Antimicrobial Usage in Orphanages: Results of the Unique Prospective Multicentre Study CORPUS

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Abstract

Objectives: The pattern of use of antimicrobials has been shown to be an independent risk factor for the emergence and spread of resistant microorganisms. It has been previously shown that orphanages are considered to be reservoirs of resistant strains, which spread to day-care centres and into clinical settings. A special study was designed to evaluate patterns of use of antimicrobials in children from different orphanages located in geographically distinct Russian cities. **Methods:** An analysis of the use of antimicrobials in the previous 12 months was performed based upon reviews of medical histories of 743 children <7 years from 11 orphanages in 4 cities of European Russia (Moscow, St Petersburg, Smolensk, Karachev). **Results:** In general, prescription of antimicrobials varied from 0.31 courses/child/year in infant orphanage No. 7 in St Petersburg to 3.63 courses/child/year in Karachev. In all orphanages, β-lactams were the most frequently prescribed (51.3 to 100% of all antimicrobials). Among them, the predominant ones were (in order of frequency): ampicillin/oxacillin (164 courses), amoxicillin/clavulanate (148), cefazolin (129), cefotaxime (119) and ampicillin (103). In general, parenteral compounds were predominantly used in orphanages, with the proportion ranging from 60.7% to almost 100%. Macrolides/lincosamides were the second most frequently prescribed in 6 out of 11 orphanages, with azithromycin being prescribed more often (98 courses), exceeding sum of all macrolides. Both co-trimoxazole and aminoglycosides were the second most frequently prescribed in 2 out of 11 institutions. **Conclusions:** There were substantial variations in the frequency of antimicrobial prescriptions with no correlation to geographic location, size of city or specific child populations. It was a tendency in all orphanages to prescribe parenteral antimicrobials in spite of the presence of suitable oral alternatives. Enforcement measures have been implemented in order to prohibit unlicensed use of some antimicrobials in studied populations.

Introduction

One of the main reasons for the observed increase in antimicrobial resistance is the high frequency of inappropriate and excessive prescribing of antibiotics.[1] The pattern of antimicrobial use has been shown to be an independent risk factor for the emergence and spread of resistant microorganisms.[2] It has been previously shown that long-term care facilities in general, and orphanages in particular, can act as reservoirs of resistant strains, which then spread into the community and into clinical settings.[3,4] It has been estimated that 25–75% of antibiotic use in long-term care facilities is inappropriate.[5] However, studies to assess antibiotic use in orphanages have not yet been performed.

Objective

To evaluate patterns of antibiotic use in children from different orphanages located in geographically distinct Russian cities.

Materials and Methods

This observational, multicentre study was carried out in 11 orphanages located in four cities of the Central and North-Western regions of the Russian Federation:

- St Petersburg – Orph 1, Orph 2, Orph 3, Orph 4
- Moscow – Orph 5, Orph 6, Orph 7
- Smolensk – Orph 8, Orph 9, Orph 10
- Karachev – Orph 11.

The medical records of 743 children <7 years of age were reviewed to assess the use of antimicrobials during the previous 12 months. Data were recorded on special case report forms, which were later entered using a double-entry approach into a custom-designed computer database.

The study was approved by the Independent Ethics Committee of the State Medical Academy (Smolensk, Russia). All information collected from the children's medical records was processed in strict confidentiality.

Descriptive statistical analysis was performed for all variables using an SAS System. Categorical variables were described by absolute frequencies and percentages. Antibiotic usage was calculated as the number of courses/child/year (and per 1000 resident days) for the total studied population, and was also calculated separately for each orphanage.

Results

Data on the use of antibiotics in the different orphanages in this study are summarised in Table 1. The number of different antimicrobials prescribed ranged from five (by international non-patent name, INN) in Orph 2 to 21 in Orph 11. Overall, a total of 37 different antimicrobials (by INN) were used in the orphanages in this study.

The most commonly administered antimicrobials are shown in Figure 1. There were substantial variations in the frequency of antimicrobial prescriptions, with no correlation to geographic location or to specific populations of children. The overall prescription of antimicrobials varied from 0.31 courses/child/year in Orph 1 to 3.63 courses/child/year in Orph 11.

