Polish Journal of Microbiology
2017, Vol. 66, No 2, 265–268

SHORT COMMUNICATION

Erythromycin or Clindamycin – is it Still an Empirical Therapy against *Streptococcus agalactiae* in Patients Allergic to Penicillin?

PIOTR LESZCZYŃSKI[1, 2], BEATA SOKÓŁ-LESZCZYŃSKA[1, 3]*, BRONISŁAWA PIETRZAK[4], ANNA SAWICKA-GRZELAK[1, 3] and MIROSŁAW WIELGOŚ[4]

[1] Department of Medical Microbiology, Warsaw Medical University of Warsaw, Warsaw, Poland
[2] Hospital Infection Control Team, Infant Jesus University Hospital, Warsaw, Poland
[3] Department of Medical Microbiology, Infant Jesus University Hospital, Warsaw, Poland
[4] I Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland

Submitted 11 August 2016, revised 10 December 2016, accepted 27 January 2017

Abstract

Retrospective analysis of *Streptococcus agalactiae* antibiotic susceptibility isolated in 2010–2013 was performed. Penicillin was still the first-line antibiotic. Due to the high percentage of strains resistant to erythromycin and clindamycin empirical treatment with these antibiotics may not be effective. Lower resistance rate to erythromycin and clindamycin among strains isolated from infected pregnant women and newborns were observed than among strains isolated from samples from patients hospitalized in other departments (29% and 47% v. 46% and 63%). The increasing resistance rate might give a rise to a new epidemiological situation.

Key words: *Streptococcus agalactiae*, clindamycin, erythromycin, susceptibility on antibiotics

GBS colonizes the oral cavity, respiratory tract, gastrointestinal and genitourinary tract. The risk of transmission is up to 70%. Postpartum infections arise from other family members or from hospital environment. GBS colonization in pregnant women in full-term pregnancy is the most important predisposing factor that increases 25 fold the risk of developing early onset disease in newborn. It varies with ethnic groups, with equal numbers of women being colonized in a transitory, intermittent or persistent manner and depends on age, sexual activity, contraceptive methods used (Bigos *et al*., 2012).

Perinatal antibiotic prophylaxis should be given to pregnant women who carry GBS in the vagina and/or rectum, if in the course of pregnancy was bacteriuria diagnosed with GBS etiology, or if the neonatal GBS infection occurred in previous children born by this patient. Indication for antibiotic prophylaxis is also 35–37 week of pregnancy before labor before, if pregnant woman in labor was admitted to the hospital after more than 18 hours after disruption of fetal membranes and in case of intrapartum fever (Bigos *et al*., 2012).

An aim of our study was the comparison of antibiotic susceptibility of *Streptococcus agalactiae* strains isolated from various samples taken healthy or infected pregnant women, neonates (group A – wards: Gynecology, Obstetrics, Pregnancy Pathology, Neonatal, Neonatal Intensive Care Unit) and other adult patients hospitalized in various hospital wards group B – wards: Internal Diseases, Urology, Transplantology, Surgery, Orthopedics) during 2010–2013.

The retrospective analysis included isolates from vaginal/rectal swabs, blood, urine, swab, cervix, blood, external ear swabs. Swabs from vagina/rectum were transported in a transport Amies medium and submitted for culture within 24 hours, they were cultured onto the Todd – Hewitt's broth (24 hours incubation, 37°C, aerobic atmosphere). They were subcultured on the CHROMagar – Strep (bioMerieux) and blood agar. Other samples were cultured according to routinely used protocol. After incubation, the cultures were reviewed for the presence of characteristic for GBS colonies and latex agglutination test detecting polysaccharide C characteristic for group B was performed (bioMerieux). Susceptibility to erythromycin, clindamycin and vancomycin was performed in case of isolates from swabs from vagina/from patients allergic to penicillin – information was given on referral form. GBS isolates other patients had susceptibility tests done routinely. Retrospective

* Corresponding author: B. Sokół-Leszczyńska, Department of Medical Microbiology, Warsaw Medical University, Warsaw, Poland; **e-mail: beata.sokol-leszczynska@wum.edu.pl**

Table I
Antibiotic resistance.

