Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

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

M.S. Rahnama'i[1*], J.H.T. Wagenvoort[2], C.J. van der Linden[1]

Departments of [1]Surgery and Intensive Care Medicine, and [2]Medical 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.[1,2] 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.[5,6] The breakpoint for sensitivity of *E. coli* was determined at a minimum inhibiting concentration (MIC) of ≤8 mg/ml in accordance with published standards.[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 χ^2 test with a Yates correction was performed.

RESULTS

Table 1 shows the characteristics of the two populations studied. There are significant differences (χ^2 Yates correction; p<0.0.5) between the two population groups with regard to stay in the ICU, mortality and ventilation days. Male patients showed a significantly higher prevalence of *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 *E. coli* strains isolated from patients in different settings are presented in *table 2*. The difference in *E. coli* resistance between 2000 and 2005 was not significant in *E. coli* strains cultured elsewhere in the hospital for either amoxicillin/clavulanate or ceftriaxone. In contrast, there was a significant difference (χ^2 with Yates correction p<0.05) between amoxicillin/clavulanate sensitive *E. coli* strains on the ICU between 2000 and 2005. Moreover, in 2005, this was also true for *E. coli* strains isolated in the hospital and the ICU, indicated with a cross in *table 2*.

In the years 2000 to 2005, the *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 *E. coli* strains was altogether less than 1%.

Table 1. *Study population and differences in patient outcome on the ICU with severe bacterial peritonitis, divided in amoxicillin/clavulanate resistant and sensitive Escherichia coli groups*[*]

	Resistant	Sensitive
Male	20 (71%)	27 (44%)
Female	8 (29%)	34 (56%)
Total number of patients	28	61
Days in the ICU[*]	14	8.3
Mortality[*]	18 (64%)	18 (30%)
Ventilation days[*]	9.9	4.9
APACHE scores	17.4	18.4

[*] χ^2 with Yates correction p<0.05.

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.[9] Because MBC values are more time consuming to obtain, they are currently

Table 2. *Numbers (N) and percentages (%) of amoxicillin/clavulanate (AC) and ceftriaxone (CO) sensitive Escherichia coli cultured in Atrium Medical Centre in all hospital departments and the ICU, showing significant decrease of sensitivity (*) between 2000 and 2005 of AC sensitive Escherichia coli on the ICU (horizontally) and in 2005 between the hospital and ICU E. coli strains (*†) (vertically)*

Setting	2000		2001		2002		2003		2004		2005	
	AC	CO	AC	CO	AC	CO	AC	CO	AC	CO	AC	CO
Hospital	N=674		N=798		N=604		N=608		N=613		N=689	
%	91	100	91	100	93	99	94	98	93	98	88*†	97
ICU	N=473		N=386		N=314		N=333		N=289		N=415	
%	82*	99	86	100	85	97	86	97	83	99	69*†	92

[*] χ^2 with Yates correction p<0.05.

considered to be the reference value for the susceptibility of a micro-organism to a drug. The MIC is used as an instrument to predict outcome of therapy. Words such as susceptible (S) to indicate that the chance of success following antimicrobial therapy is good and resistant (R) that failure is imminent, are increasingly being used. However, in providing interpretations of MIC values measured in the lab and only providing that interpretation, valuable information is lost to the clinician. It stands to reason that reporting values found together with their interpretation is superior. The MIC could be given with a probability of treatment being successful according to the *a priori* available information.[10] This, instead of a relatively crude interpretation of drug effectiveness being expressed as S (susceptible), I (intermediate) or R (resistant). These terms are open to different interpretations depending on the criteria used by different institutions.

It has been suggested that the level of a β-lactam antibiotic should be above the MIC of the targeted bacteria (around 50% of the dosing interval). The pharmacodynamic profile of amoxicillin is such that with the MICs of most bacterial strains (including *E. coli* higher than 8 mg/l) mean this target cannot be reached.[9,10] Thus most intermediately sensitive *E. coli* strains with a 'Vitek MIC' of 16 mg/l can better be considered resistant.