On average, a total of 1.8 courses of antimicrobials/child/year were prescribed, equivalent to 4.9 antibiotic courses/1000 resident days.

β-Lactams

β-Lactams were the most frequently prescribed medications in all orphanages, ranging from 51.3% to 100% of all antimicrobials (Table 1). The exposure of children to this class of antibiotics varied between orphanages, from 0.3 to 2.4 courses/child/year (an average of 1.2 courses/child/year, equivalent to 3.3 courses/1000 resident days). The number of different β-lactams used varied from two to 11 medications (by INN) in different orphanages (Table 2). A total of 20 β-lactam-containing preparations were used, with penicillins, cephalosporins and carbapenems being prescribed in the ratio of 10:9:1 (591:322:1 total courses, respectively).

Among β-lactams, the most commonly administered were: ampicillin/oxacillin (164 courses), amoxicillin/clavulanate (148 courses), cefazolin (129 courses), cefotaxime (119 courses) and ampicillin (103 courses) (Figure 2).

Macrolides

Macrolides were the second most frequently prescribed antibiotic class in four out of 11 orphanages, accounting for 11.0% of antibiotic courses in total (143 courses). This total corresponded to 0.2 courses/child/year (equivalent to 0.5 courses/1000 resident days). Two of the orphanages (Orph 1 and Orph 9) did not use this class of antimicrobials at all. A total of five different types of macrolide were prescribed, with azithromycin being the most common (68.5% of all macrolides, 98 courses in total), followed by midecamycin (35 courses), roxithromycin (6 courses) and others used less frequently (2 courses).

Figure 1. The Most Frequently Used Antimicrobials in Different Orphanges

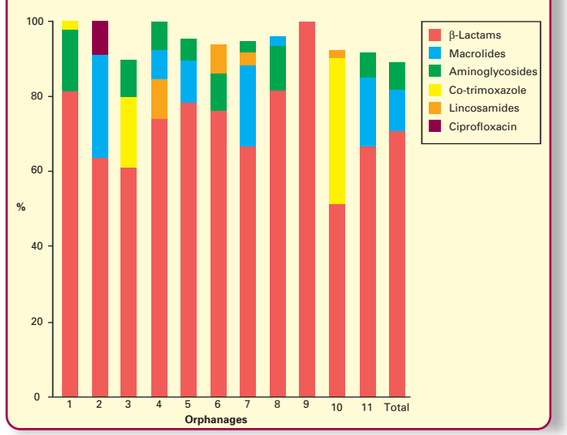

Figure 2. The Most Frequently Used β-Lactams in Different Orphanges

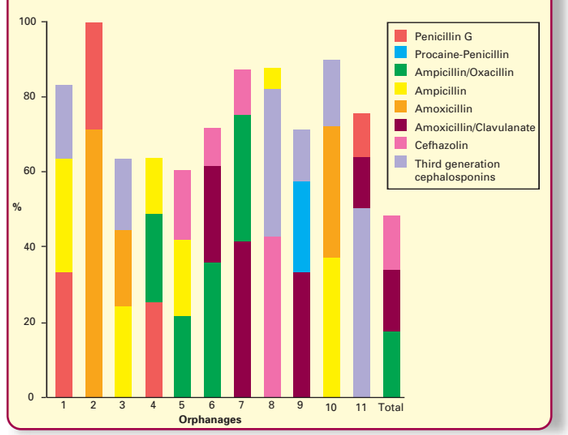

Figure 3. Use of Parenteral/Oral Antimicrobial Formulations in Different Orphanages

