Original research article

"Clinical Profile And Comparison Of Narrow Versus Broad Spectrum Antibiotic Therapy For Community Acquired Pneumonia In Children Hospitalized At Tertiary Care Centre"

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Abstract

Background: Pneumonia is the leading cause of morbidity and mortality in under 5 year age children.

Objective: To compare the effectiveness of treatment for Community Acquired Pneumonia (CAP) in children with narrow versus broad spectrum antibiotic therapy.

Methods: A prospective randomized controlled trial was conducted in Pediatric ward of tertiary care medical college hospital of southern Rajasthan from July 2017 to June 2018. Total 184 children of age group of 2 months to 18 years, admitted with a clinical diagnosis of CAP were enrolled for the study.

Results: A total 184 children were enrolled. Maximum no. of cases (93) admitted with CAP were among 2 months to 12 months of age group. All 6 parameters in our study (i.e. total duration of fever, O_2requirement, respiratory distress, length of stay, change of antibiotic and readmission) were compared between both the groups suggesting that Ampicillin having similar effect on children hospitalized with CAP when compared with Ceftriaxone.Throat swab culture in children with CAP was positive in 55% of cases. Most common organism grown on throat swab of affected children was Streptococcus pneumoniae (30%) followed by H.influenzae (15%).

Conclusion: CAP is a major health problem in children below 5 years. Most common organism for CAP in children is still S. pneumoniae. In our study narrow spectrum antibiotic coverage for CAP was associated with similar outcomes when compared with broad spectrum agent. So we highlights in our study to promote the use of narrow spectrum antibiotics in children hospitalized with CAP.

Keywords: *Community Acquired Pneumonia, Ampicillin, Ceftriaxone, S.pneumoniae.*

Introduction

Pneumonia is defined as "An acute inflammation of the pulmonary parenchyma that can be caused by various infective and noninfective origin".[1]On the basis of source of infection it has been classified ascommunity acquired, health care associated, ventilator associated and hospital acquired pneumonia. Pneumonia affects 156 million children under age of 5 years every year across the globe, and is the leading cause of morbidity and mortality in this age group.[2] More than 2 million annual deaths are estimated to occur because of pneumonia in under 5 children and almost all of them are occurring in developing world.[3]India carries the largest burden of the disease and death because of pneumonia, approximately for 43 million cases and 0.4 million deaths annually.[4]Childhood pneumonia is an important cause of morbidity and mortality worldwide. More than 2 million children younger than five years of age die from pneumonia every year, accounting for almost one-fifth of overall childhood mortality. [5]The respiratory rate thresholds for acute lower respiratory tract infection according to the WHO are a respiratory rate of > 60/minute for children less than 2 months of age, > 50/minute for children aged 2 to 12 months, and >40 /minute for children aged 1 to 5 years (WHO,1990). This easily detected diagnostic sign of pneumonia is helpful in the developing world where radiographic facilities are rarely available, trained staff are lacking, and pneumonia mortality is high. The short distance between upper respiratory tract and alveoli, the small diameter of the airways, profuse mucus production, and the immaturity of the immune defence predisposes children to pneumonia. In addition, the nasopharyngeal colonization of pneumonia causing bacteria is common in young children.[6,7,8]Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign body, hydrocarbons), hypersensitivity reactions or drug induced pneumonitis.[9]

Community-acquired pneumonia (CAP) is an acute lower respiratory tract infection (LRTI) acquired from the community with fever, cough, dyspnea, tachypnea and pleural chest pain as typical symptoms. Diagnosis is confirmed with new opacity in chest radiograph.[10,11,12]. Appropriate antibiotic prescribing is associated with favorable level of antimicrobial resistance and clinical outcome. In October 2011, Pediatrics Infectious Disease Society (PIDS) and Infectious Disease Society of America (IDSA) published guidelines for the management of CAP in children.[13]In prospective, microbiology-based studies, the leading bacterial cause is S. Pneumoniae, being identified in 30–50% of pneumonia cases.[14] The second most common organism isolated in most studies is ***H. influenzae*** type b (Hib; 10–30% of cases), followed by ***S. aureus*** and ***K. pneumoniae.Some of Indian studies had also reported as S. Pneumoniae and H.Influenzae being the most common causes of CAP in children of age group 2months to 5 years of age.[15,16]***. Narrow spectrum beta lactams effectively target S. Pneumoniae. New guidelines recommend Penicillin or Ampicillin/Amoxicillin as first line therapy for the most children hospitalized with CAP.[13]

Material and method

A prospective randomized controlled study was carried out in Pediatric ward of tertiary care hospital of southern Rajasthan attached with medical college.

