Amoxicillin/clavulanate (Augmentin®) resistant Escherichia coli in bacterial peritonitis after abdominal surgery – clinical outcome in ICU patients

M.S. Rahnama'i1*, J.H.T. Wagenvoort2, C.J. van der Linden1

Departments of 1Surgery and Intensive Care Medicine, and 2Medical Microbiology, Atrium Medical Centre, Parkstad, Heerlen, the Netherlands, *corresponding author: tel.: +31(0)43-387 72 56, fax: +31(0)43-387 52 59, e-mail: Sajjad_r@yahoo.com

ABSTRACT

Bacterial resistance to antimicrobial agents is of great concern to clinicians. Patient outcome after infection is mainly dependent on the sensitivity of the bacterium to the agent used.

We retrospectively studied 89 postoperative intensive care unit (ICU) patients with proven Escherichia coli peritonitis and investigated the clinical consequences of the E. coli resistance to amoxicillin/clavulanate. Significantly increased mortality, days of ventilation and ICU stay were noted in the co-amoxicillin/clavulanate resistant group. Furthermore, our results demonstrate that the sensitivity of E. coli to amoxicillin/clavulanate in the postoperative ICU setting has decreased in recent years. We can conclude that the current antibiotic regimen for the empirical treatment of ICU patients with peritonitis, as used in our hospital, needs to be changed. A switch, for instance, to ceftriaxone (Rocephin®) in combination with metronidazole and gentamicin, instead of the present regimen of amoxicillin/clavulanate in combination with gentamicin, seems preferable.

KEYWORDS

Abdominal surgery, amoxicillin/clavulanate, augmentin, clinical outcome, Escherichia coli, peritonitis, resistance

INTRODUCTION

In surgical practice, significant morbidity and mortality is caused by infection from resistant pathogens.1,4 Hospitals are considered to be very important for the containment of antimicrobial resistance.3,4 Resistant pathogens may cause infections that are associated with higher morbidity and mortality rates and increase medical costs. The prevalence of resistance to nearly all important micro-organism/antibiotic combinations is generally higher among isolates from patients hospitalised in intensive care units (ICU). Enterobacteriaceae have emerged as one of the major causes of infections and account for approximately 30% of all bloodstream infections. Antibiotic resistance surveillance programmes have demonstrated an increase in resistance among these gram-negative pathogens.5,6

MATERIAL AND METHODS

We retrospectively studied postoperative ICU patients and looked at the clinical consequences of Escherichia coli resistance to amoxicillin/clavulanate. The outcomes of ICU patients with severe bacterial peritonitis, empirically treated with a combination of gentamicin and amoxicillin/clavulanate, were collected. The patient charts of 89 consecutive postoperative ICU patients with peritonitis from whom E. coli was cultured between 2000 and 2005 were studied. The outcomes of ICU patients with severe bacterial peritonitis, empirically treated with a combination of gentamicin 5 mg/kg once daily and amoxicillin/clavulanate 1.2 g 4 times/day for five days, were collected. In the case of renal impairment dosage schedules were adjusted. The patients were divided into two groups: an E. coli amoxicillin/clavulanate resistant and a sensitive population according to the microbiologic cultures. The
number of days of admission in the ICU department, the number of ventilation days, the use of inotropic agents and the mortality rate of the patients were scored, together with APACHE scores. In order to determine the susceptibility of the aerobic gram-negative bacilli to the antimicrobial agent, the VITEK 2 Gram Negative Identification and Susceptibility Cards were used.\textsuperscript{1,6} The breakpoint for sensitivity of \textit{E. coli} was determined at a minimum inhibiting concentration (MIC) of ≤8 mg/ml in accordance with published standards.\textsuperscript{7-11} A MIC value of 16 mg/l was regarded as being of intermediate sensitivity and a value of ≥32 mg/l as being resistant. Rates of resistance in the hospital and the ICU were compared over the studied years. For statistical analyses, a $\chi^2$ test with a Yates correction was performed.

