ORIGINAL ARTICLE

Epidemiology of neonatal sepsis caused by multidrug resistant pathogens in a neonatal intensive care unit level 3

Devleta Hadžić[1], Fahrija Skokić[1], Selmira Brkić[2], Amina Saračević[1], Delila Softić[2], Dženana Softić[1]

[1]Paediatric Clinic, University Clinical Centre of Tuzla, [2]School of Medicine University of Tuzla; Bosnia and Herzegovina

ABSTRACT

Aim Steady progress in intensive treatment worldwide has increased the survival of immature neonates, but with multiple invasive procedures, which have increased the risk of infection, thus the bacterial resistance to antibiotics. The aim of this study was to analyse the epidemiology of multidrug resistance pathogens as causative agents of neonatal sepsis in the neonatal intensive care unit.

Methods A retrospective cohort study conducted at the Intensive care unit of the Paediatric Clinic of Tuzla over a three-year period (2016-2018) analysed epidemiology of neonatal sepsis caused by multidrug resistance pathogens. Statistical analysis applied standard methods, and the research was approved by the Ethics Committee of the institution.

Results Of the total of 921 treated neonates, multidrug resistance (MDR) pathogens among causative agents of neonatal sepsis were found in 22 neonates (2.38%) with no gender difference. Prematurity and low birth weight were confirmed as the most significant risk factors. From the maternal risk factors a significant difference was found in the first birth and *in vitro* fertilization. Clinically, MDR sepsis manifested frequently as late onset sepsis, with *longer* hospital stay and higher mortality. The findings of leukopenia, thrombocytopenia and coagulation disorders were significant. Gram negative bacteria were frequently isolated, in particular *Acinetobacter*, which showed the greatest resistance to antibiotics.

Conclusion Neonatal MDR sepsis is a threat to life, it complicates the treatment, increases costs and mortality. Outcomes can be improved by preventive strategies, earlier and more accurate diagnosis and rational use of antibiotics.

Key words: antibiotic resistance, incidence, intensive care, neonatal early onset sepsis, neonatal late onset sepsis

Corresponding author:
Devleta Hadžić
Paediatric Clinic,
University Clinical Centre of Tuzla
Prof.dr. Ibre Pašić bb, 75000 Tuzla,
Bosnia and Herzegovina
Phone: +387 35 303 733;
Fax: +387 35 303 730;
E-mail: devletahadzic@yahoo.com
ORCID ID: https://orcid.org/0000-0003-4037-3736

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INTRODUCTION

Bacterial resistance to antibiotics is one of the leading problems of medicine in the new millennium (1). Non-rational use of antibiotics has led to the genetic mutation of bacteria, creating new resistant species that spread very quickly, primarily in hospital settings, but also in the outpatient community (2). In recent decades, the creation of new antibiotics has stagnated significantly, which particularly affects the most critical categories of patients (3). Some bacteria, such as *Staphylococcus, Enterococcus, Pseudomonas and Acinetobacter*, are becoming resistant to most antibiotics that are in use (4). In addition, many invasive diagnostic and therapeutic procedures in the modern medicine increase the risk of infection, which requires permanent establishment of quality prevention and efficient treatment (5).

The immune status of all critically ill patients is impaired, which facilitates the progression of "super bacteria" (6). This is especially emphasized in the most risky areas of medicine such as surgery, intensive medicine and neonatology (7). Neonates are at highest risk for morbidity and mortality, and despite the advancement of evidence-based medicine, the problem seems to be expanding (8). Possible sources of infection for neonates are also spreading, increasing the risk of health care-associated infections with multidrug resistant (MDR) pathogens (9). Neonatal sepsis has continuously remained a top issue (10). It is very important to have current information on neonatal bacterial and other isolates and their patterns of antimicrobial susceptibility, and thus be guided in the choice of empirical antibiotic therapy (1). The mortality rate of neonatal sepsis is different and ranges from 20-75% (10). The outcome depends mainly on an early and timely identification of the cause, as well as timely onset of an adequate causal therapy (10).

