THE VARIATION OF ANTIBIOSENSITIVITY FROM 1998 AND RESPECTIVELY 2008 IN CHILDREN'S SHIGELLA ACUTE DIARRHEA IN ARAD COUNTY

Simona Dumitra[1], Sabina Morgovan[2], Liana Precup[1], Dorin Lazar[1]
[1]Vasile Goldis Western University of Arad
[2]Arad County Hospital

Abstract

Aims: The authors aim to establish the variation of antibiosensitivity from1998 and, respectively 2008, in Shigella acute diarrhea and based on the results to elaborate a therapeutic local guide

Methods: The authors study the antibiosensitivity versus resistance models, in Shigella acute diarrhea of children from Arad County admitted in the hospital during 1998 and, respectively from 2008; Difussimetric antibiotic test are performed according to the existing standards and the antibiosensitivity of the 11th most frequently used antibacterial drugs in the antibiotic sensitivity tests was noted.

The data is introduced in an Excel database and analyzed with statistical methods in SPSS 10.

Results: A significant decrease of sensitivity ($p < 0.001$) in the last 10 years is noted for Ampicillin +Sulbactam(93,33% versus 48,31%), Amoxicilin+ Clavulanic Acid (91,11% versus 54,83%), Cephalosprins of 3rd generation(97,77% versus 70,36%), followed closely by Nitrofurantoin (55,55% versus19,35%)($p = 0.002$), Nalidixic Acid (80% versus 19,35%) ($p=0.01$) and Fluroquinolones (93,33% versus 77,41%)($p=0.05$). Comparing the results obtained from both groups, we can observe that the resistance has increased for all antibiotics, except for Chloramphenicol, Gentamicin and Co-Trimoxazole (not statistically significant).

Conclusions: The antibiosensitivity at Shigella in our region to the usual anti-microbial agents (Ampicillin, Tetracycline, Sulphametoxazole/ Trimethoprim, Nalidixic Acid, Nitrofurantoin), has importantly decreased, being demandatory to limit their use.

Fluoroquinolones (at children >12 years old) and cephalosporines (at children < 12 years old), remain the choice anti-bacterial agents in the eradication of Shigella infection.

Regional antibiotherapy guidelines, periodical up-dated by chimiosensitivity studies are needed.

Key words: antibiosensitivity, antibioresistance, Shigella, child

Background

Acute diarrhea with Shigella remains an important problem of morbidity in Romania. There are studies which consider this etiology to be the first in the digestive infections of children in Romania. A 5 year study realised in 2006 by our group, which involved 387 children admitted with acute diarrhea showed that the main etiology is represented by Shigella and Salmonella strains, followed by Escherichia Coli, Campylobacter, and in a low percentage by Proteus:

Table 1- The etiology in bacterial acute diarrhea in children from Western Romania - a 5 year study (387 children).

The etiological factor	Frequency	Percentage
Shigella	**182**	**47.1**
Salmonella	**155**	**40**
Pyocyanic	**4**	**1**
Escherichia Coli	**22**	**5.7**
Proteus	**1**	**0.3**
Campylobacter	**23**	**5.9**
Total	**387**	**100.0**

It's hard to say if this percentage represents a real incidence and that is not a bacteria more easily detected in Romania!

The resistance at antibiotics in our region is not well known due to: unicentral studies, realised on small groups of children (low number of strains), limited geographical areas, short periods of time.

The data are hardly accessible, lacunary, without

being assembled in one vision which would allow us to visualize the problem.

Aim

To detect if the pattern sensitivity/resistance at antibiotics in Shigella from our geographical area has suffered statistically significant changes in the last decade.

The results could help to create regional guidelines of antibiotherapy in Shigella's acute diarrhea in children.

Methods

73 children, age 1 month – 18 years old , admitted in the Department of Infectious Diseases, Clinic of Paediatrics, Arad, Romania between 1998, respectively 2008 with the diagnosis of acute diarrhea with Shigella were included. The children were divided into 2 groups: the 1998 group(42 strains with Shigella) and the 2008 group (31 strains with Shigella).

