The Journal of Orthopaedics Trauma Surgery & Related Research

© J ORTHOP TRAUMA SURG REL RES 4 (8) 2007
Original article

Multi-Resistant Acinetobacter Baumannii related Septicemia Treatment in Burn Patients using Ampicillin-Sulbactam

JUSTYNA GLIK (1), MAREK KAWECKI (1), MARIUSZ NOWAK (1), EWA TOMANEK (2), ANNEKE ANDRIESSEN (3)

(1) Ward for Burn Care of the Centre for Burn Treatment in Siemianowice Śląskie
Chief Physician: Marek Kawecki, MD, PhD. Director: Mariusz Nowak, MD
(2) NZOZ Laboratorium Mikrobiologiczne w Sieminowicach, kierownik: Ewa Tomanek
(3) Andriessen Consultants and TVU – CRICP, London, UK

Address for correspondence/Adres do korespondencji:
Oddział Leczenia Oparzeń – Centrum Leczenia Oparzeń w Siemianowicach Śląskich
ul. Jana Pawła II 2, 41-100 Siemianowice Śląskie, Poland
tel.: 48-0-32-2292000, fax: 48-0-32-2288220, e-mail: justyna.glik@clo.com.pl

Statistic

Word count	1646
Tables	8
Figures	0
References	13

Received: 10.09.2007
Accepted: 12.10.2007
Published: 14.11.2007

Summary
The aim of this study is to evaluate the efficacy of using Ampicillin-Sulbactam (AS) for treatment of septicemia, caused by multi-resistant strains of Acinetobacter baumannii (AB), in burn patients. Forty patients were included in the analysis over 2003.
Cultures were performed on blood samples taken from these patients. Sensitivity of the strains to Ampicillin-Sulbactam was determined, marking the zones of inhibited growth and determining the Minimal Inhibitory Concentration (MIC) by using the BIOMIC system.
AB strains in 24/40 patients were shown to be completely resistant to AS.
In 10/40 or 25% of cases the isolate demonstrated medium sensitivity to AS, whereas in only 6/40 or 15% of the patients this strain proved to be completely AS-sensitive.
29/40 Patients were subjected to AS therapy. 16/29 Patients had an AB strain resistant to AS whereas 13/29 Patients showed medium or complete AS sensitivity. These 29 patients were all treated with a maximum daily dose of 3 grams of AS every six hours.
Eradication of AB from the wound bed, after completing the full course, was achieved in 20/29 patients, who fully recovered. This included 9/29 patients that demonstrated in-vitro AS resistance.
In 7/29 patients, despite the completed AS course with a maximum daily dose, a sterile blood culture and eradication of AB from the wound bed was not achieved. These patients died as a consequence.
Key words: Bacteremia, Burns, Acinetobacter baumannii, Ampicillin-Sulbactam

INTRODUCTION

Acinetobacter Baumannii (AB) is recognised to contribute significantly to burn patients' morbidity and mortality. AB strains, due to their virulence, may cause septicemia, infection of the lungs, - urinary system, - peritoneum, and wound infection.[1]

The occurrence of infection caused by AB has increased substantially during the last decade. This is mainly due to the increase in resistance to many antibiotic groups. As a result it has become one of the most common and lethal pathogens to cause hospital infections, including septicemia in burn patients (Table 1).

Multi-resistance of AB comprises beta-lactam antibiotics, aminoglycosides, and chinolones. This causes concern because the potential for treatment of AB infections, including treatment of bacteremia, is diminishing. [2,3]

Table 1. Etiological Factors of Blood Infections Occurring in Burn Patients Hospitalised in Our Centre between 2002 and 2003

No.	Microorganisms	2002		2003	
		Number of strains	Percentage	Number of strains	Percentage
1.	Acinetobacter baumannii	58	28,29%	90	25,5%
2.	Staphylococcus aureus (metacycline-resistant strains)	43	20,97%	77	21,8%
3.	Pseudomonas aeruginosa	35	17,03%	58	16,4%
4.	Staphylococcus epidermidis (metacycline-resistant strains)	25	12,19%	57	16,1%
5.	Staphylococcus aureus	19	9,27%	15	4,2%
6.	Enterococcus faecalis	10	4,88%	10	2,8%
7.	Klebsiella pneumoniae	6	2,93%	12	3,4%
8.	Escherichia coli	5	2,44%	8	2,3%
9.	Candida albicans	4	1,95%	2	0,6%
10.	Staphylococcus epidermidis MSSE	-	-	10	2,8%
11.	Streptococcus pyogenes	-	-	6	1,7%
12.	Proteus mirabilis	-	-	3	0,8%