Year	Group A (Gynecology, Obstetrics, Pregnancy Pathology, Neonatal, Neonatal Intensive Care Unit)				Group B (Internal Diseases, Urology, Transplantology, Surgery, Orthopedics Hospital Wards)			
	Benzyl-penicillin	Erythro-mycin	Clindamycin	Vancomycin	Benzyl-penicillin	Erythro-mycin	Clindamycin	Vancomycin
2010	0/19	5/15	0/4	0/12	0/69	14/33	12/25	0/87
2011	0/15	0/3	4/8	0/41	0/43	15/27	35/59	0/77
2012	0/3	11/30	30/51	0/53	0/4	16/34	51/71	0/76
2013	0/3	10/41	19/50	0/52	0/10	14/34	36/58	0/73
Total	0/40 (0%)	26/89 (29%)	53/113 (47%)	0/158 (0%)	0/126 (0%)	59/128 (46%)	134/213 (63%)	0/313 (0%)

* based on data given on lab reports, not on microbiological test

analysis was made on the basis of information contained in Hospital IT System.

Incidence of colonization in consecutive years and number of examined vaginal/rectal swabs is 12.4% in 2010 (1409); 17% in 2011 (2125); 19.6% in 2012 (2348); 16.4% in 2013 (2401), respectively. All GBS strains were isolated from healthy pregnant women not allergic to penicillin and therefore no susceptibility test was performed.

Susceptibility analysis to benzylpenicillin, erythromycin, clindamycin and vancomycin was performed for GBS isolates from group B patients. All strains were susceptible to benzylpenicillin and vancomycin. Constitutive and inductive macrolide – lincosamide – streptogramin B resistance mechanisms were identified. Results of resistance rate are presented in Table I.

Sensitivity of bacterial cultures in detection of *S. agalactiae* varies from 50 to 84.3%. Underestimation of GBS neonatal disease can be related to non-hemolytic GBS isolates (5–8% of all isolates). Sensitivity of late antenatal cultures for identifying colonization status at delivery varies from 54.3–87%; specificity 96%; positive predictive value 87% and negative predictive value 95–97%. An important limitation of the detection of GBS in culture is the need for viable organisms and for an average culture period of 48–72 hours. Even if the swab would be taken according to procedure just before labour, it can give false negative result. Routine vaginal swab culture between 35 and 37 hbd has its limitations, because approximately 6% of pregnant women is colonized later (Edwards *et al.*, 2002; Verani *et al.*, 2010; Verani and Schrag, 2010; Brown *et al.*, 2013; Savini *et al.*, 2013; Szymusik *et al.*, 2014). Incidence of GBS colonization obtained by the gold standard – culture – reported by various authors is presented in Table II.

According to de-Paris *et al.* (2011) culture method was positive in 15.96% samples, while the PCR technique in 26.99%. Of the 221 culture-negative samples, 13% were positive with PCR Positive results of intrapartum PCR DNA were reported in 35 minutes and negative results confirmed in 50 minute. According to the studies performed by Abdelazim (2013) the sensitivity and specificity of intrapartum PCR test was 98.3% and 99%, respectively. Positive predictive value of intrapartum PCR test was 86.4% and negative predictive value – 97.4% (NIHCE, 2015).

Poncelet-Jasserand *et al.* (2013) stated that 70% of early-onset neonatal GBS infections were associated with mothers whose colonization status was either unknown or negative at the time of screening (35–37 hbd). The cost of reagents and labor was 13 times higher for PCR detection than for the use of chromogenic media. Helali *et al.* (2012) estimated that positive result of screening at 35–37 week's gestation resulted in unnecessary anti-

Table II
Literature review on incidence of GBS colonization in 1995–2014 years (literature is available from corresponding author)

Country	Year	Colonization incidence (%)
Italy	1995–2007	11.3–17.9
Ireland	1998–2004	11.8–25.6
The Netherlands	2000–2002	21
Greece	2003	6.6
Turkey	2003–2005	6.5–10,6
Scandinavia	2003–2008	24.3–36.0
Czech Republic	2004	29.3
Germany	2006	16.0
United Kingdom	2006	21.3
Pakistan	2007	18
Poland	2007–2008	11.4
	2008–2012	25–30
Nigeria	2010–2011	18
Ethiopia	2011–2012	11.3–15.4
Republic of Congo	2012–2013	20
Republic of South Africa	2014	30.9

Table III
Literature review on resistance rate to erythromycin and clindamycin among *S. agalactiae* strains in 1992–2014 years (literature is available from corresponding author).