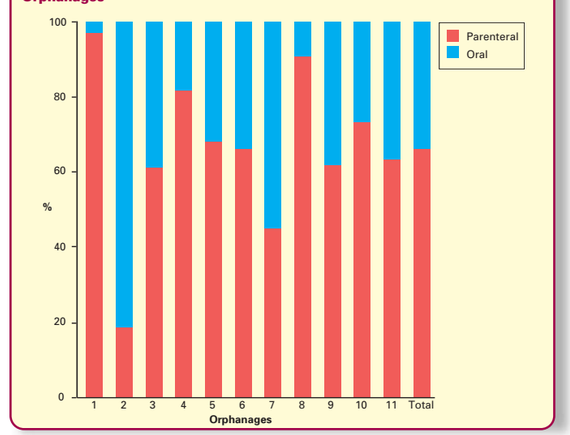

Table 1. Summary Data on Antimicrobial Use in Different Orphanges

Antimicrobial	Orph 1 n = 119	Orph 2 n = 24	Orph 3 n = 38	Orph 4 n = 60	Orph 5 n = 70	Orph 6 n = 85	Orph 7 n = 86	Orph 8 n = 114	Orph 9 n = 28	Orph 10 n = 49	Orph 11 n = 70	Total n = 743
	Courses of antimicrobials, n (%)											
β-Lactams	30 (81.1)	7 (63.6)	74 (60.7)	94 (74.0)	131 (78.0)	109 (76.2)	147 (66.2)	96 (81.4)	21 (100)	40 (51.3)	169 (66.5)	918 (70.6)
Per child/year	0.3	0.3	1.9	1.6	1.9	1.3	1.7	0.8	0.8	0.8	2.4	1.2
Aminoglycosides	6 (16.2)		13 (10.1)	10 (7.9)	10 (6.0)	14 (9.8)	7 (3.2)	14 (11.9)		1 (1.3)	17 (6.7)	92 (7.1)
Per child/year	0.1		0.3	0.2	0.1	0.2	0.1	0.1		0.02	0.2	0.1
Co-trimoxazole	1 (2.7)		23 (18.8)		5 (3.0)		5 (2.3)			30 (38.5)	6 (2.4)	70 (5.4)
Per child/year	0.01		0.6		0.1		0.1			0.6	0.1	0.1
Macrolides		3 (27.3)	8 (6.6)	10 (7.9)	19 (11.3)	4 (2.8)	49 (22.1)	2 (1.7)		1 (1.3)	47 (18.5)	143 (11.0)
Per child/year		0.1	0.2	0.2	0.3	0.05	0.6	0.02		0.02	0.7	0.2
Lincosamides			3 (2.5)	13 (10.2)	3 (1.8)	11 (7.7)	7 (3.2)	1 (0.9)		2 (2.6)		40 (3.1)
Per child/year			0.1	0.2	0.04	0.2	0.1	0.01		0.04	.	0.1
Quinolones		1 (9.1)				4 (2.8)	1 (0.5)	3 (2.5)				9 (0.7)
Per child/year		0.04				0.05	0.01	0.03				0.01
Nitrofuranes			1 (0.8)				6 (2.7)	2 (1.7)				9 (0.7)
Per child/year			0.03				0.07	0.02				0.01
Parenteral	36 (97.3)	2 (18.2)	74 (60.7)	104 (81.9)	114 (67.9)	95 (66.4)	100 (45.0)	107 (90.7)	13 (61.9)	57 (73.1)	160 (63.0)	862 (66.3)
Per child/year	0.3	0.1	1.9	1.7	1.6	1.1	1.2	0.9	0.5	1.2	2.3	1.2
Oral	1 (2.7)	9 (81.8)	26 (39.3)	23 (18.1)	54 (32.1)	48 (33.6)	122 (55.0)	11 (9.3)	8 (38.1)	21 (26.9)	94 (37.0)	439 (33.7)
Per child/year	0.01	0.4	1.3	0.4	0.8	0.6	1.4	0.1	0.3	0.4	1.3	0.6
No. of antimicrobials	7	5	17	12	14	18	18	18	7	12	21	Average = 14
Total no. of courses	37	11	122	127	168	143	222	118	21	78	254	1301
Per child/year	0.3	0.5	3.2	2.1	2.4	1.7	2.6	1.0	0.8	1.6	3.6	1.8