In both groups, the strains of Shigella flexneri were presented in the highest percentage, followed in a low percentage by Shigella sonnei, Shigella boydi. The strains of Shigella dysenteriae were identified only, in the 1998 study group:

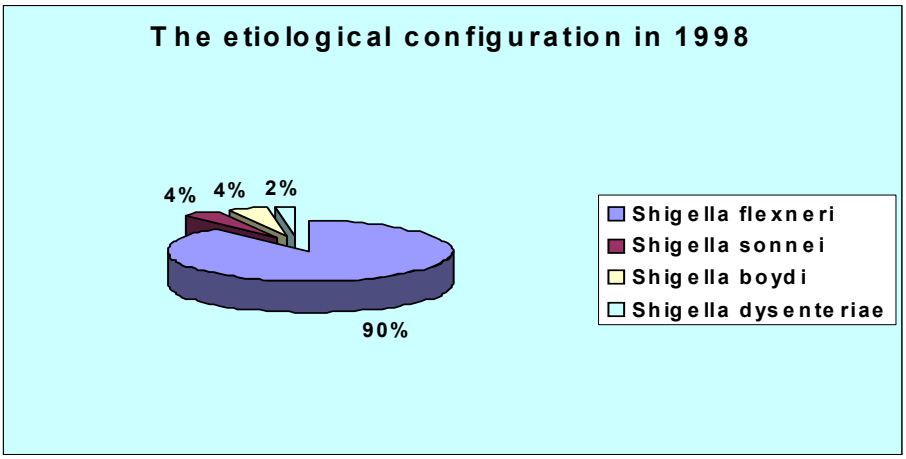

Figure 1 - The etiological configuration in 1998.

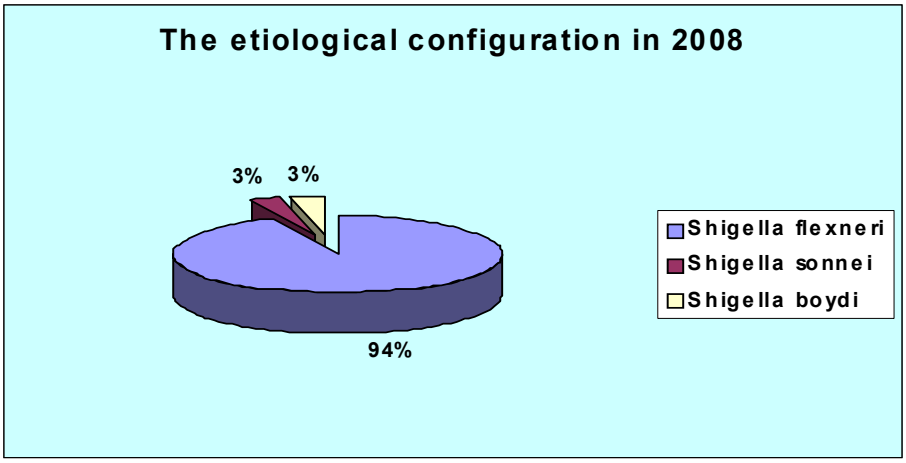

Figure 2 - The etiological configuration in 2008.

The following variables were monitored :

Antibiosensitivity – MIC (minimum inhibitory concentration) at least 2- 4 times < the level of antibiotic in serum or humours.

Antibiotic resistance - MIC > the level of antibiotic in serum or in humours.

The diffusimetric antibiotic test was performed according to the existing standards in the Laboratory of Microbiology, Clinical Emergency Hospital, Arad, Romania.

The data was introduced in an Excel database and analyzed with statistical methods in SPSS 10. The value of $p< 0.05$ was considered significant.

The variables were reported to the most frequently used antibacterial drugs in the antibiotic sensitivity tests: Ampicillin, Ampicillin + Sulbactam, Amoxicillin + Clavulanic Acid, Cephalosporins, Gentamicin, Chloramphenicol, Tetracycline, Co-trimoxazole, Nalidixic Acid, Fluoroquinolone and Nitrofurantoin.

Results and discussions

Table 2 - The comparison of antibiosensitivity 1998/2008.

