Published in final edited form as:

Am J Infect Control. 2009 November ; 37(9): 715–722. doi:10.1016/j.ajic.2009.01.008.

Long-term Control of Hospital-wide Endemic Multidrug-Resistant (MDR) *Acinetobacter baumannii* through a Comprehensive “Bundle” Approach

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Abstract

Background—*Acinetobacter baumannii* (Ab) is emerging as a multidrug-resistant (MDR) nosocomial pathogen of considerable clinical importance. Data on the efficacy of infection control measures in endemic situations are lacking. Here, we investigated the impact of a long-term multifaceted “bundle” approach in controlling endemic MDR Ab in a 950-bed tertiary care center.

Methods—Ongoing staff education, promotion of hand hygiene, strict contact and isolation precautions, environmental cleaning and targeted active surveillance in high-risk areas during periods of likely transmission and contamination were initiated in this program. To assess the efficacy of our interventions, we recorded (before and after the intervention) the epidemiological and clinical features of MDR Ab infections and determined the clonal relationship among MDR Ab bloodstream isolates by pulsed-field gel electrophoresis (PFGE).

Results—Before the “bundle” was instituted, the rate of colonization/infection was 0.82 cases per 100 admissions (1994–1995). Colonization/infection rates showed a sustained decrease after implementation of the control program in 1995 to 0.46 in 1996–1997 and to 0.21 in 1998–2003 ($P<0.001$). Co-incident with the institution of this program, the rate of bacteremia due to MDR Ab decreased six-fold during the 8-year observation period. A notable change in the clonal distribution of the MDR Ab isolates was also demonstrated.

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Conflict of interest statement

The authors have no conflict of interest.

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Conclusions—The implementation of a comprehensive and multi-faceted infection control program (“bundle”) in a tertiary care center effectively controlled the spread and clinical impact of MDR Ab.

INTRODUCTION

Multidrug-resistant (MDR) *Acinetobacter baumannii* (Ab) is an important nosocomial opportunistic pathogen with a unique ability for manifesting antimicrobial resistance. Data from the National Nosocomial Infection Surveillance (NNIS) system indicate that this pathogen is an increasing cause of hospital-acquired infections in Intensive Care Units (ICUs) in the United States, now being the fifth cause of pneumonia and the eighth most frequent pathogen recovered from bloodstream infections.¹ MDR Ab is also described as an emerging cause of illness in US soldiers wounded during military operations.² In Spain, Ab is found in most tertiary care (referral) institutions,³ and is the third leading cause of ventilator-associated pneumonia.⁴

Controlling the endemicity and dissemination of MDR Ab is a critical priority for tertiary care centers. MDR Ab may cause significant morbidity and mortality in high-risk patients⁵ and is associated with increased hospital stay.^{6, 7} Carbapenems (imipenem/cilastatin and meropenem) are considered to be “drugs of choice” for the treatment of serious infections caused by Ab. This prescribing practice may contribute both to increase carbapenem resistance among Ab and to the emergence of other carbapenem-resistant Gram-negative bacilli. Thus, infection control efforts should be focused on the management of all Ab isolates, not just those expressing the MDR phenotype. Unfortunately, carbapenem resistance in Ab is increasing worldwide and the efficacy of tigecycline and colistin as empiric therapy of suspected MDR Ab remains uncertain.^{8,9}

Many nosocomial outbreaks caused by Ab are reported, but most of them refer to specific wards, mainly ICUs.¹⁰ In some cases, the outbreaks are caused by one or a few epidemic clones and a common environmental source is either found or suspected. In such cases, identification and elimination of the environmental reservoir is usually followed by rapid control of the outbreak.¹⁰ However, in many institutions, Ab are endemic,^{3,11} a situation which is much more difficult to change.^{12–14}

Infection control measures implemented in endemic situations are costly and their long-term efficacy is not adequately studied. Few reports exist examining the impact of a multi-year comprehensive intervention.¹³ At the Hospital Universitario Virgen Macarena (HUVU), a tertiary care center in Spain, MDR Ab has been endemic since the beginning of the 1990s.¹⁵ In 1995 a comprehensive multi-faceted long-term control program was introduced. This report describes the results and clinical impact of a long-term control of endemic MDR Ab after implementation of this “bundle” approach.