Table 2. Etiological Factors of Blood Infections Occurring in Burn Patients Who Died (N = 7) between 2002 and 2003

No.	Microorganisms	2002		2003	
		Number of strains	Percentage	Number of strains	Percentage
1.	Acinetobacter baumannii	29	33,3%	43	28,6%
2.	Staphylococcus aureus (metacycline-resistant	14	16,1%	26	17,4%
3.	Pseudomonas aeruginosa	14	16,1 %	41	27 %
4.	Staphylococcus epidermidis (metacyline-resistant strains)	8	9,1%	16	10,7%
5.	Staphylococcus aureus	8	9,1%	3	2 %
6.	Enterococcus faecalis	5	5,8%	6	4 %
7.	Klebsiella pneumoniae	3	3,5%	7	4,66%
8.	Escherichia coli	5	5,8%	-	-
9.	Candida albicans	1	1,2%	2	1,3 %
10.	Staphylococcus epidermidis	-	-	2	1,3 %

Literature indicates that the use of Ampicillin-Sulbactam (AS) in treating infections caused by multi-resistant strains of AB is clinically effective [4,5,6].

The aim of this study was to evaluate clinical efficacy of the use of AS for infection of the wound bed by multi-resistant strains of AB in burn patients.

The study was carried out in 2003 at the Centre for Burn Treatment in Siemianowice Śląskie, the largest hospital for burn treatment in Poland.

PATIENTS AND METHODS

N = 40 patients with a wound bed infection caused by AB strains were included in the analysis. Patients admitted to the center were selected, using the following diagnostic criteria for of a wound bed infection:

Fever > 39° C, chills, systolic blood pressure < 90mmHg, leukocytosis count > 12.000 and isolation of AB from the wound bed.

Blood cultures were performed by marking sensitivity to AS, using Antimicrobial Disk Susceptibility Tests and marking of MIC with the Biomic system.

RESULTS

In N = 24/40 patients an AB strain was isolated, shown to be completely resistant to AS. In N = 10/40 patients, the isolated strain showed medium sensitivity to AS and in 6/40 patients the strain was sensitive to AS.

Ampicillin-Sulbactam therapy was applied in 29/40 patients of which 16/29 patients had an AB strain completely resistant to AS. In 13/29 patients there was medium or complete AS-sensitivity. These 29 patients received the maximum daily dose of the above mentioned antibiotic of 3 grams, every 6 hours.

In 20/29 patients, after completing the full course of treatment, eradication of AB from the wound bed was achieved, followed by a complete recovery. This including 9/29 patients with complete resistancy to AS.

In 7/29 patients, despite completing the full AS course, sterile blood cultures and eradication of AB from the wound bed, was not achieved. These patients died as a result of the infection (The overview is given in Table 8).

DISCUSSION

Acinetobacter baumannii strains are mostly resistant to antibiotics from the group of penicillin and cephalosporins. Our observations over a period of the last three years, show resistance of > 80% to cephalosporins of the third and fourth generation.

Resistance to carbapenems within the Acinetobacter baumannii types is increasing. Until recently, carbapenems were among the most effective beta-lactam antibiotics, with little known resistance. [7] Resistance is mainly found in the strains from patients in intensive therapy - and burn wards. This resistance is usually accompanied by resistance to other antibiotic groups. [6]

Even though imipenem is more active than meropenem and is still considered the most effective antibiotic

Table 3. Antibiotic Sensitivity of the Acinetobacter baumannii Strains in 2001 till 2003