The rate of multidrug resistant pathogens is different at different centres (11). Commonly, MDRs include gentamicin-resistant *Klebsiella species*, third-generation cephalosporin-resistant gram-negative organisms, methicillin-resistant *Staphylococcus*, and, more recently, carbapenem-resistant gram-negative species (3). Although the problem of antibiotic resistance is more pronounced in some countries, the bacteria do not recognize state borders. According to the recommendations of the World Health Organization (WHO) and the European Centre for Diseases Prevention and Control (ECDC) (1), the control of the spread of multidrug resistance pathogens must involve not only health care professionals, but also the governments and community (5). It is best to use our own recommendations for antibiotic administration, derived from analysis of local susceptibility and dynamics of the infection. Certainly, we are obliged to follow the pharmacological and antimicrobial guidelines for the choice of empirical and etiological therapy. Therefore, continuous epidemiological monitoring of local susceptibility patterns to antibiotic agents is necessary to establish a rational treatment strategy. There is insufficient data published on this topic from Bosnia and Herzegovina, even from the region, especially in the case of critically ill neonates.

The aim of this study was to analyse the epidemiology of multidrug resistance pathogens as causative agents of neonatal sepsis in the neonatal intensive care unit level 3.

PATIENTS AND METHODS

Patients and study design

A retrospective cohort study, which included all consecutive neonates with positive blood culture, from those treated at the Neonatal Intensive Care Unit (NICU) of the Paediatric Clinic in Tuzla (capacity of 20 beds, level III) over a three-year period (2016 to 2018). All neonates with proven multidrug resistant (MDR) pathogens isolated from blood culture were designated as a test group, MDR sepsis group. They were compared with a control group consisting of the rest of neonates from the neonatal sepsis group, marked as non-MDR sepsis group.

The study was approved by the Ethics Committee of the University Clinical Centre of Tuzla.

Methods

Clinical and demographic data were obtained from medical records and electronic databases of patients treated in the NICU, including gender, gestational age, birth weight, perinatal risk factors for neonatal sepsis, maternal and neonatal (presence of central venous catheter, length of mechanical ventilation, parenteral nutrition and length of hospitalization), clinical presentation,

laboratory findings (C-reactive protein - CRP, complete blood cell count - CBC, the highest and lowest value for white blood cell count - WBC, absolute neutrophil count - ANC, immature -to-total neutrophil ratio - I/T ratio, platelet count, and coagulation status), applied therapy and outcome. During admission, clinical status of neonates was scored by the SNAP-PE (Score for Neonatal Acute Physiology - Perinatal Extension) and CRIB II (Clinical Risk Index for Babies) score (12). From laboratory findings we particularly analysed potential markers of infection. Early onset of neonatal sepsis was defined as an infection that develops in the first 72 hours of life, and late onset neonatal sepsis was defined as an infection that develops after 72 hours of life (10). Multidrug resistant bacteria were considered to be those showing resistance to three or more antimicrobial classes. Particular attention was paid to possible isolates of methicillin-resistant *Staphylococcus*, vancomycin-resistant *Enterococcus*, gentamicin-resistant *Klebsiella*spp, third-generation cephalosporin-resistant gram-negative organisms and carbapenem-resistant *Enterobacteriaceae*. There was no prophylactic administration of fluconazole in the NICU at the time of the study, and empiric antibiotic therapy for neonatal sepsis included ampicillin with gentamicin for suspected early onset neonatal sepsis, and ceftazidime with amikacin for neonatal sepsis suspected of nosocomial pathogens. This initial antibiotic therapy was corrected according to confirmed isolates, including meropenem and/or vancomycin, if necessary, depending on further clinical course and findings in particular patient.

Statistical analysis

Standard methods of descriptive statistics (central tendency measures, dispersion measures) were used. Parametric and non- parametric significance tests (χ2-test, Student's t- test) as well as linear correlation method were used to test the significance of differences between the samples. Statistical hypotheses were tested at a significance level of α= 0.05, e.g. the difference between the samples was considered significant at $p< 0.05$.

RESULTS

During the three-year period, 921 neonates were treated at the NICU (Table 1).