METHODS

Setting

HUVU is a 950-bed acute-care university hospital located in Seville, Spain. It has a 30-bed ICU for both medical and surgical patients. MDR Ab demonstrating *in vitro* resistance to ≥ 3 antibiotics (e.g., ceftazidime, ampicillin/sulbactam, imipenem/cilastatin, tobramycin, amikacin and ciprofloxacin) was a significant nosocomial pathogen recovered from patients in our hospital since 1990. Since less than 3% of Ab isolated between 1994 and 2003 were not MDR, we refer only to MDR Ab in this report. Using definitions established by the Centers for Disease Control and Prevention (CDC) all MDR Ab were nosocomially acquired (i.e., recovered from patients who were hospitalized for ≥ 48 h) (www.cdc.gov).

Epidemiological investigation

A multidisciplinary team composed of an ICP, a microbiologist, an epidemiologist and an infectious diseases physician implemented the program. The study was approved by the Institutional Review Board of HUVM and the local Ethics Committee. Three time periods were analyzed: 1994–1995 (pre-intervention period), 1996–1997 (immediate post-intervention period) and 1998–2003 (late post-intervention period).

Cases were defined as patients from whom MDR Ab was isolated from a clinical sample (e.g., blood, sputum, urine) from January 1994 to December 2003. Epidemiological and clinical data of all patients from whom MDR Ab was isolated were prospectively recorded. Between 1994 and 2003, bimonthly and yearly rates of MDR Ab colonization/infection and bacteremia (new cases per 100 admissions and per 1,000 patient-days) were calculated. This value was expressed as an “incidence density of colonization/infection and bacteremia”. The presence and types of infections were evaluated according to CDC criteria. In particular, patients from whom MDR Ab was isolated from clinical samples but without criteria for infection were considered to be colonized¹⁶. Isolates detected by active surveillance (see below) were not defined as cases and were not included in the rates since the analysis was not performed regularly during the 8-year study period.

Annual prevalence data concerning co-morbidities, invasive procedures and number of diagnoses were obtained from yearly point prevalence studies using an established method.

¹⁷ The clinical and prognostic features of bacteremia due to MDR Ab in our hospital were previously published.¹⁸ Our previous study identified specific risk factors for colonization with MDR Ab in the ICU (e.g., nasogastric tube feeding and the use of urinary catheters).¹⁹ In the present study, these invasive procedures in aggregate were considered as surrogate markers of frequent medical intervention and they were measured in a yearly basis from 1994 to 2003 (see Table 2).

Data concerning antimicrobial consumption from 1994 to 2003 were obtained from the HUVM Pharmacy Service and were expressed in terms of daily defined doses (DDD) per 1,000 patient-days.

Intervention

A comprehensive, multi-faceted, six-point infection control program (“bundle”) was instituted on September 1995 and consisted of the application of the following measures:

1. Instruction in basic hygiene (i.e., hand washing, appropriate use of gloves) through an intensive education program.. To support and facilitate basic hygiene, dispensers for alcohol-based hand-rubs were installed in every room in 2000;
2. A policy encouraging contact and isolation precautions for all patients colonized or infected with MDR Ab (i.e., placing patients in single rooms or cohorting in open-structured units) was instituted and maintained daily by an infection control practitioner (ICP). Contact precautions were maintained during the entire hospitalization period and were also enforced for every diagnostic or therapeutic procedure performed on colonized patients. The number of patients in whom contact precautions and isolation were applied was also recorded. In addition, contact and isolation precaution were applied to every patient re-admitted to HUVM with a history of MDR Ab colonization and infection. This was carried out until colonization was ruled out.
3. Active surveillance included weekly rectal, perineal and pharyngeal swabs (plus a tracheal aspirate if the patient was on mechanical ventilation) in all patients admitted to the ICU for >2 days during periods of ongoing transmission (i.e., occurrence of

new cases potentially related to a previous one, during the same admission periods and the same area). Active surveillance was systematically performed in the ICU only during 4 periods of ongoing transmission (November-December 1995, July-November 1998, April-June 2000, January-April 2002).

