted from the original criteria of Kunin *et al.* [4], allows the evaluation of all aspects of antimicrobial prescribing, as there are: justifications of the prescription, more effective alternatives, less toxic alternatives, less expensive alternatives and drugs with a narrower spectrum. In addition duration of treatment and dosing, including interval and route of administration, and finally timing, are taken into account. This flow chart is an important tool in the assessment of quality of antimicrobial drug utilization. It not only works to assess the proper use of antibacterial drugs [5,8], but also that of antifungal drugs like fluconazole [9]. It can be used for in-depth studies of antimicrobial prescribing in the hospital setting, and also for a training instrument for students and residents in medicine, microbiology and hospital pharmacy. With this flow chart, initial ('empiric') therapy can be judged, as well as 'definite' treatment, once the results of the microbiological investigations are known.

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STREAMLINING

Adjustment of the initial antimicrobial therapy based on the results of the microbiological laboratory and the clinical course is one of the most relevant steps in antimicrobial prescribing, since it clearly diminishes the selection pressure on the micro-organisms in hospital. This adaptation of treatment has originally been called 'streamlining' for economic reasons and for reduction of toxicity [10]. It comprises not only the change from a broad ('empiric') spectrum to a narrow (targeted) spectrum, but also from combination therapy (mainly with aminoglycosides) to single drug therapy and from newer to older drugs. One should add also the change from intravenous to oral therapy. Many prescribers tend to stick to the original therapy according to the motto 'never change a winning team', and it may take quite some effort on the part of

