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Impact of an intervention in the use of sequential antibiotic therapy in a Brazilian university hospital

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ABSTRACT

Introduction: Sequential antibiotic therapy (SAT) is safe and economical. However, the unnecessary use of intravenous (IV) administration usually occurs. The objective of this work was to get to know the effectiveness of an intervention to implement the SAT in a teaching hospital in Brazil. **Methods:** This was a prospective and interventional study, historically controlled, and was conducted in the *Hospital de Clínicas*, *Universidade Federal de Uberlândia*, State of Minas Gerais, Brazil, a high complexity teaching hospital having 503 beds. In each of the periods, from 04/04/05 to 07/20/05 (pre-intervention) and from 09/24/07 to 12/20/07 (intervention), 117 patients were evaluated. After the pre-intervention period, guidelines were developed which were implemented during the intervention period along with educational measures and a reminder system added to the patients' prescription. **Results:** In the pre-intervention and intervention periods, the IV antibiotics were used as treatment for a average time of 14.8 and 11.8 days, respectively. Ceftriaxone was the antibiotic most prescribed in both periods (23.4% and 21.6% respectively). Starting from the first prescription of antibiotics, the average length of hospitalization time was 21.8 and 17.5 days, respectively. The SAT occurred only in 4 and 5 courses of treatment, respectively, and 12.8% and 18.8% of the patients died in the respective periods. **Conclusions:** Under the presented conditions, the evaluated intervention strategy is ineffective in promoting the exchange of the antibiotic administration from IV to oral treatment (SAT).

Keywords: Antibiotics. Antimicrobial. Antibiotic policy. Switch therapy

INTRODUCTION

In many developing countries, the availability and the use of antibiotics are poorly controlled, resulting in high rates of microbial resistance[1]. Brazil has a Unified Health System (SUS), which provides for all actions and health services which are gratuitously provided by the governments. SUS is applied to the entire Brazilian population[2], and the health authorities are concerned about the proper use of antibiotics[3].

Serious bacterial infections should be, and are traditionally treated with IV antibiotics. However, after clinical improvement, the oral treatment (OT) can be used. Besides, the prolonged and unnecessary use of IV, although not desirable, usually occurs[4].

One of the data used to evaluate the use of antibiotics in hospitals described by the European Surveillance of Antimicrobial Consumption (ESAC) is the proportion of oral versus parenteral use. (ESAC moved to European Centre for Disease Prevention and Control – ECDC - in 2011 and is now named ESAC-Net)[5].

Sequential antibiotic therapy (SAT) refers to the exchange from the parenteral route to the oral treatment as soon as the patient is clinically stable. Clinical and laboratory criteria are suggested so as to identify the patients who are sufficiently stable to enable therapy change[6]. It is already clear that SAT is safe, and economical, and that it improves the quality of healthcare[4,7].

Oral formulations are cheaper then IV ones, leading to a reduction in the following: time of preparation and administration, work of nursing staff, drug waste and length of hospitalization. The OT is also easy to continue at home[8-10]. Moreover, the reduction of the hospital stay and the length of catheter use, due to SAT, may lead to a reduction in hospital infection incidence[8,11,12].

As a consequence of the increasing economic pressure, it becomes necessary to control hospital costs which are deeply influenced by the use of intravenous drugs, thus the SAT strategy is being more and more implemented. Therefore, studies are considered necessary in order to reduce the use of IV antibiotics in the treatment of hospitalized patients[13]. Previous studies with SAT differ as to the characteristics of the intervention, of the hospital, of the infectious syndromes and of the antibiotics tested[6,14-17].

In this context, the purpose of this present study was to discover the frequency of SAT practice and, especially, an effective strategy to reduce the use of IV antibiotics by the implementation of the SAT in a teaching hospital in Brazil.

METHODS

This prospective, historically controlled, interventional study was conducted at the Clinical Hospital of the Federal University of Uberlândia (HCU). The HCU is a public teaching

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hospital, having 503 beds and has a 100% health insurance agreement with the Unified Health System (SUS) of Brazil. Data were collected during the pre-intervention (PIP) and the intervention (IP) periods.

During PIP, from April 4 to July 20, 2005, from Monday to Friday, the researchers visited all the patients hospitalized in the internal medicine wards (52 beds), in the surgery wards (128 beds) and in the intensive care unit for adults (15 beds). All the patients who initiated use of IV antibiotics on the day of the visit or on the day before were included in the study. These patients were followed up for at least 60 days, or up to discharge or death.