Boyed *et al*. have previously reported the higher prevalence of *E. coli* resistance to amoxicillin/clavulanate in men.[10] There has not been a good explanation for this phenomenon other than the fact that urinary tract infections in men are often complicated and treated by antibiotics for a longer period.

Bruinsma *et al*. (2002) studied antibiotic use and antibiotic resistance of *E. coli* and stated that the differences in antibiotic consumption observed might lead to changes in antibiotic resistance in the near future. They strongly recommended surveillance of antibiotic use and antibiotic resistance to control the development of antibiotic resistance as surveillance provides epidemiological data on the basis of which antibiotic guidelines can be amended.[12,13] In order to prevent resistance, it is advised to limit the use of antimicrobial agents to certain clear indications.[14]

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=340). 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.[14]

When resistance rates of a species approach the 10% threshold, the efficacy of that particular antimicrobial agent decreases.[14,15] 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.

ACKNOWLEDGEMENTS

We kindly thank Keith Campbell for his advice and corrections of the manuscript.

REFERENCES

1. Mohammedi I, Denis A, Duperret S, Chapuis F, Ploin D, Petit P. Risk factors for amoxicillin-clavulanate-resistant Escherichia coli in ICU patients Ann Fr Anesth Reanim. 2003;22(8):711-5.
2. Du B, Long Y, Liu H, et al. Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae bloodstream infection: risk factors and clinical outcome. Intensive Care Med. 2002;28(12):1718-23.
3. Bukholm G, Tannaes T, Kjelsberg AB, Smith-Erichsen N. An outbreak of multidrug-resistant Pseudomonas aeruginosa associated with increased risk of patient death in an intensive care unit. Infect Control Hosp Epidemiol. 2002;23(8):441-6.
4. Gastmeier P, Groneberg K, Weist K, Rüden H. A cluster of nosocomial Klebsiella pneumoniae bloodstream infections in a neonatal intensive care department: Identification of transmission and intervention. Am J Infect Control. 2003;31(7):424-30.

5. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. Clin Infect Dis. 2003;36(11):1433-7.

6. Tam VH, Gamez EA, Weston JC, et al. Outcome of bacteremia due to pseudomonas aeruginosa with reduced suspectibility to piperacillin-tazobactam: indications on the appropriateness of the resistance breakpoint. Clin Infect Dis 2008;45(6):862-7.

7. Ling TK, Tam PC, Liu ZK, Cheng AF. Evaluation of VITEK 2 rapid identification and susceptibility testing system against gram-negative clinical isolates. J Clin Microbiol. 2001;39(8):2964-6.

8. Wheat PF. History and development of antimicrobial susceptibility testing methodology. J Antimicrob Chemother. 2001;48(suppl 1):1-4.

9. Mouton JW. Breakpoints: current practice and future perspectives.Int J Antimicrob Agents. 2002;19(4):323-31.

10. Boyd LB, Atmar RL, Randall GL, et al. Increased fluoroquinolone resistance with time in Escherichia coli from >17,000 patients at a large county hospital as a function of culture site, age, sex, and location BMC Infect Dis. 2008;8:4.

11. White AR, Kaye C, Poupard J, Pypstra R, Woodnutt G, Wynne B. Augmentin (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. J Antimicrob Chemther. 2004;53(suppl 1):i3-20.

12. Bruinsma N, Filius PM, De Smet PA, Degener J, Endtz P, van den Bogaard AE, Stobberingh EE. Antibiotic usage and resistance in different regions of the Dutch community. Microb Drug Resist. 2002;8(3):209-14.

13. Van Klingeren B, Michel MF, Wagenvoort JH. Management of the resistance problem by using an antibiotic protocol. Ned Tijdschr Geneeskd. 1992;136(18):860-4.

14. Nethmap 2006 consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. www.nethmap.nl.

15. Frei CR, Wiederhold NP, Burges DS. Antimicrobial breakpoints for gramnegative aerobic bacteria based on pharmacokinetic – pharmacodynamic models with Monte Carlo simulation. J Antimicrob Chemother 2008;61:621-8.