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DE-ESCALATION AND STREAMLINING OF ANTIMICROBIAL THERAPY

Inge C. GYSSENS

Department of Medicine, Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Radboud University Medical Centre, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, THE NETHERLANDS
inge_gyssens@skynet.be

Prolonged administration of a broad spectrum antibiotic has important ecologic consequences. A comparison of two empirical antibiotic policies with a different spectrum in a neonatal ward has demonstrated that the combination of cefotaxime with amoxicillin favoured the selection of resistant *Enterobacter* strains compared to a regimen with penicillin and tobramycin (De Man et al., 2000).

De-escalation in the ICU

The quality of empirical therapy in the ICU is largely determined by the availability of local surveillance data on microbial resistance and by the information that prescribers have on the local epidemiology of infections and the causative organisms. The microbiology laboratory plays a major role in the aggregation, analysis and reporting of surveillance data and provides a major contribution towards the choice of empiric therapy ("well educated guess"). Guidelines for empirical therapy that are based on this surveillance should be available in every ICU.

The incidence of sepsis has increased in the last years of the previous century, although the overall mortality rate among patients with sepsis has declined. From the available literature, it has become clear that it is important to start effective antibacterial therapy as soon as possible. The American Surviving Sepsis Campaign guidelines recommend starting antibacterial therapy within the first hour of presentation (Dellinger et al, 2008). Nevertheless, it is essential to have both blood cultures and cultures from suspected sites of infection taken before starting therapy in order to confirm the working diagnosis as well as to make de-escalation possible. De-escalation involves the practice of administering broad-spectrum empirical antibiotic therapy together with early reassessment and subsequent narrowing or discontinuation of therapy based on clinical improvement and the results of cultures and antibacterial susceptibility tests. The term has been created in intensive care medicine. In other settings this strategy is called "streamlining". The accessibility of microbiology laboratory facilities is crucial for the identification of a pathogen and determination of its susceptibility to facilitate and streamline a definitive therapy with a spectrum of action that is less broad than the blindly chosen empirical therapy. De-escalation should be pursued systematically as soon as possible in order to prevent resistance and unnecessary costs. When the patient is in stable condition, sequential therapy or step down therapy from parenteral to oral administration is preferable and allows for outpatient therapy (Eron et al., 2001). The decision to change or stop antibiotic therapy should be made at day two or three, at the time that culture data are available and when the clinical condition of patients who are likely to respond has improved. However, there is still no consensus on what exact criteria the decision to either change or stop antibiotic therapy should be made. For example, it is not clear when it is justified to assume that a particular isolated microorganism is a coloniser and not a pathogen or to stop antibiotic therapy, solely on the basis of a negative culture. The result of a culture depends on several factors such as previous antibiotic therapy, culture techniques and specific properties of the pathogen involved (Niederman, 2006;Lisboa et al, 2006). Therefore, the decision to discontinue therapy should be based on the combination of the lack of clinical evidence of infection together with negative culture results.

No prospective studies have been per-

formed to evaluate the safety and efficacy of de-escalation in patients with sepsis. Several prospective studies evaluating the outcome of de-escalation in patients with VAP showed that de-escalation is safe and effective (Leone et al, 2007; Lisboa et al, 2006; Micek et al, 2004). A prospective observational study was conducted in a medical-surgical intensive care unit during a 36-month period. To assess the rate of appropriateness of empirical antimicrobial therapy for VAP and to evaluate de-escalation in patients with ventilator-associated pneumonia treated according to local pathway, and to identify the bacteria responsible for recurrence of ventilator-associated pneumonia A limited-spectrum therapy was used in 79 patients (69 %). Empirical antimicrobial therapy was appropriate in 100 patients (85 %). The mortality rate was significantly higher in the patients in whom empirical therapy was inappropriate than in those in whom treatment was appropriate (47 vs. 20 %, p=.04). De-escalation was done in respectively 26 % and 72 % of patients with early- and late-onset ventilator- associated pneumonia, whereas treatment was escalated in 27 patients (23 %) (Leone *et al*, 2007).

Recent studies have shown that the duration of antimicrobial therapy of some infections can be shortened. In a French ICU, among patients who had received appropriate initial empirical therapy, with the possible exception of those developing nonfermentative Gram-negative bacilli infections, comparable clinical effectiveness against VAP was obtained with the 8 and 15 –day regimens. The 8-day group had less antibiotic use (Chastre, JAMA 2003).

Streamlining in hospital departments

Replacing an antibiotic by another antibiotic with a narrower spectrum but also active against the isolated microorganism is at present a strategy used by infectious disease consultants worldwide. The rationale is to avoid selective pressure caused by blind broad spectrum antimicrobial drug therapy. This strategy has not been well documented by prospective randomised studies.

In the Netherlands and Scandinavia, the tailored narrow spectrum definitive therapy with older drugs has been taught for years and «prudent prescribing» is the result (Van der Meer and Gyssens, 2001) (Røder et al., 1993) (Cars et al., 2001). A limited number of audits have been conducted to analyze whether streamlining was applied. In Maki and Schuna's study, continuation of definitive therapy with unnecessarily broad spectrum drugs was considered inappropriate in less than 10 %, by Wilkins et al. in less than 16 % (Wilkins *et al.*, 1991), and by Gyssens et al. in 4-7 % (Gyssens *et al.*, 1997). Overconsumption of broad spectrum drugs was frequent in patients with bacteremia in Israel (Elhanan *et al.*, 1997). In Belgium this amounted to 29 % of prescriptions for definitive therapy prescribed by clinicians lacking additional training in infectious diseases; for patients prescribed antibiotics by infectious diseases specialists this was still relatively high, i.e. 19 % (Byl *et al.*, 1999). The strategy of streamlining was applied more frequently for patients with ID consultation than for controls (Fluckiger *et al.*, 2000).

In conclusion, de-escalation may reduce the emergence of resistant bacteria, which in turns reduces the need for broad-spectrum antibiotics, breaking the vicious circle of antibiotic overuse and increasing resistance.

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