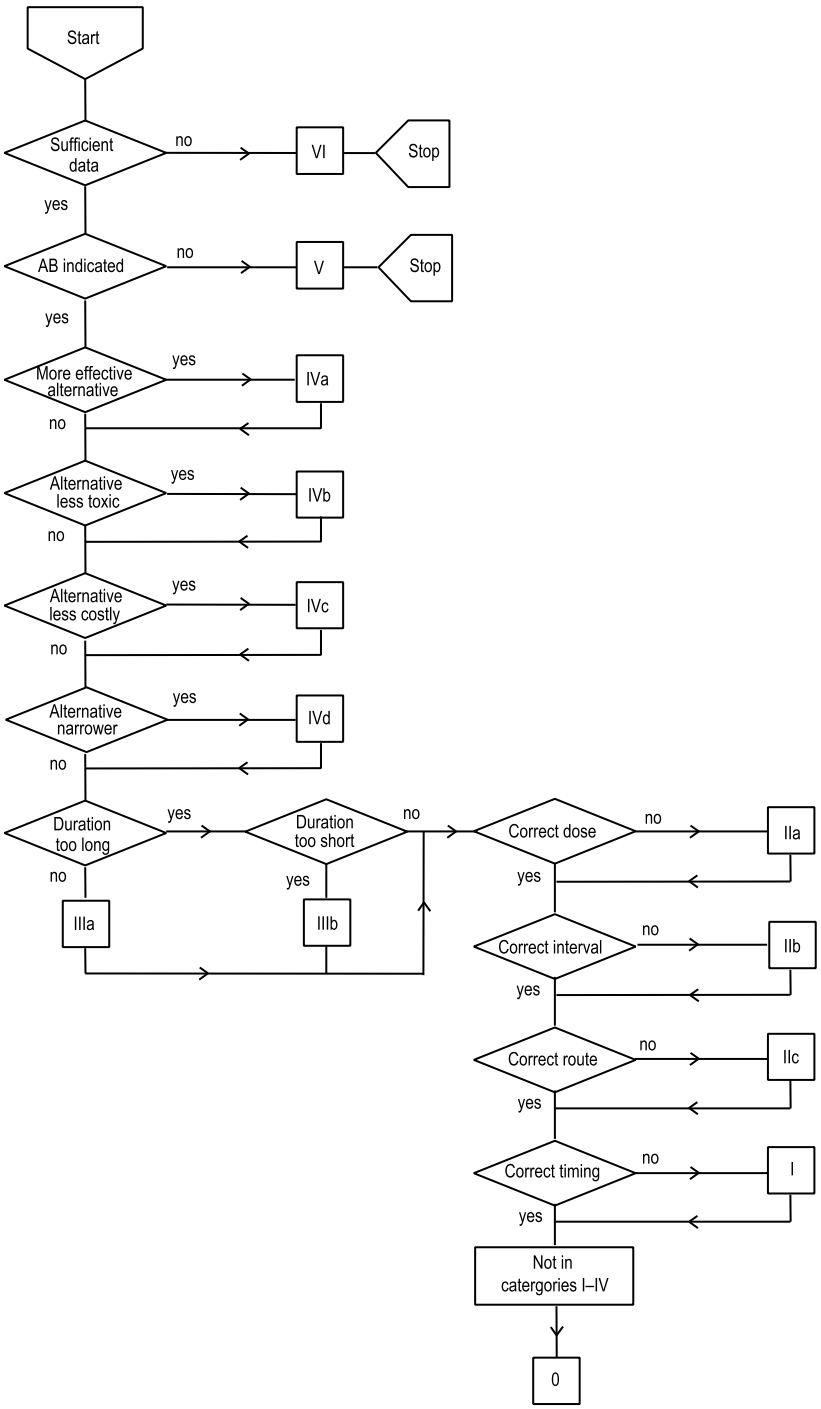

Figure 1 Flow chart for assessment of quality of antimicrobial drug prescription. (Adapted from [8].) An antibiotic prescription can be assessed as any of the numbers (0 through VI) or a combination.

the consulting infectious disease specialist or medical microbiologist to convince the doctor to streamline the therapy. Although the effect and feasibility of streamlining is hardly evidence-based, the collective experience in many centers strongly suggests that it is feasible, safe and effective.

Not only does streamlining limit the selection pressure, but it usually also results in cost containment. The switch to older drugs has the advantage that there is a large clinical experience with the drugs used. An additional advantage is that toxic drugs, such as aminoglycosides, may be given for no longer than a few days.

The early switch from intravenous to oral treatment, which has been shown to be feasible [11,12], also has obvious advantages; not only is the spectrum of the oral drugs usually more narrow, the switch prevents complications from the prolonged intravenous infusion (such as thrombophlebitis, bacteremia, fungemia) and it contains costs. A question which has not been solved is, whether the greater effect of oral antibiotics on the gastrointestinal flora is disadvantageous in terms of emergence of resistance in the long run.

An area in medicine where streamlining seems to be rarely practiced is hematology/oncology. Here, it is common practice to add antibiotics rather than to stop an initially started antibiotic, but modification with discontinuation of the initial choice has been done[13].

THE QUALITY OF EMPIRIC THERAPY

Adequate and timely streamlining does not imply that the choice of the initial antibiotic regimen does not matter. The initial treatment should aim at the most likely causative micro-organisms taking into consideration their antimicrobial susceptibility and resistance. In this respect, there is a great difference between community-acquired and nosocomial pathogens. Major pathogens for a patient with a community-acquired infection are pneumococci, streptococci, *Staphylococcus aureus*, meningococci, *Escherichia coli* and *Salmonella* species. Despite increasing resistance problems for micro-organisms such as pneumococci and *S. aureus*, the initial antibiotic regimen for community-acquired infections can still be different from those for nosocomial infection, i.e. the spectrum of the regimen can be less broad and the latest developed drugs are not needed.

Erroneously, many intensive-care physicians believe that severe community-acquired infections need treatment with third generation cephalosporins or carbapenems. Infectious disease specialists, medical microbiologists and hospital pharmacists may have a hard job changing such prescribing habits.

The relatively new recommendation to use levofloxacin for all cases of community-acquired pneumonia may be justifiable in the United States and some other areas of the world with resistant pneumococci (and a small risk of legionella and other 'atypical' pathogens) [14], but it should not be followed elsewhere. It is not difficult to imagine what will happen if all cases of suspected community-acquired pneumonia in the world are being treated with this quinolone. Thus, national guidelines for prudent use of antibiotics are necessary to guide the physician in daily practice.