	Sensitivity 1998		*Sensitivity 2008*		
	No	***%***	***No***	***%***	***P***
A	*9/45*	*20*	*2/31*	*6.45*	*insignificant*
A + S	*42/45*	*93.33*	*15/31*	***48.38***	***<0.001***
A+ C	*41/45*	*91.11*	*17/31*	***54.83***	***<0.001***
Ceph 3rd gen	*44/45*	*97.77*	*22/31*	***70.86***	***<0.001***
G	*15/45*	*33.33*	*13/31*	*41.83*	*insignificant*
C	*6/45*	*13.33*	*12/31*	*38.70*	***0.02***
T	*2/45*	*4.44*	*1/31*	*3.22*	*insignificant*
S/T	*16/45*	*35.5*	*12/31*	*38.7*	*insignificant*
Nx	*36/45*	*80*	*15/31*	*48.38*	*0.01*
Fluoroq	*42/45*	*93.33*	*27/31*	***77.41***	*0.05*
N	*35/45*	*55.55*	*6/31*	*19.35*	*0.002*

A-Ampicillin, ***A + S*** Ampicillin + Sulbactam, ***A+ C*** Amoxicillin + Clavulanic Acid, ***Ceph 3rd gen*** Cephalosporins, ***G*** Gentamicin, ***C*** Chloramphenicol, ***T*** Tetracycline, ***S/T*** Co-trimoxazole, ***Nx*** Nalidixic Acid, ***Fluoroq*** Fluoroquinolone and ***N*** Nitrofurantoin

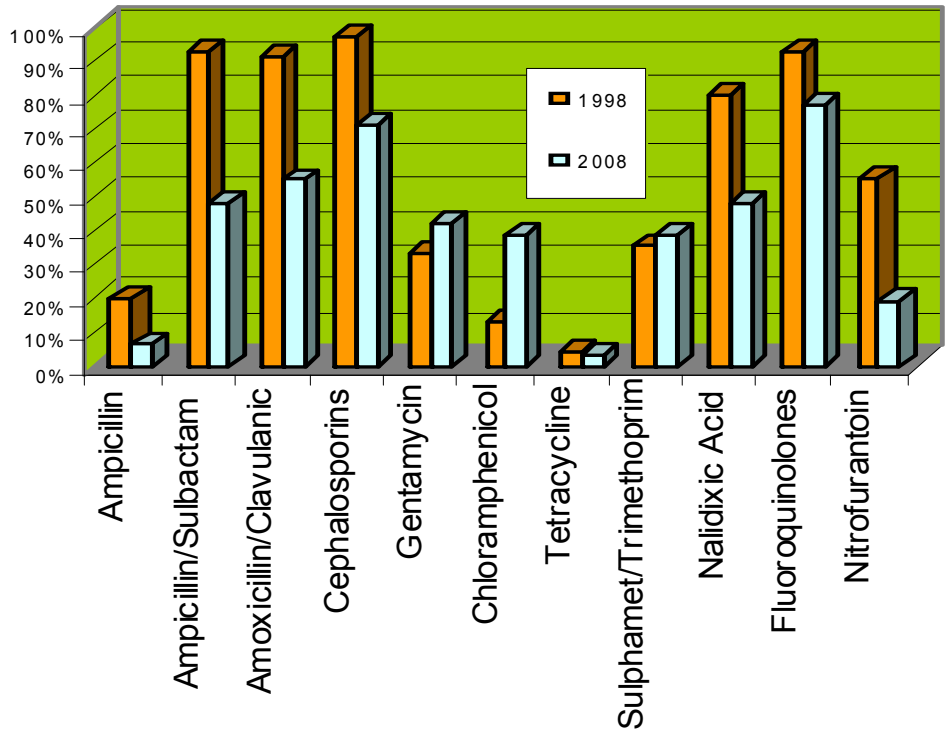

Figure 3 - The comparison of antibiosensitivity 1998/2008.

The comparative data analyse show that the highest sensitivity is for Cephalosporins, Fluoroquinolones, Amoxicillin and Clavulanic Acid, Nalidixic Acid.

A significant decrease of sensitivity ($p < 0.001$) in the last 10 years is noted for Ampicillin +Sulbactam, Amoxicilin+ Clavulanic Acid, Cephalosprins of 3rd generation, followed closely by Nitrofurantoin ($p = 0.002$), Nalidixic Acid ($p = 0.01$) and Fluroquinolones ($p = 0.05$).

For Ampicillin a percentage decrease is mantained without being significant statistically.

A statistically significant increase of Chloramphenicol's sensitivity is observed.