Antibiotic	2001r.	2002r.	2003r	Fluctuation of resistance
Colistin	2,5%	1,0%	0,0%	↓
Netilmicin	28,5%	26,1%	38,6%	↓↑
Ampicillin-Sulbactam	32,4%	37,4%	51,5%	↑↑
Meropenem	36,5%	51,7%	67,6%	↑↑
Imipenem	37,2%	52,5%	67,6%	↑↑
Piperacillin-Tazobactam	75,2%	76,9%	93,4%	↑↑
Ceftazidime	88,6%	78,2%	93,8%	↓↑
Amikacin	87,0%	90,2%	97,7%	↑↑
Gentamicin	90,9%	92,5%	97,7%	↑↑
Ciprofloxacin	97,1%	86,3%	94,8%	↓↑
Cefotaksime	97,2%	93,4%	98,5%	↓↑
Cefepime	0,0%	60,4%	86,4%	↑↑

Table 4. Analysis of Patients with Blood Infection Caused by a Strain of Resistant Acinetobacter baumannii Who Were Treated with Ampicillin-Sulbactam

Patients in Whom Eradication of the Microor anism from Blood Was Achieved

No.	Sex	Age	% TBSA	Third-degree burns
1.	M	42	55%	25%
2.	M	41	41%	5%
3.	M	28	62 %	38 %
4.	M	23	51 %	38 %
5.	M	41	49 %	45 %
6.	M	43	47 %	10 %
7.	M	37	56 %	2%
8.	M	42	60 %	40 %
9.	F	60	47 %	10 %
Average value		39	52 %	23 %

against Acinetobacter species, however it is not effective for all strains [1]. Sensitivity studies of AB in our Centre in 2001-2003 indicate an ever-increasing resistance to carbapenems, of > 70%.

Lack of sensitivity to aminoglycosides, such as gentamicin and amicacin may be due to various resistance mechanisms, such as the production of enzymes.

We noted that the highest sensitivity (60%-70%) of AB for aminoglycosides was observed to be netilmicin. However, this antibiotic could not be administered, due to insufficient availability to our Center.

Until the beginning of the 1990's, new fluorochinolons demonstrated effectivity against AB strains; however, in the last decade there has been a rapid growth of strains which are resistant to this group [1]. We noted that 85-95% of the strains were found to be resistant to chinolons.

A combination of beta-lactam antibiotics with beta-lactamase inhibitors, such as sulbactam, may in certain situations, represent an alternative for the treatment of severe infections caused by multi-resistant AB strains [8, 9].

Our observations indicate an in-vitro effectivity for ampicillin with sulbactam to AB strains; the sensitivity approached 50-60 % (Table 3).

Knowledge in the area of epidemiology, microbiology, antibiotic therapy and clinical experience are indispensable in the prevention of infections caused by multi-resistant strains. Limiting of these epidemics is possible only through working with multidisciplinary teams. Standards should be implemented for effective hospital hygiene. The importance of hand – and surface hygiene, as well as education of personnel should be taken on board.

Table 5. Analysis of Patients with Blood Infection Caused by a Strain of Resistant Acinetobacter baumannii, Who Were Treated with Ampicillin-Sulbactam

Patients in Whom Eradication of the Microorganism from Blood Was Not Achieved

No.	Sex	Age	% TBSA	Third-degree burns
1.	F	75	43%	28%
2.	F	81	30%	15%
3.	M	48	77%	66 %
4.	M	32	90 %	80 %
5.	M	23	56 %	35 %
6.	F	78	49 %	20 %
7.	M	52	30 %	18%
	Average value	55	53,5 %	37 %

Table 6. Analysis of Selected Diagnostic Parameters in Patients with Blood Infection Caused by Resistant Acinetobacter baumannii, Who Were Treated with Ampicillin-Sulbactam (MIC 48)

Patients in Whom Eradication of the Microorganism from Blood Was Achieved

No.	Antimicrobial Disk Susceptibility Tests	MIC	Albumin Level	Leukocyte Level	Type of Infection
1	6 mm (R)	48	1,8	19,4	Multi-
2.	9 mm(R)	48	2,6	9,5	Multi-
3.	6 mm(R)	48	2,3	17,9	Multi-
4.	6 mm(R)	48	2,3	7,6	Multi-
5.	10mm(R)	32	2,9	9,1	Multi-
6.	6 mm(R)	48	2,8	10,9	Multi-
7.	11mm(R)	24	2,5	10,7	Single-
8.	10mm(R)	32	2,6	9,4	Single-
9.	10 mm(R)	32	2,1	4,5	Single-
	Average value		2,4	11 thousands	