THE TIMING OF ANTIMICROBIAL TREATMENT

For an optimal effect of antimicrobial drugs the timing of administration is of great importance. From our own research, as well as from the literature, we have learned that this is a topic of concern. One area where timing of administration has a great impact is in antibiotic prophylaxis in surgery. In two hospitals in the Netherlands, we found that the timing of administration of such prophylaxis is very inaccurate, ranging from several hours too early to several hours too late [15]. It is known from the literature that such inaccuracies are associated with an increase of wound infections [16]. By a series of interventions, the timing of administration of the perioperative prophylaxis could be greatly improved. One important solution for this problem was to make the anesthetist responsible for this medication [17].

A second area where there are problems is in the emergency room. Even for patients in need of urgent therapy, there may be a delay of several hours in administration of the first dose of antibiotic [6]. A median interval of 5 h was found from time of admission to administration of antibiotics. This problem of delayed initiation with antibiotics in acute infections is multifactorial. With guidelines handling patients with serious infections and for ordering immediate treatment, guidelines on obtaining culture samples, lectures to medical and nursing staff, improvement of availability of antibiotics in the emergency department, and removal of financial restraints on stocking and ordering of antibiotics, we were able to diminish the delay significantly [18].

DURATION OF TREATMENT

An area of considerable misunderstanding among practitioners and pharmacists is the duration of antibiotic treatment. Many pharmacists and doctors believe that a prolonged course of antibiotics is better than a short course in view of the emergence of resistant micro-organisms. This issue has been recently taken up by Lambert [19].

It is evident that any antibiotic treatment affects three populations of micro-organisms: i. the causative micro-organisms; ii. the endogenous microflora of the patient; iii. the environmental microflora. As a logical consequence, the duration of antibiotic treatment should be:

- long enough to combat the causative organism;
- short enough to spare the endogenous microflora of the patient;
- short enough to spare the environmental microflora.

There is little evidence in the literature about the duration of treatment necessary to combat the causative micro-organism. It is clear that the duration of treatment of infection has become shorter over the past years, and this is a favorable development with respect to emergence of resistant micro-organisms among the endogenous flora, as well as the environmental flora.

THE ROLE OF PHARMACEUTICAL INDUSTRY

Despite the availability of antibiotic formularies and guidelines, in which balanced advice is given to the prescribing doctor, the pharmaceutical industry tries to influence actual prescribing by promotional interventions. An example of apparently successful promotion is the increase in prescribing of amoxicillin-clavulanic acid in the Netherlands. The clinical efficacy of this antibiotic combination is poorly documented in the literature. Still, the drug has gained enormous popularity in the Netherlands, with a threefold rise in prescription in hospitals (from 4 ddd per 100 bed-days to 12 ddd per 100 bed-days between 19991 and 1996) [20].

A point of great concern is that innovation in the pharmaceutical industry has been largely directed towards the development of broad-spectrum drugs such as oral carbapenems, broad-spectrum macrolides and super quinolones. The question is whether such new drugs will solve the current clinical problems. First of all, treatment with such broad-spectrum drugs is likely to have drastic effects on the colonizing microflora, resulting in recolonization with resistant micro-organisms, such as fungi. As a consequence infections with such micro-organisms will occur. Secondly, the current resistance problems and threats are especially associated with Gram-positive micro-organisms (such as penicillin-resistant pneumococci, multi-resistant *Staphylococcus aureus* and epidermidis, vancomycin-resistant enterococci, multi-resistant mycobacteria), for which targeted drugs are urgently needed.

CHANGES IN PRESCRIBING BEHAVIOR

Given the growing problem of microbial resistance, antibiotic stewardship is what we would wish every prescriber to have. This means that we have an immense task in trying to change prescribing habits. This is of course most urgent in those countries with high antibiotic consumption and high resistance rates.

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