Table 1. Characteristics of 921 patients admitted to the neonatal intensive care unit (NICU)

Characteristics	No (%) of patients
Gestational age (weeks)	
Term (≥37GW)	420 (45.6)
Preterm (<37GW)	501(54.4)
Late preterm (34-36GW)	328 (35.6%)
Very preterm (<32GW)	173 (18.7)
Extremely preterm (<28GW)	58 (6.2)
Birth weight (grams)	
Low (<2500 g)	278 (30.1)
Very low (<1500g)	116 (12.5)
Extremely low (<1000g)	38 (4.1)
Mechanical ventilation within NICU stay	330 (35.8)
Surgery within NICU stay	46 (4.9)
Sepsis	
Clinically confirmed	396 (42.9)
Confirmed on blood cultures	187 (20.3)
MDR sepsis	22 (2.38)
Total	921 (100)

GW, gestational weeks; NICU, neonatal intensive care unit; MDR, multidrug resistance pathogen

Of the total of 921 treated neonates, multidrug resistance (MDR) pathogens among causative agents of neonatal sepsis were found in 22 (2.38%), evenly in both genders.

Perinatal risk factors for the development of neonatal sepsis were analysed in the MDR sepsis group, and compared with the control non-MDR sepsis group (Table 2). Immaturity and low birth

Table 2. Perinatal risk factors in the neonates with multidrug resistant (MDR) and non MDR sepsis

Variable	No (%) of patients in the group		p
	MDR (n=22)	Non-MDR (n=165)	
Gestational age (weeks)			
Preterm	17 (77.3)	63 (38.2)	0.0005
Late preterm	4 (18.2)	37 (22.4)	0.6546
Very preterm	13 (59.1)	26 (15.8)	0.0001
Extremely preterm	2 (9.1)	3 (1.8)	0.0456
Birth weight (grams)			
Low (<2500g)	15 (68.2)	49 (29.7)	0.0004
Very low (<1500g)	2 (9.1)	9 (5.5)	0.5016
Gender			
Male	13 (59.1)	103 (62.4)	0.7645
Female	9 (40.1)	62 (37.6)	0.7645
Mode of delivery			
Caesarean section	8 (36.4)	59 (35.8)	0.956
Vaginal	14 (63.6)	106 (64.2)	0.956
Apgar score (AS)			
AS in the first minute <5	9 (40.1)	47 (28.5)	0.2641
AS in the fifth minute <5	6 (27.3)	25 (15.2)	0.1522
Maternal risk factors			
No	12 (54.5)	92 (55.8)	0.9082
Firstborn	19 (86.4)	94 (57.0)	0.0081
In vitro fertilization	4 (18.2)	4 (2.4)	0.0006
Infections in pregnancy	3 (13.6)	29 (17.6)	0.64
Amniotic infectious	2 (9.1)	24 (14.5)	0.4912
PROM	2 (9.1)	38 (23.0)	0.1351

PROM, premature rupture of membranes

weight were statistically significant among perinatal risk factors originating from neonates. Gender and mode of delivery did not show significant difference between the groups. Maternal risk factors showed low significance, especially for the first birth and *in vitro* fertilization, that were significantly more frequent in the MDR group compared to the control.

The MDR sepsis was observed in neonates with significantly lower gestational age (33.59±3.1 vs. 36.27±3.3), lower birth weight (1852.08±746.3 vs. 2841.78±805.9) and lower Apgar scores in the first and fifth minute (Table 3).

Table 3.Clinical characteristics of the neonates with multidrug resistant (MDR) and non MDR sepsis

Variable	MDR (n=22)	Non-MDR (n=165)	p
GA (weeks) (mean±SD)	33.59±3.1	36.27±3.3	0.0004
BW (g) (mean±SD)	1852.08±746.3	2841.78±805.9	<0.0001
AS 1st minute (mean±SD)	5.6±1.0	6.98±2.3	0.0061
AS 5th minute (mean±SD)	6.63±3.0	7.78±1.67	0.0073
PRM (h) (mean±SD)	2.02±0.5	5.18±11.3	0.1924
CRIB II (mean±SD)	6.3±3.8	3.94±4.08	0.0243
SNAPEPE II (mean±SD)	32.3±15.7	23.51±24.99	0.0873
Early onset of sepsis (No, %)	7(31.8)	105 (63.6)	0.0043
Late onset of sepsis (No, %)	15(68.2)	60 (36.4)	0.0043
Gram-positive bacteria (No, %)	4(18.2)	120(72.7)	>0.0001
Gram-negative bacteria (No, %)	18(81.8)	45(27.3)	>0.0001
Meningitis (No, %)	6(27.3)	56 (34.0)	0.5308
Pneumonia (No, %)	10(45.5)	35(21.2)	0.0123
Increase in PVR (No, %)	4(18.2)	6(3.6)	0.0041
Severe IVH (No, %)	9(40.1)	5(3.0)	>0.0001
Initial acute renal failure (No, %)	12(54.5)	34(20.6)	0.0005
IVIG (No, %)	12(54.5)	27(16.4)	<0.0001
Mechanical ventilation (No, %)	14 (63.6)	25 (15.2)	<0.0001
Parenteral nutrition (No, %)	18 (81.8)	45 (27.3)	<0.0001
Inotropes (No, %)	17(72.3)	40(24.2)	0.0001
NICU stay (days) (mean±SD)	20.7± 10.8	12.40±6.93	<0.0001
Outcome			
Survivors (No, %)	18 (81.8)	158(95.8)	0.0086
Non-survivors (No, %)	4 (18.2)	7(4.2)	0.0086