Table 7. Analysis of Selected Diagnostic Parameters in Patients with Blood Infection Caused by a Resistant Acinetobacter baumannii Who Were Treated with Ampicillin-Sulbactam (MIC 48)

Patients in Whom Eradication of the Microorganism from Blood Was Not Achieved

No.	Antimicrobial Disk Susceptibility Tests	MIC	Albumin Level	Leukocyte Level	Type of infection
1	6 mm (R)	48	2,2	7,7	Multi-microbial
2.	6 mm(R)	48	1,6	11,9	Single-microbial
3.	6 mm(R)	48	1,2	14,1	Single-microbial
4.	6 mm(R)	48	1,7	12,7	Multi-microbial
5.	6 mm(R)	48	1,7	10,9	Multi-microbial
6.	6 mm(R)	48	1,7	16,2	Multi-microbial
7.	6mm(R)	48	1,9	6,7	Single-microbial
Average value			1,7	11,4 thousands	

Monitoring of hospital infections and an appropriate antibiotic policy are among the most important measures to reduce the incidence of hospital infections caused by multi-resistant pathogens. [1,10,11,13]

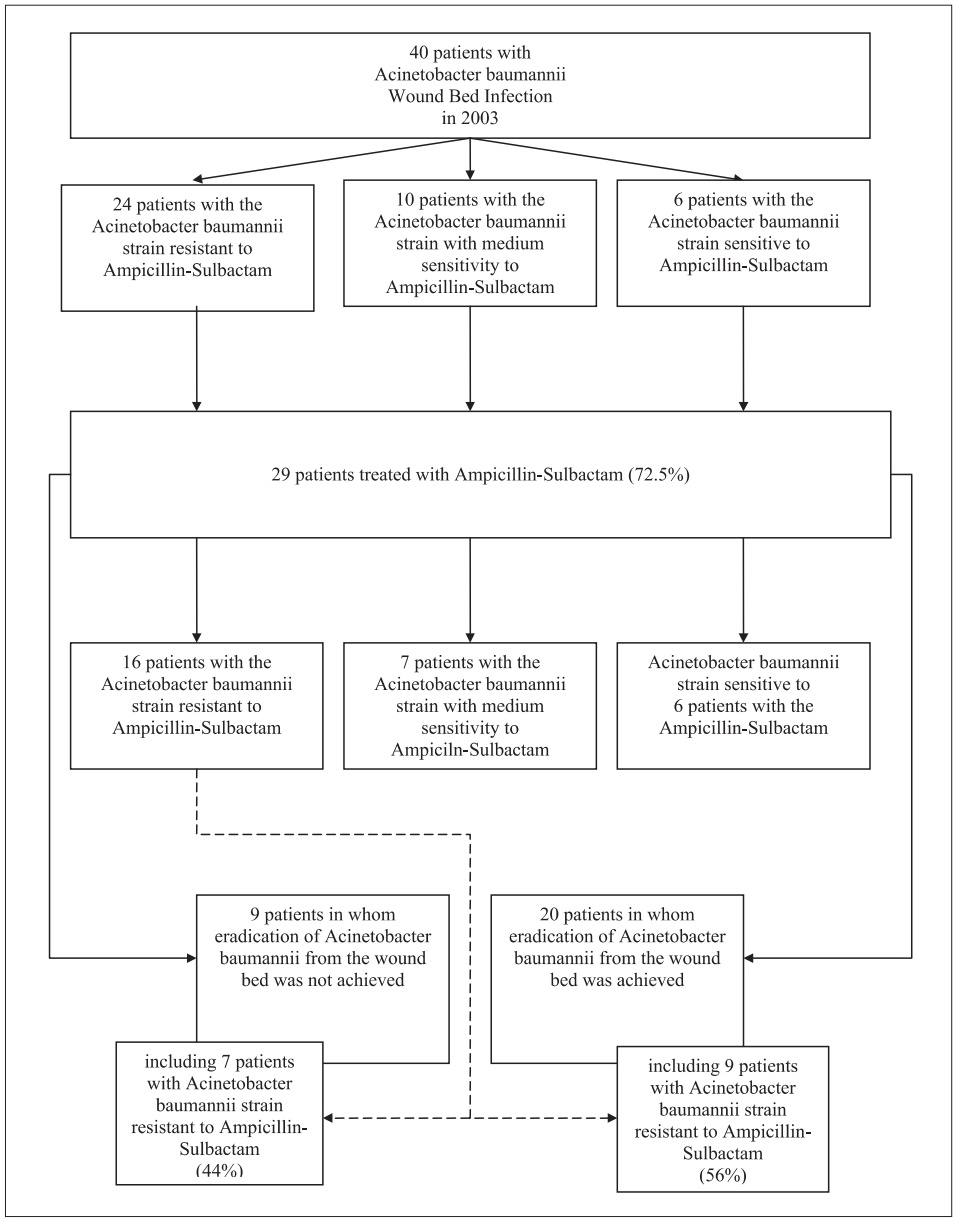
Multi-resistant, hospital-acquired infections should be viewed as a primary issue and not just attributed to a specific hospital.