Country	Year	Antibiotic resistance (number of resistant strains/ number of tested strains)	
		Erythromycin	Clindamycin
Spain	1992–2009	30/212	30/212
New Zealand	2002–2004	8/88	13/88
Italy	2002–2005	15/91	15/91
Poland	2006–2010	6/22	5/22
Australia	2002–2006	3/47	1/47
Portugal	2006–2011	9/43–22/95	7/120–17/97
Egypt	2008	5/38	9/38
Syria	2008	39/72	25/72
Myanmar	2009–2010	4/47	4/47
Israel	2010	15/88	15/88
Nigeria	2010–2011	5/58	5/58
Malesia	2010–2011	24/103	18/103
Ethiopia	2011–2012	2/17	3/17
Republic of South Africa	2012	27/128	22/128

biotic prophylaxis for 13,6% of pregnant women in the study compared to 4,5% for women using the intrapartum PCR test. This resulted in incremental costs of €36 and €173 to the health care system and hospital, respectively, for each mismanaged patient. Molecular tests have not identified susceptibility to antibiotics (penicillin, erythromycin, clindamycin) (Church *et al*., 2011; Kasahara *et al*., 2010).

Penicillin is still the first-line antibiotic effective against GBS. Recently non-penicillin-susceptible GBS isolates have been reported in Japan and the United States due to a Q557E mutation in *pbp2x* (Kasahara *et al*., 2010). The substantial increases of erythromycin-resistant GBS isolates were observed in England and Wales (< 3% in 1990s to 15% in 2010 (Clifford *et al*., 2011). Clifford *et al.* (2011) observed higher number of strain resistant to clindamycin than to erythromycin in isolates from New Zealand and Australia. Seo *et al.* (2010) have described GBS strains resistant to clindamycin and susceptible to erythromycin belonging to serotypes Ia, Ib, III and VIII. This mechanism was based on gene *lnu (B).* Arana *et al.* (2014), in 2014, reported the first human *S. agalactiae* isolate in Europe with new mechanism of resistance to clindamycin based on gene *lnu (B).* In 2014 in USA two vancomycin-resistant invasive *S. agalactiae* strains were isolated (both serotype II, multilocus sequence type 22). The strains were carrying van G elements (Srinivasan *et al*., 2014). The increasing resistance rate might give a rise to a new epidemiological situation. Furthermore, women arriving from various countries with high resistance rates to erythromycin or/and clindamycin might be admitted to Polish hospitals. They may constitute reservoir of multiresistant *S. agalactiae*. Lack of knowledge of local epidemiological data can contribute to ineffective empirical therapy. In the Table III are presented resistance rates to erythromycin and clindamycin in various countries in the world.

Experts had revised procedures that could improve current practices for prevention of perinatal GBS disease and facilitate consensus towards European guidelines and their implementation. If a woman is determined to be at high risk for anaphylaxis, a vaginal-rectal swab should be collected between 35–37 weeks gestation and susceptibility to clindamycin and erythromycin should performed by means of D-zone test. Erythromycin is not recommended because of high rates of resistance present in GBS and to subtherapeutic concentrations in amniotic fluid and fetal serum. Clindamycin could be a proper choice (Di Renzo *et al*., 2015).

The increasing resistance rate might give a rise to a new epidemiological situation. Annual resistance pattern analysis performed by local microbiological laboratory is required for an effective empiric therapy. Additionally, at the time of migrating refugee population knowledge of epidemiological data might contribute to better medical care.

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