4. Cultures of hands of healthcare workers (i.e., physicians and nurses who had recently cared for colonized patients) and the environment were performed at 3 time points in the ICU, coinciding with periods of ongoing transmission in that unit (November 1995, November 1998 and April 2000), as a way to reinforce the importance of environmental reservoirs and cross-transmission.
5. A strict environmental cleaning policy following CDC recommendations²⁰ for rooms and for any object which might have come into contact with colonized patients was implemented. Some devices (e.g., sphygmomanometers, stethoscopes) were dedicated only for use with the source patient whenever possible and were kept inside the room;
6. Regular meetings with staff (including physicians, nurses, physical therapists, and students) of affected areas were held every 2 to 4 weeks during the first year of intervention, and every 2–3 months afterwards, and were compulsory for ICU staff. In addition, all staff was periodically informed about the evolution of rates as part of the educational program (monthly in ICUs, quarterly in other units).

Microbiological studies

Identification and antimicrobial susceptibility testing (AST) of Ab were performed using the MicroScan Walk-Away system (Dade-Behring, Sacramento, Ca, USA) from 1994 to 2001, and using Vitek-2 (bioMérieux, Marcy L'Étoile, France) from 2002 to 2003. The phenotypic tests proposed by Bouvet and Grimont were also used.²¹ Genotyping of bloodstream isolates was first performed by pulsed-field gel electrophoresis (PFGE) as previously described.²² Genomic DNA was digested with *Sma*I (Boehringer-Mannheim, Madrid, Spain) and resolved in 1% pulsed-field certified agarose (Bio-Rad Laboratories, Hercules, CA) using the CHEF-DR II system (Bio-Rad Laboratories). The electrophoresis conditions were 15°C at 6 V/cm² for 22 hours. The initial and final switch times were from 1 to 10 seconds for 10 hours and 10 to 35 seconds for 12 hours. The gel was stained with ethidium bromide (5 µg/mL) for 20 minutes, visualized under ultraviolet light, and photographed with a Polaroid MP-4 camera (Concord, MA). Only the first isolate per bacteremic episode was studied. Blood cultures that yielded Ab after 2 weeks of resolution of the first one were considered a new episode. Isolates were assigned to clonal groups, according to the criteria advanced by Tenover *et al.*²³ In addition to PFGE, amplified ribosomal DNA restriction analysis (ARDRA) was performed on representative isolates to confirm identity.²⁴

Active surveillance samples and samples from hands of healthcare personnel and the environment were taken following published recommendations.^{25,26} All samples were inoculated on brain heart infusion broth (Oxoid, Madrid, Spain) for 24 hours at 35°C. Subcultures were done using MacConkey agar (Oxoid) supplemented with cefotaxime (Sigma, Madrid, Spain) at a final concentration of 4 mg/L. Suspected colonies were identified to species level as mentioned above.

Statistical analysis

The chi-squared for trend (Mantel extension) was used to compare MDR Ab rates; odds ratio (OR) and 95% confidence intervals (CI) were calculated. Software Epi InfoTM version 3.4 (CDC, Atlanta, GA) was used for statistical analysis.

RESULTS

Identification of patients with colonization/infection due to MDR *A. baumannii*

From January 1994 to December 2003, MDR Ab was isolated in clinical samples from 971 patients that were hospitalized on 21 different wards. The clinical characteristics of these patients are shown in Table 1. Using criteria established by the CDC,¹⁶ 602 patients (62%) were considered to be infected (i.e., respiratory tract, 35%; urinary tract, 18%, skin and soft tissue, 18%, primary bacteremia, 17%, intra-abdominal, 3%; other, 8%). In the remaining 369, MRD Ab was considered a colonizer only. Overall, 418 patients included in this study died during hospitalization (crude mortality rate, 43%). The crude mortality rate was higher among patients with infection compared to those only colonized (284/602, 47% vs. 134/369, 26%, $P<0.001$). Additionally, 119 patients, not initially detected using clinical samples, were identified as colonized by MDR Ab using surveillance cultures.