The use of IV metronidazole (because it can be used as an antiparasitic) and the use of IV cefazolin (because it is commonly indicated prophylactically) did not motivate inclusion in the study. Some patients were hospitalized for more than 60 days after beginning the IV antibiotic, but for the calculation of the average time of hospitalization only 60 days were considered. It was considered to be a new course when a new IV antibiotic was introduced after the patient had remained without an IV antibiotic for more than one day. It was considered SAT when, at any time, an oral antibiotic was introduced to replace some IV antibiotic.

From the second half of 2005 Guidelines for the Use of Antibiotics were elaborated. These contain recommendations for the empirical treatment of community-acquired or hospital-acquired pneumonia, urinary tract infections, intra-abdominal infections and for sepsis in adults. They include the recommendation of the ideal time to perform SAT. The guidelines were written by two infectious disease physicians from the Hospital Infection Control Service (HICS), and by one biochemist pharmacist, directly involved in the research. They were based on specialized scientific literature and on the profile of the susceptibility to microorganisms isolated in the HCU. After that, they were submitted for approval to the Control Committee of Antibiotic (CCA) and to the Hospital Infection Control Committee (HICC) of the HCU.

Between PIP and IP, in addition to the elaboration and approval of the guidelines, other facilitator and educational strategies were developed such as the following: a) standardization of new antibiotics by OT: azithromycin 500mg; clindamycin 300mg; moxifloxacin 400mg; sultamicillin tosylate (ampicillin/sulbactam) 375mg; b) availability of electronic version of the guidelines starting from July 20, 2007, on the main page of HCU intranet, accessible by a single click on the icon; c) presentation of the guidelines to physicians and to medical students working in some evaluated wards; d) printed copies were supplied to the physicians on duty; e) printed copies were fixed to the specific murals in the prescription rooms.

After implementation of these strategies, the IP was started on September 24 and finished on December 20, 2007, when the number of patients was the same of the first period. This strategy was done by convenience and the data collection followed the same methodology for data collection as that of the previous period. The same beds that were visited in PIP were also visited in IP.

The following was also performed, daily fixing of labels **(Figure 1)**, from Monday to Friday, on patients' prescription suggesting to their physicians to revise the therapy with IV antibiotics.

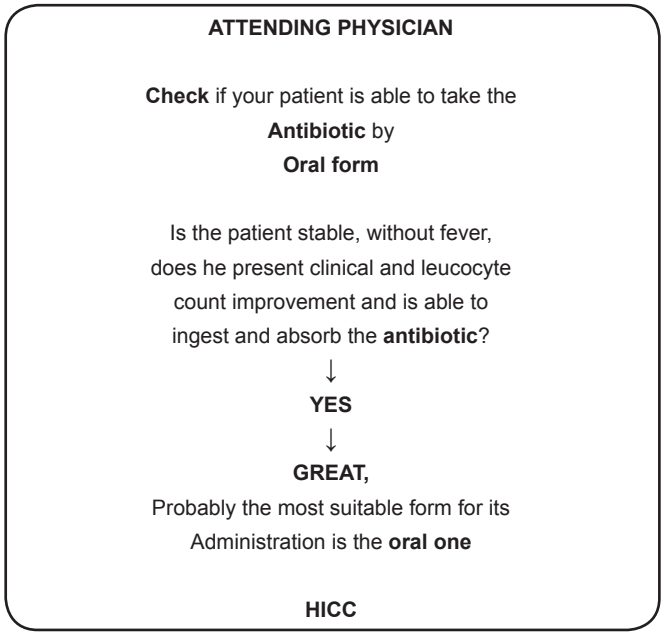

FIGURE 1 - Label with the clinical and laboratory criteria to perform Sequential Antibiotic Therapy.

HICC: Hospital Infection Control Committee.

In the PIP, data were collected by the biochemist pharmacist researcher and a third year medical student, and in IP, similar activities were performed by the researcher and a fourth year nursing student. Any doubts that may have arisen during the data collection were discussed with the infectious disease physician, who is the study coordinator.