Study period: Jan.2019 to Dec. 2019

Study population: Total 184 children of age group of 2 months to 18 years were admitted with a clinical diagnosis of CAP were enrolled for the study.

Inclusion criteria:

1. Children only whose parents have given consent to participate in the study will be included in this study.
2. Children of age group 2 months to 18 years of age hospitalized with diagnosis of CAP.
3. Evidence of respiratory illness (cough/increased work of breathing).

4. Chest radiograph showing Pneumonia (e.g. Infiltrates or consolidation)
5. Patients who received a minimum of 2 days antibiotic therapy during hospitalization

Exclusion criteria:

1. Children whose parents refused for participation in the study.
2. Children with severe pneumonia who required ICU admission within 48 hours of hospitalization.
3. Children with some congenital/chronic respiratory illness. (e.g. Cystic fibrosis, asthma ,lung malformation)
4. Complicated pneumonia (defined as imaging study indicating moderate to large pleural effusion, lung abscess , necrosis or bronchopulmonary fistula)
5. Children who got hospitalized within last 30 days due to any illness
6. Children who received staphylococcal coverage / macrolide monotherapy within last 7 day

Prior written informed consentwas obtained from the parents or available relatives of each child. Confidentiality of data was ensured.Cases were enrolled within 6 hours of admission.All the enrolled children included in the study were divided into 2 groups: Patient with odd no. of sequences named as group A and patient with even no. as group B.Basic information of the child, detailed clinical history and treatment history was obtained followed by general physical and systemic examination done. All the informations were recorded on structured proforma.Routine investigations includingHemoglobin, TLC, DLC and Chest x-ray were done in all the patients at time of admission. Sample for blood culture was collected in every patient before starting antibiotic. Similarly throat swab sample was also taken for culture of organism.

Pneumonia was diagnosed as per WHO ARI control program. Respiratory rate was counted for one full minute when the child was calm, sleeping or feeding. Fast breathing was defined as respiratory rate above the limit as defined by WHO17. The presence of subcostal indrawing, suprasternal indrawing and intercostal indrawing was assessed. Positive findings were noted on basis of symptoms and clinical examination.

Microbiology:

Processing of 368 samples (184 blood culture + 184 throat swab culture)was done in Microbiology Department of the institute. All the samples were collected with aseptic precautions by using standard sterile techniques and transported to the laboratory as soon as possible maintaining optimum transportation conditions.

The following procedures were carried out in the laboratory –

1. Gram's staining
2. Bacteriological culture
3. Biochemical reactions
4. Antibiotic sensitivity testing

Direct gram stained smear of the samples observed under microscope to detect the presence and type of bacteria and to correlate it with the growth obtained on culture plate.Primary inoculation was done on the Thio-glycolate broth, Mac Conkey media and Blood agar. Colony characteristics were observed.

Antimicrobial susceptibility testing:

The isolates tested by the disc diffusion method (modified Kirby-Bauer method) on Muller Hinton agar (Hi-Media) following the zone size criteria which is recommended by the CLSI .

After initial workup selection of antibiotic was decided according group. Group A patients received narrow spectrum antibiotic therapy in form of injection Ampicillin intravenously at dose of 50mg/kg/dose every 6 hourly while group B received broad spectrum antibiotic therapy in form of injection Ceftriaxone intravenously at dose of 50mg/kg/day divided in two doses.