GA, gestational age; SD, standard deviation; BW, birth weight; AS 1st min, Apgar score in the first minute; AS 5th minute, Apgar score in the fifth minute; PRM, premature rupture of membranes; CRIB II, clinical risk index for babies scoring system; SNAPEPE II, score for neonatal acute physiology-perinatal extension; PVR, pulmonary vascular resistance; IVH, intraventricular haemorrhage; IVIG, intravenous immunoglobulins NICU, Neonatal intensive care unit

Clinically, neonatal sepsis caused by MDR pathogens manifested more frequently as late onset sepsis (p<0.004), more often with Gram-negative bacteria (p<0.0001), and with higher values of neonatal disease severity scoring systems (p<0.02 and p<0.008), comparing to the control non-MDR sepsis group (Table 3). Neonates with MDR sepsis often had multi-organ dysfunction and required more supportive therapy. Almost all neonates with MDR sepsis received parenteral nutrition, required mechanical ventilation support, received intravenous immunoglobulins more often, comparing to the control non-MDR sepsis group. They also required longer intensive treatment (20.7±10.8 vs.12.4±6.93 and had a higher mortality rate comparing to the control non-MDR sepsis group (p<0.008) (Table 3).

There were no significant differences in CRP levels between MDR and non-MDR sepsis group. Also, there were no significant differences in the absolute or immature neutrophil count to total neutrophil ratio between MDR and non-MDR sepsis group (Table 4). Neonates with MDR sepsis had slightly lower leukocyte values (10.56±3.1 vs. 14.12±8.4), and they had significantly more often recorded leukopenia, comparing to the control non-MDR sepsis group (p<0.0003)(Table 4). Significant differences in platelet counts were also recorded, neonates with MDR sepsis had lower platelet count (160.31±3 vs. 223.27±116.6), and they had significantly

Table 4. Laboratory characteristics in the neonates with multidrug resistant (MDR) and non MDR sepsis

Variable	MDR sepsis (n=22)	Non-MDR sepsis (n=165)	p
CRP (mg/L) (mean±SD)	38.06±0.5	21.69±40.1	0.0576
CRP <5 mg/ℓ (No, %)	12 (54.5)	88 (53.3)	0.9156
CRP >5 mg/ℓ (No, %)	10 (45.5)	77 (46.7)	0.9156
Htc (L/L) (mean±SD)	0.53±0.29	0.51±0.10	0.5169
Htc anaemia (No, %)	2 (9.1)	5 (3.0)	0.1554
Htc normal (No, %)	14 (63.6)	124 (75.2)	0.2449
Htc polycythemia (No, %)	6 (27.3)	36 (21.8)	0.5614
Leukocytes (x109/L) (mean±SD)	10.56±3.1	14.12±8.4	0.05
Leukocytes <6 (No, %)	9 (40.9)	19 (11.5)	0.0003
Leukocytes >13 (No, %)	6 (27.3)	69 (41.8)	0.1924
ANC (x109/L) (mean±SD)	4627.36±883.0	6056.70±4551.2	0.1444
ANC <1800 (No, %)	5 (22.7)	33 (20.0)	0.7675
ANC >13000 (No, %)	1 (4.5)	23 (13.9)	0.2150
IT ratio	0.088±0.02	0.082±0.09	0,7562
Platelets (x109/L) (mean±SD)	160.31±30.0	223.27±116.6	0.01
Platelets <150 (No, %)	11(50.0)	39 (23.6)	0.008
Albumin (g/L) (mean±SD)	26.13±19.0	27.57±4.2	0.4
coagulation status normal (No, %)	7 (31.8)	95 (57.6)	0.02
coagulation status disrupted (No, %)	15 (68.2)	70 (42.4)	0.02

CRP, C reactive protein; Htc, haematocrit; ANC, absolute neutrophil count; IT ratio, immature/total neutrophil ratio;

more often recorded thrombocytopenia, comparing to the control non-MDR sepsis group ($p<0.008$). Also, coagulation disorders were more frequently observed in the test compared to the control group ($p<0.02$) (Table 4).