Table 2. Summary Data on β-Lactams Use in Different Orphanages

β-Lactam	Orph 1 n = 119	Orph 2 n = 24	Orph 3 n = 38	Orph 4 n = 60	Orph 5 n = 70	Orph 6 n = 85	Orph 7 n = 86	Orph 8 n = 114	Orph 9 n = 28	Orph 10 n = 49	Orph 11 n = 70	Total n = 743
	Courses of antimicrobials, n (%)											
Penicillin G	10 (33.3)	2 (28.6)	7 (9.5)	24 (25.5)	14 (10.7)	9 (8.3)	4 (2.7)	1 (1.0)	3 (14.3)	7 (17.5)	20 (11.8)	101 (11.0)
Procaine-Penicillin									5 (23.8)			5 (0.5)
Oxacillin			2 (2.7)		1 (0.8)		1 (0.7)	2 (2.1)		1 (2.5)		7 (0.8)
Ampicillin	9 (30.0)		18 (24.3)	14 (14.9)	27 (20.6)	3 (2.8)	6 (4.1)	5 (5.2)	2 (9.5)	15 (37.5)	4 (2.4)	103 (11.2)
Amoxicillin		5 (71.4)	15 (20.3)	1 (1.1)	2 (1.5)	4 (3.7)			7 (33.3)	14 (35.0)		48 (5.2)
Carbenicillin					2 (1.5)	1 (0.9)	3 (2.0)				5 (3.0)	11 (1.2)
Ampicillin/Oxacillin	2 (6.7)		9 (12.2)	22 (23.4)	28 (21.4)	39 (35.8)	49 (33.3)				15 (8.9)	164 (17.9)
Amoxicillin/Clavulanate				12 (12.8)	20 (15.3)	28 (25.7)	61 (41.5)	3 (3.1)	1 (4.8)		23 (13.6)	148 (16.1)
Cefazolin	3 (10.0)		8 (10.8)	8 (8.5)	24 (18.3)	11 (10.1)	18 (12.2)	41 (42.7)	2 (9.5)	1 (2.5)	13 (7.7)	129 (14.1)
Cephalexin						3 (2.8)					3 (1.8)	6 (0.7)
Cefaclor					8 (6.1)							8 (0.9)
Cefuroxime								4 (4.2)			1 (0.6)	5 (0.5)
Cefotaxime	6 (20.0)		11 (14.9)	12 (12.8)	5 (3.8)	7 (6.5)	2 (1.4)	31 (32.3)		1 (2.5)	44 (26.0)	119 (13.0)
Ceftriaxone			2 (2.7)	1 (1.1)				2 (2.1)			31 (18.3)	36 (3.9)
Ceftazidime			1 (1.4)				1 (0.7)	5 (5.2)			10 (5.9)	17 (1.9)
Others			1 (1.4)			2 (1.8)		2 (2.0)	1 (4.8)	1 (2.5)		7 (0.8)
Total β-lactams	30	7	74	94	131	107	145	96	21	40	169	914
Per child/year	0.3	0.3	1.9	1.6	1.9	1.3	1.7	0.8	0.8	0.8	2.4	1.2

Aminoglycosides

Aminoglycosides were the second most frequently administered class of antimicrobials in three out of 11 orphanages, and the third most common in terms of total prescriptions. These agents were not used at all in two orphanages (Orph 2 and Orph 9). A total of 92 courses of aminoglycosides were administered (0.1 courses/child/year). Gentamicin was used most frequently (80.4% of all aminoglycosides, 74 courses), followed by amikacin (17.4%, 16 courses) and netilmicin (2.2%, 2 courses).

Co-trimoxazole

Co-trimoxazole was the second most frequently prescribed antimicrobial in two orphanages (Orph 3 and Orph 10), accounting for 18.8% and 38.5% of all prescriptions, respectively, and for 0.6 courses/child/year (1.6 courses/1000 resident days) in both of these institutions. Overall, co-trimoxazole was the fourth most commonly used antimicrobial (5.4% of all agents, 70 courses). This compound was not used at all in five out of 11 orphanages, which reduced the total exposure to 0.1 courses/child/year.

Lincosamides

Lincosamides were the second most commonly used antimicrobial, after β-lactams, in one orphanage (Orph 4), where they accounted for 10.2% of all antimicrobials (0.2 courses/child/year). In four orphanages lincosamides were not used at all. In total, lincosamides comprised 3.1% of all agents administered, corresponding to 0.1 courses/child/year.

Other agents

Other agents were administered much less frequently: **quinolones** were used in only four orphanages while **nitrofuranes** were administered in only three orphanages (0.7% of all antimicrobials and 9 courses for each of these antimicrobial classes). Quinolones recorded in the database included 8 courses of nalidixic acid and 1 course of ciprofloxacin (in Orph 2, where this corresponded to 9.1% of all antimicrobials used). The use of nitrofuranes included 4 courses of furazidine and 5 courses of furazolidone. Metronidazole was administered in one orphanage (Orph 11) (9 courses, 3.5% of all antibiotics used in this institution and 0.1 courses/child/year).