Patients were discharged once the symptoms relieved and need of intravenous therapy was not there with further advice to complete 7 to 10 days of therapy with oral antibiotic therapy.
Effect of narrow versus broad spectrum antibiotic therapy compared in both the groups based upon following parameters in each group:

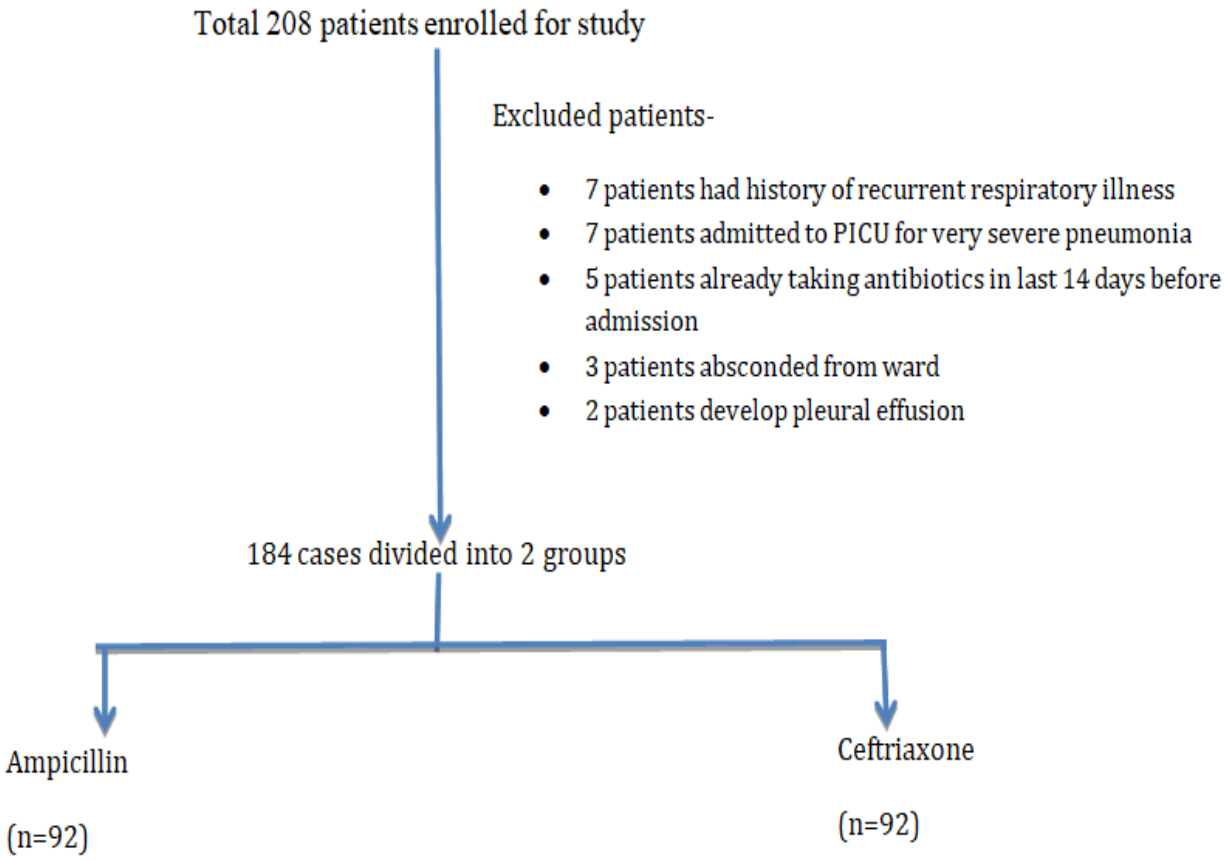
1. Duration of fever (Temp. >38 ^{0} c).
2. Duration of supplemental oxygen required (hours).
3. Hospital length of stay (LOS) measured in hours.
4. Signs of respiratory distress.
5. Readmission within 15 days of discharge from hospital.
6. Required changing of antibiotics.

Statistical analysis:

Data analysis was done by SPSS software (20.0 trial version) and appropriate statistical tests were used to find out the final results.

Results

Total 208 children of age group 2months to 18 years were admitted with diagnosis of CAP in children ward of the hospital, out of them 24 children were excluded and final 184 children categorized into two groups (92 each).



Maximum no. of cases admitted with CAP were among 2 months to 12 months of age group(93) followed by 1- 2year (26) and 2-3(28*)* year of life. Patients older than 5 year were only 9.8% (18)of total patients with CAP(Table 1). All patients admitted for CAP were having tachypnoea and chest indrawing *(100%)* at admission. But fever *(94.6%)* and cough *(92.4%)* was not consistent finding in all children.