Gram-negative bacteria were more frequently isolated in the MDR sepsis group, in particular *Acinetobacter*, which showed the greatest resistance to antibiotics (Table 5). Gram-negative bacteria were generally resistant to Gentamicin, while *Enterobacter* and *Acinetobacter* were resistant to several antibiotics; in two cases *Acinetobacter* was carbapenem-resistant, which has limited therapeutic antibacterial choices. We had no recorded *in vitro* resistance to vancomycin, colistin and fluconazole.

Table 5. Multidrug resistant (MDR) pathogens in neonatal sepsis

Bacterial isolate	No (%) of strains			p
	Total (n=22)	EOS (n=7)	LOS (n=15)	
Gram-positive bacteria	4	2 (28.6)	2 (13.3)	0.386
Staphylococcus	2	1 (14.3)	1 (6.7)	0.5641
Enterococcus	2	1 (14.3)	1 (6.7)	0.5641
Gram-negative bacteria	18	5 (71.4)	13 (86.7)	0.386
Escherichia coli	3	1 (14.3)	2 (13.3)	0.9492
Klebsiella	4	1 (14.3)	3 (20.0)	0.7468
Enterobacter	3	1 (14.3)	2 (13.3)	0.9492
Proteus	1	1 (14.3)	-	0.1339
Pseudomonas	2	-	2 (13.3)	0.3116
Acinetobacter	5	1 (14.3)	4 (26.7)	0.5182

EOS, early onset sepsis; LOS, late onset sepsis

DISCUSSION

Despite the steady progress in the intensive treatment of neonates worldwide, neonatal sepsis remains a top issue, as one of the major causes of neonatal morbidity and mortality (10). Current reports indicate that sepsis causes about a quarter of all neonates deaths, and sepsis mortality has increased by 10-15% every year in the last 2 decades (10). Suspected neonatal sepsis is a common indication for admission to the NICU (13-16). Blood culture is the gold standard for the confirmation of sepsis. The prevalence of culture proven neonatal sepsis is different in various studies, from 10% to 50%, which depends on criteria and sampling technique, as well as from quality of health care and hospital services in various countries (17). The incidence of blood culture-proven sepsis in our NICU currently is 20.3%.

The diversity of etiology of sepsis varies from one region to another region, and changes over time even in the same place. This is attributed to differences in quality of life, predisposing factors for infection, and usage of antibiotics (14 - 20). Neonatal sepsis caused by multidrug resistant (MDR) pathogens is an important cause of morbidity and mortality in critically ill neonates (7,14,20). In our study multidrug resistance pathogens among causative agents of neonatal sepsis were found in 22 neonates (2.38%). Generally, prevalence of MDRs is reported higher (21-24). According to Behmadi et al. (11), pathogens in late onset sepsis were significantly resistant to antibiotics, ranging from 13.6–47.8%. Analysing Gram-negative neonatal sepsis in their 8-year cohort study, Tsai et al. (20) found that MDRs accounted for 18.6% of all neonatal Gram-negative bacteraemia in the NICU. The results of Yusef et al. (25) show that MDRs are the most common cause of sepsis at their NICU and are associated with higher mortality compared with non-MDR sepsis. Multiply, the neonates are at risk of infection, and as is known, sources may originate from maternal disease, infections, interventions during pregnancy and/or childbirth, or postnatally, and come again out of the hospital, or even from the community (10). Unfortunately, they can all be MDR sources (14). Perinatal risk factors for neonatal infection have been investigated in numerous studies (13-18). Gestational immaturity and low birth weight in our study were confirmed as the most significant risk factors for the onset of MDR sepsis. According to Afonso and Blot (13) gradual decrease in susceptibility to routine antibiotic is more highlighted in lower birth weight and premature neonates. There were no gender differences between MDR and non-MDR sepsis group in our study, although, other studies found male predominance (11). Townsel et al. (18) in their contemporary review, exploring gender differences in critically ill preterm neonates, found that male predominance maintains a gender gap in neonatal outcomes. Similar conclusion was made in a research by Roy et al. (19) reporting statistically significant association between male gender and mortality among culture-positive neonates.