On the 6th of September, 2001, the Polish health authorities introduced a law on infectious diseases. A registration system regarding hospital infections was put in place. It is mandatory for all health care institutions to control methods of infection treatment, such as the use of antibiotics. Institutions must develop and implement infection control committees, working with specialized infection control teams, etc.

In close collaboration with the infection control team, the committee analyses the use of antibiotics, against the background of frequently occurring infections, their etiology and the ever-changing sensitivity to antibiotics. These teams must jointly develop the strategies to limit an increase in resistance to antibiotics.

Correct identification of the AB species along with other "dangerous pathogens" with genotypical methods is necessary, to ensure awareness of the role of various genomic species of AB within the hospital epidemiology and the associated correct antibiotic treatment. Before starting treatment of AB bacteremia it is important to conduct a clinical examination of the patient in order to eliminate the possibility of pseudo - bacteremia and thereby avoiding unnecessary treatment [12]. Incorrect diagnostics may be a cause for treatment failures. The clinical symptoms of bacteremia caused by AB are not specific. Bacteremia caused by AB strains has a high mortality and is difficult to distinguish from other caus-

Table 8. Analysis of Burn Patients with a Wound Bed Infected by Strains of Acinetobacter baumannii in 2003



es of morbidity and mortality in burn patients [12] (Table 2).

In the past the AB strain was determined on the basis of increase in resistance. This way there was no certainty as to whether it was the same - or several clones. Now errors in diagnostics in our Centre are reduced as standards for collection of materials and microbiological analysis were introduced.

The reaction of AB to antibiotic treatment with AS may depend on factors, such as:

- Factors associated with the patient, i.e., age, condition of the immune system, trauma and its severity, level of plasma proteins, etc
- Factors associated with the microorganisms causing the infection, i.e.virulence

The more exstensive the burn and the older the patient, the lower the albumin blood level may be. As a result the administered antibiotics may be less effective. Younger patients with less extensive burns and a higher albumin blood-level may respond better to the treatment. (Table 4, 5).

The microorganisms that caused the infection may also influence the efficacy AS therapy. AB has various properties influencing its virulence, such as the ability to create a biological membrane or biofilm. This is not only a method for linking the bacterial cell with the host cell, but may also influence the microorganism's virulence.

This biofilm creates resistance to the defense mechanisms of the host. It may disrupt phagocytosis, suppress antigens and/or breaks down the antibiotic and the antibodies.

The created biofilm may undergo fragmentation, together with the microorganisms present, it may be released into the blood circulation causing bacteremia, septic blockages and sources for secondary infection. With the disintegration of the cell, release of endotoxins occurs, which may lead to septic shock.

Based on the factors influencing the effectiveness of antibiotic treatment, we suggest that a biofilm was not formed in 9/29 patient group with the multi-resistant AB strain (Table 8). Due to their level of albumin, adequate linkage with the antibiotic was created and full eradication of AB from the wound bed occurred, although AB was shown, in vitro, resistant to AS.

In 7/29 patients we noted that despite application of the full AS course, eradication of AB from their blood was not achieved. This may be caused by a reduced permeability of the cell membrane to AS, due to the formation of a biofilm and/or blood levels of proteins too low to bond with the antibiotic.