Outcome measures for both groups were compared in form of total duration of fever, O_2 requirement and signs of respiratory distress (in form of tachypnoea, grunting, chest retractions). All outcomes were measured in duration of hours from the time of hospitalization.Table 2 depicts thattotal duration of fever in Ampicillin group was 18.4 hours which was almost similar to Ceftriaxone group (18.9 hours). Difference among these was statistically not significant (p 0.636).Similarly duration of O_2 required in both groups was also similar (Ampicillin: 14.6 vs. Ceftriaxone: 17.7 hours). p value 0.58 suggests that this difference was also not significant.Signs of respiratory distress in Ampicillin group were lasted for a mean of 36.0 hours which was quite similar to Ceftriaxone group (mean 37.9 hrs). p value 0.392 is suggesting of this difference not significant.
Out of 92 patients received Ampicillin, 8 patients (8.7%) required change of antibiotic during their hospitalization, while Ceftriaxone group required change of antibiotic in 5(5.4%) patients(Table 3). (p=0.388) suggesting of difference between both groups in this parameter to be not significant.We compared the total length of stay in hospital for I.V. antibiotics in both group (Table 4). Patients in Ampicillin group had lesser stay in hospital as compared to Ceftriaxone group (77.2 vs 80.6 hrs, p =0.149). The difference was not significant so both drugs were similar in this outcome also.Out of 92 patients in each group only 2 patients in each group required readmission with 15 days after discharge from hospital(Table 5). So all 6 parameters in our study (i.e. total duration of fever, O_2, respiratory distress, LOS, change of antibiotic and readmission) were compared between both groups and they were statistically not significant suggesting that Ampicillin having similar effect on children hospitalized with CAP when compared with Ceftriaxone.

In our study we sent blood and throat swab samples for culture and sensitivity of organism in every patient. Out of 184 patients only 13 (7%) patients have shown growth of some organism in their blood sample obtained from venipuncture (Table 6).Throat swab culture in children with CAP were positive in more number of cases 96 (55%) as compared to blood culture of same patients (positive in 7%). It is suggestive of that throat swab culture is a better mode for detection of causative organism responsible for pneumonia in children. Table 6 depicts thatmost common organism grown on throat swab of affected children was Streptococcus pneumonia (30%) followed by H.influenzae (15%). These two are the most common organism responsible for CAP in children between age group 2 months to 5 years of age.We found that out of those 96throat swab culture positive cases 17 were resistant to Ampicillin (9.2%) and 15 Patients (8.2%) were resistant to Ceftriaxone. It suggest that sensitivity pattern for organisms causing CAP in local population is similar in both narrow (Ampicillin) and broad (Ceftriaxone) spectrum groups (Table 7). Most common organisms for CAP in children (S.pneumoniae, H.influenzae) are having similar sensitivity and resistance pattern for both group of antibiotics.52% of S. pneumoniae positive case were from age group 2-12months while only 1 case was >5 year age. Similarly H.influenzae was also common in infantile age (39%).

Table 1: Distribution of cases according age group

Age	Total cases N (%)
2mo-12mnths	93 (50.5)
1-2 Years	26 (14.1)
2-3 Years	28 (15.2)
3-4 Years	15 8.2)
4-5 years	4(2.2)
5-18 years	18(9.8)
Total	184 (100)

Table 2: Comparison of Ampicillin and Ceftriaxone group.

	Drug	N	Mean	Std. Deviation	T value	P value
Duration of fever (in hours)	AMP	92	18.4239	7.78027	0.474	0.636
	CEFT	92	18.9022	5.76473		
Duration of O2adm.(in hours)	AMPI	92	14.6739	10.77044	1.910	0.058
	CEFT	92	17.7500	11.06983		
Signs of Resp.Distress (in hours)	AMPI	92	36.0652	13.86418	0.859	0.392
	CEFT	92	37.9348	15.62318		

Table 3: Distribution of CHANGE/ADD Antibiotic according to Antibiotic Drug Given

		DRUG		Total	Chi Sq	P value
		AMPI	CEFT			
CHANGE/ADD Antibiotics	NO	84	87	171		
		91.3%	94.6%	92.9%		
	YES	**8**	**5**	**13**	0.745	0.388
		8.7%	5.4%	7.1%		
Total		92	92	184		
		100.0%	100.0%	100.0%		

Table 4: Distribution of Length of stay (in hours) according to Antibiotic Drug Given