Table 3 -Antibiotic resistance 1998/2008.

	Resistance 1998		Resistance 2008		
	No	%	No	%	P
A	15/45	33.33	28/31	90.32	<0.001
A + S	1/45	2.22	7/31	22.58	<0.001
A+ C	2/45	4.44	6/31	18.35	0.05
Ceph 3rd gen	1/45	2.22	6/31	18.35	0.02
G	20/45	44.44	17/31	54.83	insignificant
C	30/45	66.66	15/31	48.38	insignificant
T	30/45	66.66	28/31	93.56	0.002
S/T	20/45	44.44	16/31	51.61	insignificant
Nx	6/45	13.33	10/31	72.25	0.05
Fluoroq	2/45	4.4	7/31	24.58	0.02
N	18/45	40	20/31	64.51	0.05

A-Ampicillin, ***A + S*** Ampicillin + Sulbactam, ***A+ C*** Amoxicillin + Clavulanic Acid, ***Ceph 3rd gen*** Cephalosporins, ***G*** Gentamicin, ***C*** Chloramphenicol, ***T*** Tetracycline, ***S/T*** Co-trimoxazole, ***Nx*** Nalidixic Acid, ***Fluoroq*** Fluoroquinolone and ***N*** Nitrofurantoin

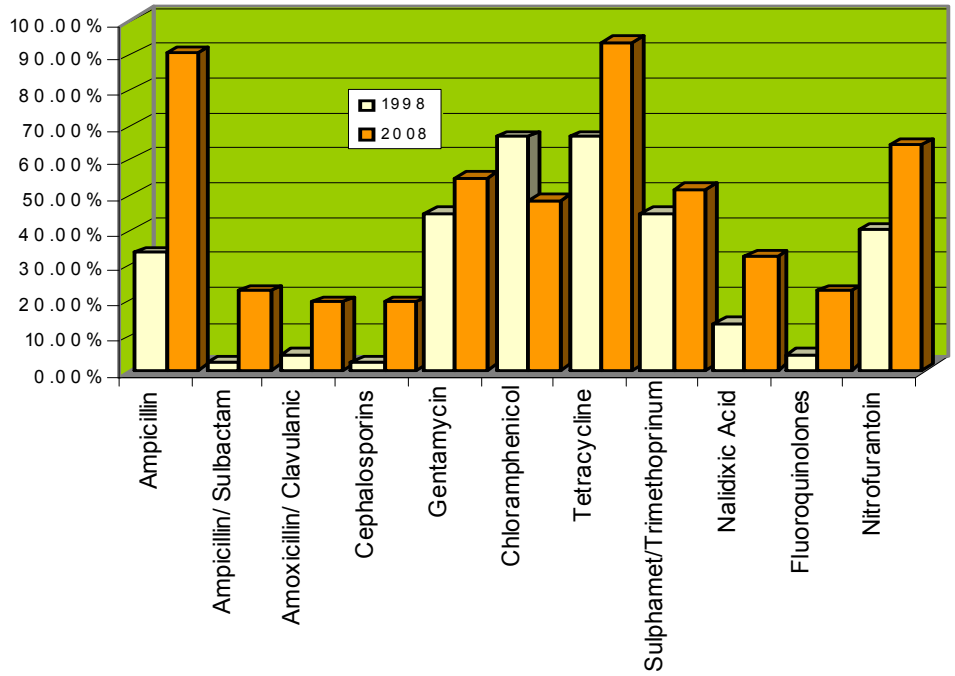

Figure 4 - Antibiotic resistance 1998/2008.

Comparing the results obtained from both groups, we can observe that the resistance has increased for all antibiotics, except for Chloramphenicol (is not statistically significant).The highest antibiotic resistance in 2008 is for Tetracycline, Ampicillin, Nalidixic Acid and Nitrofurantoin The increase of antibiotic resistance in the last decade is observed for Ampicillin, Tetracycline, Ampicillin+ Sulbactam, Cephalosporins 3rd generation, Fluoro-quinolones, Nitrofurantoin and Nalidixic Acid. Gentamycin and Sulphamethoxazole/ Trimethoprim don't show significant changes.