In our study maternal risk factors showed low significance, especially for the first birth and *in vitro* fertilization, that were more frequent in the MDR group compared to the control. This is quite different from other studies that mostly reported infections, prolonged rupture of the membrane, and lack of prenatal care (16).

Clinically, in our study neonatal sepsis caused by MDR pathogens manifested more frequently as late onset sepsis, with higher values of neonatal disease severity scoring systems, requiring more supportive therapy and longer intensive treatment, and finally higher mortality rate comparing to the control non-MDR sepsis group. The results of other studies are generally similar (20-22). Intensive treatment in critically ill neonates involves invasive procedures, that are also risk factors of infection (23,24). These are the so-called specific points of attention, given that most health-associated infections in intensive care units are associated with the use of therapeutic devices (24). Recommendations for the proper use of all appliances and medical materials (probes, catheters, suction of secretions, maintenance of venous catheters, etc.), as well as monitoring and preventing the spread of infection, are mandatory (1).

The timing of exposure, neonatal immune status, and causative agent virulence influence the clinical expression of neonatal sepsis (13). Immunologically impaired response, especially in premature neonates, whose prolonged stay in NICU, with more invasive procedures, makes them suitable for healthcare associated infection and multidrug resistant pathogens (24).

The length of intensive treatment was significantly longer in the MDR group (20.7 ± 10.8 days) compared to the control non-MDR sepsis group (12.40 ± 6.93 days). The available evidence suggests a higher incidence and mortality rate of late-onset sepsis in premature and very low birth weight neonates, but pathogen distribution and risk exposure for MDRs are similar for all neonates admitted to the NICU (15,16,21,22).

There are different reports on the utility of laboratory parameters in the assessment of neonatal sepsis, and certainly, it is a significant tool in all sepsis scoring systems (17, 26-28). In our study, neonates with MDR sepsis had slightly lower leukocyte values, with more often recorded leukopenia, and lower platelet count with more frequently recorded thrombocytopenia, and without significant difference in the values of CRP, absolute neutrophil count or I/T ratio, comparing to the control non-MDR sepsis group. Also, coagulation disorders were more frequently observed in the test compared to the control group. The results of other studies are similar (27,28). The association of thrombocytopenia and coagulation disorders in septic patients is known (27), but in neonates, thrombocytopenia usually predominates in reports, while reports of coagulation status of neonates are less frequent. Klingenberg et al. (17) concluded that neonatal sepsis is an active condition, and that careful assessment of clinical manifestations in combination with properly selected biomarkers can be used to support or deny the diagnosis of sepsis, all aimed at a more rational use of antibiotics. Gram negative bacteria were more frequently isolated in the MDR sepsis group, in particular Klebsiella and *Acinetobacter*, which showed the greatest resistance to antibiotics. Our results showed similarity to the studies from Jordan (25), Greece (29), Taiwan (20), and Egypt (21), which report better sensitivity causes of early onset sepsis, while late onset sepsis pathogens showed a greater level of resistance, particularly in very preterm and extremely low birth weight neonates. The high prevalence of neonatal sepsis caused by MDR pathogens in some regions, as reported in India (7,22), Taiwan (20) and others, is partly explained by the use of antibiotics, for a class above the World Health Organization recommendations. Differences between multidrug resistant pathogens and their corresponding drug sensitive complement were not analysed in our study, because MDR infections are still rather rare. Because the treatment has not produced satisfactory results, modern medicine is increasingly promoting the prevention, education, responsibility and permanent control of hospital infections (1).

In conclusion, neonatal MDR sepsis has a risky clinical course and outcome. It is a threat to life, it complicates treatment, prolongs NICU stay, increases costs and mortality. Recovery of those neonates depends on timely clinical suspicion, adequate treatment and supervision. Reasonable and rational use of antibiotics is the only right choice in today's challenges. Outcomes may be improved by preventative strategies, earlier and accurate diagnosis, which require monitoring of local epidemiological data to improve the treatment.

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TRANSPARENCY DECLARATION

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