	DRUG	N	Mean	Std. Deviation	T value	P value
Length of stay (hours)	AMPI	92	77.2717	15.58536	1.450	0.149
	CEFT	92	80.6087	15.63242		

Table 5: Distribution of READMISSION according to Antibiotic Drug Given

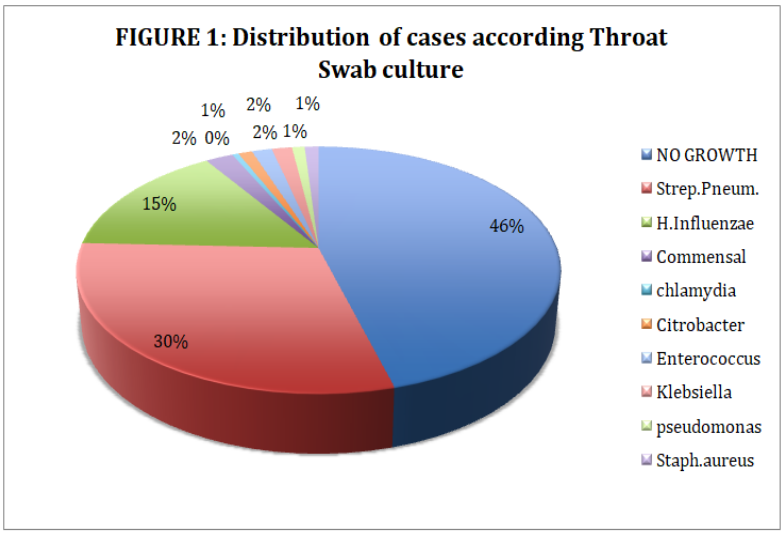
		DRUG		Total	Chi sq	P value
		AMPI	CEFT			
READMISSION	NO	90	90	180		
		97.8%	97.8%	97.8%		
	YES	**2**	**2**	**4**	0.000	1.00
		2.2%	2.2%	2.2%		
Total		92	92	184		
		100.0%	100.0%	100.0%		

Table 6: Growth on Blood culture & Throat Swab culture in patients with CAP

Organism on Blood culture	Frequency (%)	Organism on Throat Swab culture	Frequency (%)
NO GROWTH	171 (92.9)	NO GROWTH	84(45.7)
Strep.pneum.	9 (4.9)	Strep.pneumoniae	55(29.9)
commensal.	1 (0.5)	H. Influenzae	28(15.2)
Klebsiella	1 (0.5)	Chlamydia	1(0.5)
Pseudomonas	1 (0.5)	Citrobacter	2(1.1)
Staph. aureus	1 (0.5)	Commensal	4(2.2)
Total	184 (100)	Enterococcus	3(1.6)
		Klebsiella	3(1.6)
		Pseudomonas	2 (1.1)
		Staph.aureus	2 (1.1)
		Total	184(100)

Table 7: Distribution of sensitivity for Ampicillin &Ceftraixone.

Sensitivity for AMP	Frequency	Percent	**Sensitivity for CEFT.**	Frequency	Percent
NO GROWTH	88	47.8	NO GROWTH	88	47.8
Resistance	**17**	9.2	Resistance	**15**	8.2
Sensitive	79	42.9	Sensitive	81	44.0
Total	184	100.0	Total	184	100.0



Discussion:

According to our study majority of children admitted with CAP were among infantile age group. 50% of cases were of age group 2months to 12 months and only 9.8% of cases were older than 5 year of age.Williams BG et al[5]Bryce J et al[2]and Wardlaw T et al[18] observed in their studies that childhood pneumonia is an important cause of morbidity and mortality worldwide.

In our study all children were having respiratory distress in form of tachypnoea at time of admission as we used WHO criteria for defining Pneumonia.Palafox and colleagues found that the presence of tachypnea was the single most sensitive and specific clinical indicator of pneumonia, with 74 % sensitivity and 67 %specificity among children less than 5 years of

age.[19]Duration of fever in Ampicillin group (18.4 hrs) was similar to Ceftriaxone group (18.9hrs) (p value 0.636).Williams DJ et al [20] in their retrospective cohort study observed that duration of fever in patients receiving narrow spectrum antibiotic was similar to braod spectrum group when they studied among 43 children hospitals.