A decrease of sensitivity for all antibiotics is observed, except for Chloramphenicol; the decrease is statistically significant for 6 of them. An alarming phenomenon is the decrease for the antibiotics more recently introduced as therapy: Ampicillin/Sulbactam, Amoxicillin/ Clavulanic Acid, Cephalosporins of 3rd generation, Fluoroquinolones.The increase of resistance for all antibiotics is observed except for Chloramphenicol (not statistically significant)

The increase of resistance is significant for Ampicillin, Tetracycline, but alarming as well for

Ampicillin/Sulbactam, Cephalosporins of 3rd generation, Fluoroquinolones, Nitrofurantoin and Nalidixic Acid. Gentamycin and Sulphametoxazole/Trimethroprim don't show significant changes.

Based upon these findings we tried to create a local guideline for using antibiotics in Arad county in Shigella acute diarrhea in childhood. The first recommended antibiotic choice should be represented by fluoroquinolones (children >12 years old) and cephalosporins (children < 12 years old):

Table 4 - Local guidelines of antibiotic therapy in Shigella's infection.

First choice	To avoid
Fluoroquinolones **Cephalosporins**	**Ampicillin** **Tetracyclin** **Nitrofurantoin** **Sulphametoxazole/Trimetoprim**

Many international studies (1, 2, 4, 5, 7, 9, 10, 11, 12, 13, 14, 15) show that the antibiotic susceptibility patterns are variable for each geographical region.

The pattern of antibiotic susceptibility in Arad is characterised by the following features:

- increase of resistance to the classic antibiotics, as well as to the more recently introduced antibiotics, whose efficiency degraded progressively in the last decade.
- the resistance has increased compared to the previous studies performed in Romania Musta (7), Jugulete (9):
- the level of the antibiotic resistance is:
  - a little bit higher than the European one, showed by the studies of Vrints (16) Belgium, Haukka (6) - Finland, Samonis (12) Greece.
  - under the European one described by Karacan-Turkey (8).
  - similar to the ones described by Diniz Santos-Latin America (2), Peirano- Brasil(11), Fulla-Chile (4).
  - under the Asian one described by Uppal (15), Pazhani (10)– India and under the African one described by Asrat – Ethiopia (1) and Sire-Senegal (13).

The normal questions to be asked, after analysing these results are: What happened in the last decade to determin such an important decrease of antibiosensitivity of the usual anti-microbial agents at Shigella, in our region? What are the responsable factors which influenced this outcome?

An answer to these questions, could be, the increased unreasonable administration of antibiotics in the last decade due to various reasons: unreasonable prescriptions in simple or toxigene acute diarrhea; use of reserve antibiotics which determine a fast errosion of their efficacity; non -adequate dosage of therapy (low dosage, mistakes in the administration rhythm, medical interractions); lack of patient compliance; a large availability of antibiotics on the pharmaceutical market , allowing, also, an important self-medication of the patient.

A study on self-medication with antimicrobial drugs (5), realised in 19 European countries in 2006, showed that Romania has the 4th position in keeping an antibiotic storage at home after Italy, Spain and Lithuania, has the 2nd place in self-medication after Lithuania and occupies the 8th place, for prescribed antibiotic use after Slovakia, Italy, Croatia, Malta, Ireland, Israel and Spain.

The future solutions in controling this alarming phenomen, could be the beginning of a national programme to centralize all the important studies regarding the antibiotic resistance(ABR); creating regional guidelines of antibiotic therapy in acute diarrhea; continuous medical training for using the antibiotics with discrimination; involvement of creating opinion leaders in the field of child infectious pathology; mass-media involvement for informing the public opinion on the real danger of what antibiotic abuse means and restriction of self-medication and of access to antibiotics without prescription.

Conclusions

1. The antibiosensitivity at Shigella in our region to the usual anti-microbial agents (Ampicillin, Tetracycline, Sulphametoxazole/ Trimethoprim, Nalidixic Acid, Nitrofurantoin), has importantly decreased, being demandatory to limit their use.
2. Fluoroquinolones (at children >12 years old) and cephalosporines (at children < 12 years old), remain the choice anti-bacterial agents in the eradication of Shigella infection but start to develop significant resistance in the last decade.
3. Regional antibiotherapy guidelines, periodical up-dated by chimiosensitivity studies are needed.