Dynamics of *A. baumannii* infection and colonization

The tracking of the bimonthly incidence-density of colonization/infection and bacteremia due to MDR Ab is shown in Figure 1. The incidence-density of colonization/infection was 0.82 cases per 100 admissions during 1994–1995. After the implementation of the comprehensive control program, the incidence-density decreased to 0.46 cases per 100 admissions during 1996–1997 (OR=0.56; 95% CI: 0.49–0.65; $P<0.001$) and to 0.21 during 1998–2003 (OR=0.26; 95% CI: 0.22–0.29; $P<0.001$). Co-incident with this reduction, the rate of bacteremia due to MDR Ab decreased from 0.19 cases per 100 admissions during 1994–1995 to 0.08 during 1996–1997 (OR=0.47; 95% CI: 0.34–0.65; $P<0.001$) and to 0.03 during 1998–2003 (OR=0.19; 95% CI: 0.14–0.26; $P<0.001$). The median daily number of patients for whom contact precautions and isolation were implemented due to colonization with MDR Ab decreased from 10 in 1995 to 2 in 1998 and thereafter ($P<0.001$).

The clinical features of patients admitted to the ICU, as recorded in annual point prevalence studies, are summarized in Table 2. Patients' ages, comorbidities, and number of invasive procedures did not significantly change throughout the study period.

The consumption of antimicrobial agents at HUVIM during the period of study is shown in Figure 2. The DDD/1,000 patient days of carbapenems (i.e., imipenem/cilastatin, meropenem) and aminoglycosides (i.e., amikacin, tobramycin, gentamicin) did not significantly change in 1996–1997 with respect to 1994–1995. The consumption of fluoroquinolones (i.e., ciprofloxacin, ofloxacin, levofloxacin), amoxicillin-clavulanate, and piperacillin/tazobactam increased during 1998–2003, while DDD/1,000 patient days of extended-spectrum cephalosporins (i.e., cefotaxime, ceftriaxone, ceftazidime) decreased from 1999 onward.

Active surveillance

Overall, 119 patients were detected as colonized using active surveillance. In particular, 73 (61%) ICU-patients were detected by active surveillance as colonized by MDR Ab during these periods. Rectal and/or pharyngeal swabs (or tracheal aspirate if intubated) grew MDR Ab in 66 (90%) of these 73; perineal swabs yielded MDR Ab in the other 7 patients. In addition, 22 colonized patients were detected during sporadic active surveillance investigations performed in other wards. Notably, among 139 patients admitted from other hospitals, 24 (17%) were detected as colonized at admission.

Environmental and hand sampling

In each of three periods during which environmental sampling was carried out, MDR Ab was isolated in 12 to 13 of 50 samples (24% to 26%) obtained from surfaces and objects surrounding colonized patients (e.g., respirators, bed rails, monitors) and in 10 to 25 of samples (20% to

50%) obtained from surfaces in the medical and nurses' offices (e.g., tables, computers, medical charts). In addition, MDR Ab was isolated in 3 to 5 of 25 hand samples (12% to 20%) obtained from health care workers. Significant differences among the 3 periods were not found.

Molecular epidemiology and antimicrobial susceptibility

Clonal relatedness was determined by PFGE in all 191 MDR Ab bloodstream isolates obtained from 1995 to 2003 (isolates from 1994 were unavailable) and in those isolated from environmental cultures and hands of health care workers.

As shown in Figure 3, using criteria established by Tenover et al.,²⁴ 42 unique PFGE profiles were identified among blood isolates. In particular, 7 PFGE profiles (clones 1, 2, 8, 10, 20, 21, and 26) were found in 61% of episodes ("predominant clones"). ARDRA of representative PFGE clone types confirmed the identity of these isolates as Ab.

Clonal diversity was much greater during 1995 (47% of episodes caused by 7 predominant clones) than during 1997–2003 (70% of cases caused by 3 clones only). Fifteen isolates obtained from environmental sources and seven from the hands of health care workers were found to be clonally-related to predominant clones isolated from blood cultures taken during similar periods of time.

During the period of study, the most active antimicrobial agents *in vitro* were meropenem, ampicillin/sulbactam, and tobramycin (70%, 82% and 78% of susceptible isolates, respectively). The evolution of susceptibility across the study period is shown in Table 3. Clonally-related isolates frequently showed discrepancies in their susceptibility patterns (e.g., different clonally-related isolates could be susceptible or resistant to imipenem).