A total of 4 courses of doxycycline were recorded in Orph 10 (5.1% of all antimicrobials in this site, 0.1 courses/child/year) and one course of rifampicin was used in Orph 6 (0.7% of all antibiotics in this institution).

Parenteral compounds

In general, parenteral compounds were predominantly used in 9 out of 11 orphanages (Figure 3). Exposure of children to parenteral compounds varied from 0.1 to 2.3 (average 1.2) courses/child/year, while exposure to oral antimicrobials ranged from 0.01 to 1.4 (average 0.6) courses/child/ year.

Discussion

The results of this study demonstrate the excessive, and possibly inappropriate, use of antibiotics in orphanages, with substantial variations in the frequency of individual antimicrobial prescriptions.

The use of antimicrobials in some of the institutions (e.g. in Orph 11) was as high as 3.63 courses/child/year, equivalent to 9.9 courses/1000 resident days. In 9 out of 11 orphanages parenteral compounds were administered more often than oral antimicrobials, despite the availability of oral formulations with comparable efficacy.

Antimicrobial agents that may cause severe toxic reactions (e.g. aminoglycosides, co-trimoxazole and lincosamides) were commonly used. Overall, only β-lactams and macrolides were prescribed more frequently, although in 7 out of 11 orphanages they were administered more frequently than macrolides).

On the basis of microbiology data, the administration of gentamicin and co-trimoxazole seems to be inappropriate, considering the high rates of resistance to these compounds in Russia. The use of outdated antimicrobials, (such as the combination of ampicillin with oxacillin, carbenicillin) was recorded in 8 out of 11 orphanages, with the highest (30.8%) in Orph 6.

There were 4 courses of doxycycline registered in Orph 10 (5.1% of all antimicrobials in this site, 0.1 courses/child/year) and 1 case of ciprofloxacin administration in Orph 2 (where this corresponded to 9.1% of all antimicrobials used). Neither of these antimicrobials are currently approved for paediatric use in Russia.

The pattern of antimicrobial use described probably reflects the failure to implement unified standards of medical care in orphanages, and the lack of antibiotic policies in particular. Generally, children with more severe infections should be hospitalised, and the use of parenteral compounds (e.g. imipenem and cefepime) in out-patient settings should be strongly discouraged.

One of the limitations of this study is the lack of published data on antimicrobial use in orphanages, making it impossible to make a comparison of our data. In addition, the non-applicability of ATC/DDD methodology in children led to the necessity of employing other measures, such as the number of courses per child/year.

Finally, there is a need to correlate the pattern of use of antimicrobials with the resistance patterns shown by colonising/infecting pathogens. Such studies are now under way.

Conclusions

- The frequency of antimicrobial prescriptions varied substantially, and had no correlation with geographic location or specific populations of children.
- In all orphanages there was a tendency to prescribe parenteral antimicrobials, despite the availability of suitable oral alternatives. This indicates a failure to implement standards of medical care and antibiotic policies.
- Enforcement measures have been designed to prohibit the unlicensed use of some antimicrobials in studied populations.

Acknowledgement

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References

1 *WHO Pharmaceutical Newsletter* 2000; 4: 1.
2 Improved Use of Antimicrobials Needed to Combat Drug Resistance. http://www.medscape.com/viewarticle/411216?src=search [cited 25 February, 2005].
3 Kauffman CA, Hedderwick SA, Bradley SF. Antibiotic resistance: issues in long-term care. *Infect Med* 1999; 16: 122–128.
4 Stratchounski LS, Kozlov RS, Kretchikova OI, Zharkova LP, Petrochenkova NA, Poupard JA. Orphanages as hot spots of pneumococcal resistance: results from multicentre study CORPUS in Russia. In: Proceedings of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 30 October – 2 November 2004. Washington, DC, USA. Poster 103.
5 Nikole LE, Bentlew DW, Garibaldi R, Neuhaus EG, Smith PW. SHEA position paper: antimicrobial use in long-term care facilities. *Infect Control Hosp Epidemiol* 2000; 21: 537.

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