**RESULTS**

Table 1 shows the characteristics of the two populations studied. There are significant differences ($\chi^2$ with Yates correction; \textit{p}<0.05) between the two population groups with regard to stay in the ICU, mortality and ventilation days. Male patients showed a significantly higher prevalence of \textit{E. coli} resistance to the amoxicillin/clavulanate combination compared with female patients. The scored use of inotropic agents did not show a significant difference between the sensitive and the resistant group.

The APACHE scores of the two patient groups were comparable. This means that the difference in mortality between sensitive and resistant patients cannot be explained by their initial overall disease severity as estimated by the APACHE score.

The percentages of amoxicillin/clavulanate sensitive \textit{E. coli} strains isolated from patients in different settings are presented in table 2. The difference in \textit{E. coli} resistance between 2000 and 2005 was not significant in \textit{E. coli} strains cultured elsewhere in the hospital for either amoxicillin/clavulanate or ceftriaxone. In contrast, there was a significant difference ($\chi^2$ with Yates correction \textit{p}<0.05) between amoxicillin/clavulanate sensitive \textit{E. coli} strains on the ICU between 2000 and 2005. Moreover, in 2005, this was also true for \textit{E. coli} strains isolated in the hospital and the ICU, indicated with a cross in table 2.

In the years 2000 to 2005, the \textit{E. coli} strains were for 96% sensitive to the other administered antibiotic, gentamicin, in both treatment schedules. Resistance to both antibiotics occurred in none of the treated patients. Combined resistance to both antimicrobial agents of all \textit{E. coli} strains was altogether less than 1%.

**DISCUSSION**

For many years, methods have been sought to measure and define the absolute value of susceptibility of micro-organisms to antimicrobial agents. The value most often used is the minimal inhibitory concentration (MIC), although the minimum bactericidal concentration (MBC) has also been employed.\textsuperscript{9} Because MBC values are more time consuming to obtain, they are currently
Amoxicillin/clavulanate resistant *E. coli* is an underestimated problem in ICUs. In the protocol of many hospitals, amoxicillin/clavulanate is initiated empirically in patients with peritonitis. This combination is often used as its broad spectrum covers the anaerobe flora, including the prominently cultured *Bacteroides fragilis*. In our population, the mortality in the group of patients with amoxicillin/clavulanate resistant *E. coli* was found to be significantly higher than in the amoxicillin/clavulanate sensitive group. Days of stay in the ICU and ventilation days were also significantly longer. These outcomes may indicate that we have to alter the empirical antimicrobial therapy in postoperative peritonitis patients admitted to the ICU contrary to the SWAB (Stichting Werkgroep Antibiotica Beleid; in English: Working Party on Antibiotic Policy) guideline which lists amoxicillin/clavulanate as an option in the treatment of secondary bacterial peritonitis in the Netherlands (http://customid.duhs.duke.edu/NL/Main/Diagnosis.asp?DiagnosisID=140). When choosing ceftriaxone, the sensitivity percentages remain higher than 95% for the principal pathogen (*E. coli*) (table 2). Coverage for anaerobes can be secured by the addition of metronidazole.

It seems that the sensitivity percentage of *E. coli* has decreased in the last five years. This is particularly true for the ICU population in the hospital in our study. This may be explained by the increased amoxicillin/clavulanate prescription by family physicians. When resistance rates of a species approach the 10% threshold, the efficacy of that particular antimicrobial agent decreases. This was also the case for our specific group of ICU patients.

Considering the results of our study, we can conclude that the current antibiotic regimen for the empirical treatment of ICU patients with peritonitis, as used in our hospital, should be changed: a combination of, for instance, ceftriaxone, metronidazole and gentamicin instead of amoxicillin/clavulanate in combination with gentamicin seems preferable. We believe that this change of protocol could result in reducing mortality and possibly the number of ventilation days of ICU patients. Follow-up studies are needed to evaluate the outcome of such antibiotic regimen changes.

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**REFERENCES**