DISCUSSION

Presently, MDR Ab is considered one of the most difficult MDR organisms to contain^{12–14, 27–29} and information about the impact of long-term control measures is lacking. Herein, we report that the implementation of a multi-year, comprehensive, multi-faceted control program ("bundle") throughout an entire hospital was followed by a marked and sustained decrease in the rates of MDR Ab colonization and infection. Our data also show that there was a reduction in the rate of bacteremia (0.82 to 0.21/100 admissions) due to this organism and in the daily number of patients kept in isolation (10 to 2). To our knowledge, this is the first report of an association between the reduction of incidence density of Ab and a decrease in frequency of bloodstream infection. The success of our intervention strategy is consistent with a report by Apisarnthanarak et al. which showed that a multifaceted approach is successful in reducing MDR Ab.³⁰

Despite the importance of MDR Ab as a nosocomial pathogen, insufficient attention has been paid to the control of these MDR Gram-negative bacilli. Evidence based guidelines with specific recommendations for the control of these organisms are still lacking.³¹ Another important observation is the relationship between the implementation of this "bundle" of interventions and the change in number of circulating clones of MDR Ab causing infection. At the onset of the study period, there was significant clonal diversity among MDR Ab strains, a situation that has been found in other studies.³² As our study progressed, we noted the reduction in incidence/density of colonization/infection and bacteremia rates occurred in parallel to a marked reduction in the clonal diversity of the isolates. Two possible explanations are offered: i) the intervention was very effective in controlling most of the clones, but could not eradicate unique ones; ii) strict surveillance and isolation may have stopped the influx of new strains.

We emphasize that our intervention did not include specific measures related to antimicrobial use. In fact, changes in consumption of specific antimicrobials occurred more than 4 years after the implementation of the control program, when the rate of colonization/infection with MDR Ab had already decreased. This difference is in sharp contrast to other reports which emphasized the reduction in antibiotic use as being important.^{11,12}

Although these results are very encouraging, inherent limitations of quasi-experimental studies should be taken in mind.³³ Rates of MDR Ab colonization and infection were very high during the 2 years preceding the implementation of the “bundle”. Since it is known that endemic situations do not spontaneously “reverse” in other centers,^{12–14} our data argue against regression to the mean (Hawthorne effect) as being the main explanation for our results. Controlling for potential confounding variables is difficult in such clinical and epidemiological studies and is rarely attempted. In our analysis, we could not control confounding due to changes in antimicrobial consumption and case-mix since specific bimonthly data for these variables were not available. However, the yearly rates of antibiotic consumption and features of admitted patients from annual point prevalence studies did not vary during the study period, suggesting that the reduction of the MDR Ab rates were related to the control program. Other limitations of the present study are that we i) could not evaluate the individual impact of each measure implemented, and ii) PGFE-relatedness criteria proposed by Tenover et al. might not be suitable in the analysis of a protracted, endemic event. Nevertheless, we advance that the data provided by this analysis are useful to understand the dynamics of MDR Ab in our center.

In conclusion, we show that a comprehensive “bundle” approach was highly effective in controlling a multi-year complex outbreak of MDR Ab. Our results also suggest that colonized patients^{27,34} and environmental contamination^{13,24,27,35,36} are important reservoirs for MDR Ab. The influx of colonized patients admitted from other centers was probably also significant since cross-transmission was previously suspected.³⁷ A multi-faceted program including the detection of colonized patients by means of active surveillance, reinforcement of hand hygiene, environmental investigation and cleaning, and contact precautions successfully reduced cross-transmission. Although active surveillance is time-consuming and costly,¹² it may underscore the educational message and encourage staff participation. The daily presence of an ICP in units with colonized patients was also crucial to the success of the “bundle”. As evidence based guidelines with specific recommendations for the control of MDR Ab are evolving, a multi-disciplinary, comprehensive and long-term hospital-wide effort may be our best approach to control complex endemic situations caused by MDR *A. baumannii*.

Acknowledgments

The study was supported in part by Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III - FEDER, Spanish Network for the Research in Infectious Diseases (REIPI C03/14) and Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008), and FIS PI051019. CM was the recipient of a fellowship from the Asociación Sanitaria Virgen Macarena. RAB is supported by the Merit Review Award and Geriatric Research Education and Clinical Care VISN 10 from the Department of Veterans Affairs, and the NIH (RO1 AI072219). AE is supported by AstraZeneca and NIH (RO1 AI072219 to RAB and RO1-AI045626 to Louis B. Rice). FP is supported by the Wyeth Fellowship in Antimicrobial Resistance.