Despite the course set in, we still face a number of issues, such as what determined the success and failure of AB treatment with AS in the patients observed in our study?

The adequate treatment of patients that were suffering from a multi-microbial type of infection, such as gram-positive flora or non-oxygenated flora, as well as correct diagnosis and microbiological identification, remains difficult (Table 6, 7).

CONCLUSIONS

1. Correct diagnosis is mandatory to improve outcome of treatment. In order to determine whether an outbreak of AB is caused by the same clone of Acinetobacter baumannii, it is necessary to conduct genotype identification.
2. In treating difficult infections caused by Acinetobacter baumannii, combined treatment with several antibiotics should be considered to improve clinical outcome.
3. For wound bed infection caused by multi-resistant strains of AB, despite in vitro resistance, the application of Ampicillin with Sulbactam in a maximum daily dose, may be an effective treatment. It was noted to be an alternative to netilmicin.
4. In order to limit Acinetobacter baumannii outbreaks it is necessary to develop and implement standard procedures for diagnostics and treatment, such as an adequate antibiotic policy.

For the future other than pharmacological methods for treating infections are required such as vaccination and/or use of bacteriophages.

References/Piśmiennictwo:

1. *E. Stefaniuk : Pałeczki Acinetobacter spp.- nowy wielooporny czynnik etiologiczny zakażeń szpitalnych. Nowa Klinika vol 6 No 5 1999r : 529-532.*
2. *Iskandar S.B.,Guha B. ,Krishnaswamy G,Roy T.M: Acinetobacter baumannii pneumonia: a case report and review of the literature. Tenn- Med.2003 Sept;96 (9) ; 419-422.*
3. *Levin A. S.:Treatment of Acinetobacter spp infections. Expert Opin. Pharmacother. 2003 Aug: 4 (8): 1289- 96.*
4. *Levin A.S.,Levy C.E., Manrigue A. E., et al..: Severe nosocomial infections with imipenem- resistant Acinetobacter baumannii treated with ampicillin/sulbactam. Int. J. Antimicrob. Agents 2003 Jan.; 21 (1) : 58-62.*
5. *Livemore D.M: The impact of carbapenemase on antimicrobial development and therapy. Curr. Opin. Investig . Drugs .2002 Feb. 3 (2) :218-224*
6. *Tatmanotkun M., Gurcan S., Ozer B: Annual trends in antibiotic resistance of nosocomial Acinetobacter baumannii strains and the effect of synergistic antibiotic combinations. New Microbiol. 2004 Jan : 27 (1) :21-28*
7. *Ko W.C., Lee H.C., Chiang S. R .,Yan J. J et al.: In vitro and vivo activity of meropenem and sulbactam against a multidrug-resistant Acinetobacter baumannii strain. J. Antimicrob. Chemother.2004 Feb; 53 (2): 395-5.*
8. *Higgins P.G, Wisplinghoff H.,Stefanik D: In vitro activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically. Antimicrob.Agents .Chemother. 2004 May 48 (5): 1586-1592.*
9. *Smolyakow R, Borer A.,Riesenberg K: Nosocomial multi-drug resistant Acinetobacter baumannii bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J.Hosp. Infect. 2003 May 54 (1) :8-32*
10. *El Shafie S. S, Leni- Garcia M.: Investigation of an outbreak of multidrug-resistant Acinetobacter baumannii in trauma intensive care unit. J. Hosp. Infect. 2004 Feb: 56 (2): 101-105*
11. *Simor A. E., Lee M, Vearncombe M.: An outbreak due to multiresistant Acinetobacter baumannii in burn unit: risk factors for acquisition and management. Infect. Control. Hosp. Epidemiol. 2002 May 23 (5) :261-267*
12. *Cisneros J.M., Rodriguez-Bano J.: Nosocomial bacteremia due to Acinetobacter baumannii: epidemiology, clinical features and treatment. Clin. Microbiol. Infect.2002 Nov;8 (11):687-693*
13. *Wong T.H., Tan B. H., Ling M.L: Multi-resistant Acinetobacter baumannii on burns unit - clinical risk factors and prognosis. Burns 2002 Jun; 28 (4): 349-357.*