References

1. Asrat D. – Shigella and Salmonella serogroups and their antibiotic susceptibility patterns in Ethiopia - East Mediterr Health J. 2008 Jul-Aug;14(4):760-7
2. Diniz-Santos DR, Santana JS, Barretto JR, Andrade MG, Silva LR – Epidemiological and microbiological aspects of acute bacterial diarrhea in children from Salvador, Bahia, Brazil, Braz J Infect Dis. 2005 Feb; 9 (1): 77-83. 4.
3. Dumitra S – Predictive factors of the bacterial etiology in acute diarrhea in children – Patterns of antibiotic sensitivity and resistance in Shigella and Salmonella

strains, at children admitted with acute diarrhea in the county of Arad and Timis during 2001-2004, Ph D Thesis, University of Medicine and pharmacy "Victor Babes", Timisoara, Romania.
4. Fulla N, Prado V, Duran C, Lagos R, Levine MM - Surveillance for antimicrobial resistance profiles among Shigella species isolated from a semirural community in the northern administrative area of Santiago, Chile, Am J Trop Med Hyg. 2005 Jun; 72 (6): 851-4.4.
5. Grigoryan L. et al - Self medication with antimicrobial drugs in Europe 2006, Emerg. Infect. Dis, 2006
6. Haukka K, Siitonen A.- Emerging resistance to newer antimicrobial agents among Shigella isolated from Finnish foreign travellers. Epidemiol Infect. 2008 Apr;136(4):476-82. Epub 2007 Jun 20.
7. Jugulete G, Luminos M, Iagaru R, Mantescu R, Botea S –The bacterial dysenteriae in chlidren – the antibiotic therapy correlated with the actual chimioresistance in Shigella - Infectio.ro, 2005, nr. 3.
8. Karacan C, Tavil B, Topal Y, Zorlu P, Tayman C - Evaluation of shigellosis in a Turkish children's hospital - Pediatr Int. 2007 a. Oct;49(5):589-92.
9. Musta V. - Contributionsi regardin thr ethiopathogenic corelations in enteric infantile infections – PhD Thesis, University of Medicine and Pharmacy, Timişoara, 2001.
10. Pazhani GP, Niyogi SK, Singh AK, Sen B, Taneja N, Kundu M, Yamasaki S, Ramamurthy T.- Molecular characterization of multidrug-resistant Shigella species isolated from epidemic and endemic cases of shigellosis in India - J Med Microbiol. 2008 Jul;57(Pt 7):856-63.
11. Peirano G, Souza FS, Rodrigues DP; Shigella Study Group – Frequency of serovars and antimicrobal resistance in Shigella Spp from Brazil - Mem Inst Oswaldo Cruz. 2006 May;101(3):245-50
12. Samonis G, Maraki S, Christidou A, Georgiladakis A, Tselentis Y – Bacterial pathogens associated with diarrhoea on the island of Crete, Eur J Epidemiol. 1997 Oct; 13 (7): 931-6.
13. Sire JM, Macondo EA, Perrier-Gros-Claude JD, Siby T, Bahsoun I, Seck A, Garin B Antimicrobial resistance in Shigella species isolated in Dakar, Senegal (2004-2006) Jpn J Infect Dis. 2008 Jul;61(4):307-9.
14. Streit JM, Jones RN, Toleman MA, Stratchounski LS, Fritsche TR – Prevalence and antimicrobial susceptibility patterns among gastroenteritis-causing pathogens recovered in Europe and Latin America and Salmonella isolates recovered from bloodstream infections in North America and Latin America: report from the SENTRY Antimicrobial Surveillance Program (2003), Int J Antimicrob Agents. 2006 May; 27 (5): 367-75.
15. Uppal B, Mittal SK - Nosocomial diarrhea, Indian J Pediatr. 2004 Oct; 71 (10): 883-5..
16. Vrints M, Mairiaux E, Van Meervenne E, Collard JM, Bertrand S.J - Surveillance of antibiotic susceptibility patterns among Shigella sonnei strains isolated in Belgium during the 18-year period 1990 to 2007 - Clin Microbiol. 2009 May;47(5):1379-85. Epub 2009 Mar 25.

Correspondence to:
Simona Dumitra,
Victoriei Street 1-3, Arad
E –mail: dumitrasimona@yahoo.com