We gratefully acknowledge all hospital staff and other members of the Committee for Infection Control and Antibiotic Policy for their collaboration in the implementation of the program; P. Blasco for providing the data from prevalence studies; A. Millán for helping in the data management; and D. L. Paterson for a critical review of the manuscript.

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Figure 1.

Evolution of the rates of multi-drug resistant *Acinetobacter baumannii* during the study period. Data are expressed as number of new cases of colonization/infection (squares) and bacteremia (circles) per 100 admissions. The infection control program was implemented on September 1995 (arrow).

Figure 2.

Consumption of antimicrobial agents during the study period. Data are presented as daily defined doses (DDD) per 1,000 patient-days. Aminoglycosides includes gentamicin, tobramycin, and amikacin. Extended-spectrum cephalosporins include cefotaxime, ceftriaxone, and ceftazidime. Fluoroquinolones includes ciprofloxacin, ofloxacin and levofloxacin. Carbapenems include imipenem and meropenem.

Figure 3. Evolution of the clonal relationship (PFGE profiles) among 191 multi-drug resistant *Acinetobacter baumannii* isolates from blood cultures. Data are presented as absolute numbers per year.

Table 1

Features of 971 patients colonised or infected by *Acinetobacter baumannii* (patients detected as colonised only by means of surveillance cultures are not included) from January 1994 to December 2003. Data are expressed as no. of patients with the feature (%), except where indicated.

Median age in years (range)	66 (16–94)
Median previous hospital stay in days (range)	20 (2–169)
Male sex	602 (62)
Type of service	
ICU	476 (49)
Medical	282 (29)
Surgical	213 (22)
Diabetes mellitus	292 (30)
Chronic respiratory disease	127 (13)
Neoplasia	78 (8)
McCabe's classification of chronic underlying disease	
Non fatal	437 (45)
Ultimately fatal	456 (47)
Rapidly fatal	78 (8)
Vascular catheter	688 (71)
Parenteral hyperalimentation	77 (8)
Mechanical ventilation	359 (37)
Urinary catheter	661 (68)
Surgery	331 (43)
Previous antimicrobial treatment	865 (89)
Cephalosporins	553 (57)
Penicillins	350 (36)
Fluoroquinolones	282 (29)
Carbapenems	165 (17)
Aminoglycosides	146 (15)

Table 2

Data from annual point-prevalence studies performed in University Hospital Virgen Macarena, 1994–2003.

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
No. of patients surveyed	675	697	688	708	671	634	715	725	705	709
Median age (years)	55	58	58	58	61	61	60	61	61	60
No. of diagnoses (mean)	1.7	1.5	1.5	1.5	1.6	1.7	1.7	1.7	1.7	1.2
No. of comorbidities ¹ (mean per patient)	1	0.9	1.0	0.7	0.8	0.9	0.8	0.9	0.9	1.3
No. of invasive procedures ² (mean per patient)	0.9	0.9	1.1	0.9	0.9	1.1	1	1	1.1	1.2

¹ Includes diabetes mellitus, chronic pulmonary disease, chronic renal insufficiency, liver cirrhosis, neoplasia, and immunosuppressive condition.

² Includes intravascular catheters, urinary catheters, nasogastric tubes, and tracheal intubation.

Table 3

Evolution of antimicrobial susceptibility of *A. baumannii* isolated from blood cultures. Data are expressed as percentage of susceptible isolates.

	1995 (N=64)	1996 (N=24)	1997 (N=27)	1998 (N=18)	1999 (N=12)	2000 (N=15)	2001 (N=9)	2002 (N=11)	2003 (N=11)
Meropenem	62	72	53	87	57	91	85	91	73
Ceftazidime	23	28	15	20	22	7	5	7	0
Ciprofloxacin	6	13	7	16	29	7	3	7	0
Tobramycin	13	15	7	17	26	88	67	88	95
Amikacin	20	23	29	30	31	56	77	56	67
AMP-SB*	63	60	68	67	52	92	92	92	83

* AMP-SB: ampicillin-sulbatam