Total duration O_2 supplementation required was less in narrow spectrum group (Ampicillin 14.6 hrs vs Ceftriaxone 17.7 hrs), but this difference is statistically not significant (p value 0.058).Marry N Queen [4] also observed that children receiving narrow spectrum antibiotics were having less duration of oxygenation (mean 15.6 hrs) as compare to children who received broad spectrum antibiotics (mean 21.8 hrs). This difference was also not significant (p value 0.18). Out of 92 patients received Ampicillin, 8 patients (8.7%) required change of antibiotic during their hospitalization, while Ceftriaxone group required change of antibiotic in 5(5.4%) patients. (p=0.388) suggesting of difference between both groups in this parameter to be not significant.We compared the total length of stay in hospital for I.V. antibiotics in both group **(**Table 4). Patients in Ampicillin group had lesser stay in hospital as compared to Ceftriaxone group (77.2 vs 80.6 hrs, p =0.149).Williams DJ et al [20] compared the LOS in both groups in terms of total days and they found it similar (3-4 days for both narrow & broad spectrum groups) while Marry N Queen [4] mentioned it in total hours. Though it was shorter in narrow spectrum groups (43 hrs vs 52.3 hrs, p=0.04). Out of 92 patients in only 2 patients in each group required readmission with 15 days after discharge from hospital. Williams DJ et al [20] compared the readmission within 14 days while Marry N Queen [4] compared readmission within 7 days of discharge from hospital. In both studies difference between both groups was not significant.

So all 6 parameters in our study (i.e. total duration of fever, O_2, respiratory distress, LOS, change of antibiotic and readmission) were compared between both groups and they were statistically not significant suggesting that Ampicillin having similar effect on children hospitalized with CAP when compared with Ceftriaxone.In our studythroat swab culture in children with CAP were positive in more number of cases (55%) as compared to blood culture of same patients (7%). It is suggestive of that throat swab culture is a better mode for detection of causative organism responsible for pneumonia in children.Das et al [21] also demonstrated the same difference while comparing results of blood culture and OPS and BAL samples from children with CAP. Only 4 samples were positive in blood culture out of 180, while 131 children showed growth of organism in their OPS and BAL samples. The difference was significant.

Most common organism grown on throat swab of affected children was Streptococcus pneumoniae (30%) followed by H.influenzae (15%). These two are the most common organism responsible for CAP in children between age group 2 months to 5 years of age.Various other studies like Nantanda R et al [22] Hortal M et al [23] and Gratten M et al [24] have found S.pneumoniae & H.influenzae to be the most common isolate from respiratory samples of children with CAP. S.aureus and K.pneumoniae were detected as leading cause of pneumonia by Johnson et al[25]. Das et al [21] also found S.pneumoniae and H.influemzae as the leading cause of CAP in children under 5 year.There were total 96 patients in whom throat swab culture was positive. We found that out of those 96 cases 17 were resistant to Ampicillin (9.2%) and 15 Patients (8.2%) were resistant to Ceftriaxone. It suggest that sensitivity pattern for most common organisms causing CAP in local population is similar in both narrow (Ampicillin) and broad (Ceftriaxone) spectrum groups of antibiotics.

Conclusion:

We can summarize results of our study as CAP is a major health problem in childrenbelow 12 months. In the modern era of antibiotic resistance we should avoid overuse of broad spectrum antibiotics. Most common organism for CAP in children is still S.pneuminae and its sensitivity to narrow spectrum antibiotics like Ampicillin is good in local population also. So misconception about PIDS and IDSA guideline that this has to be followed in developed countries is not true.

Narrow spectrum antibiotic coverage for CAP associated with similar outcomes when compared with broad spectrum agents. There was no difference in total duration of fever, O_2 requirement, respiratory distress, length of stay in hospital, change of antibiotic and readmission rates. So we highlights in our study to promote the use of narrow spectrum antibiotics in children hospitalized with CAP.There exist many reasons to preferentially use penicillins as first line antibiotic therapy for CAP. First penicillins provide appropriate coverage for the most prominent pathogen, S.pneumoniae. Second treatment of patients with non-central nervous system penicillin-resistant pneumococcal infections with penicillins has not been associated with treatment failures. Finally the use of broad spectrum antibiotics has been shown to increase the risk of developing subsequent infections with resistant organisms.

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