Statistical analysis

The StatCalc, module of the EpiInfo 2000, a software distributed by the Center of Disease Control and Prevention was used to analyze the practice of SAT. The Chi-square test with Yates correction was used to evaluate the secondary variables. The Mann-Whitney test through BioStat 3.0, national software of public domain was used to evaluate the difference in the duration of the course of antibiotic treatment and the length of hospital stay from the first antibiotics prescription, in both study periods. Results are reported as statistically significant at $p < 0.05$.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and the project was approved by the Ethics Committee in Research of the UFU, under process number CEP 022/05.

RESULTS

One hundred and seventeen patients were evaluated in the PIP and 117 in the IP. The characteristics obtained are shown in **Table 1.**

TABLE 1 - Characteristics of the patients evaluated during the periods of pre-intervention (April 4 to July 20, 2005) and intervention (September 24 to December 20, 2007), Clinical Hospital, Uberlândia, State of Minas Gerais, Brazil.

Variable	Pre-intervention period	Intervention period	p value
Patients (n)/course of treatment	117/135	117/130	0.90
Age (years old): mean and range	53.38±18.51; (17-94)	51.98±19.79; (13-89)	0.17
Gender: male	72 (61.5%)	75 (64.1%)	0.89
Length of hospital stay* (days): mean and range	21.81±15.78; (03-60)	17.45±14.44; (02-60)	0.01
Wards of the Hospital (n)			
surgery wards	61	65	0.69
intensive care unit for adults	25	20	0.69
internal medicine ward	31	32	1.00
total of patients	**117**	**117**	
Indications (n)			
respiratory tract infection	43	25	0.03
intra-abdominal infection	18	29	0.08
urinary tract infection	13	11	0.91
infection of skin and soft tissues	10	10	0.89
osteoarticular system infection	8	5	0.62
sepsis	7	11	0.41
surgical site infection	8	11	0.57
infection of the biliary	7	10	0.57
others	12	9	0.72
total	**126**	**121**	

* Length of hospital stay since the first IV antibiotic prescription on.

The IV antibiotics prescribed, in the PIP and in the IP, were ceftriaxone (23.4% and 21.7% of the cases, respectively), cefepime (18.3% and 15.6%), vancomycin (11.7% and 8.7%), levofloxacin, gatifloxacin or ciprofloxacin (12.1% and 10.6%), clindamycin (8.8% and 8%), amikacin or gentamicin (7% and 2.7 %), imipenem or meropenem (6.6% and 8%), oxacillin (4.8% and 3%), ampicillin or ampicillin-sulbactam (4% and 7.2%), cefazolin (1.5% and 3%), crystalline penicillin (1.1% and 0.8%), piperacillin-tazobactam (0.4% and 0%) and trimethoprim + sulfamethoxazole (0.4 and 0.4%). In the PIP and IP, respectively, the mean duration of the use of IV antibiotics per course of treatment, was 14.79 and 11.75 days ($p < 0.01$) and medians were 13.0 and 9.0 days.

In the PIP and PI, 69 (59%) and 66 (56.4%) patients, respectively, received more than one IV antibiotic, simultaneously. Twenty nine (24.8%) and 38 (32.5%) received antibiotics through a central venous catheter (CVC). At the beginning of treatment, 45 (38.5%) and 58 (49.6%) patients, respectively, were not receiving nutrition through the digestive tract, 60 (51.3%) and 46 (39.3%) were nourished orally, 12 (10.3%) and 13 (11.1%) through probe (nasoenteral, nasogastric, oroenteral or gastrostomy) (**Table 2**).

From the first prescription of antibiotics, the length of the hospital stay was more than 60 days for 6 (5.1%) patients in the PIP and for 5 (4.3%) patients in IP (**Table 1**). In the PIP and IP, respectively, 96 (82.1%) and 90 (76.9%) patients were discharged, and 15 (12.8%) and 22 (18.8%) died.

In the PIP, SAT occurred in 4 (3%) of the 135 courses of treatment, and in IP, it occurred in 5 (3.9%) of the 130 courses ($p = 0.95$) (**Table 3**). It was also observed that, after SAT, there was a return to IV route in two of these cases, one in each study period.

TABLE 2 - Type of intravenous route and nutrition prescribed for patients evaluated during the periods of pre-intervention and of intervention, Clinical Hospital of Uberlândia, State of Minas Gerais, Brazil.

	Pre-intervention period*(n=117)		Intervention period** (n=117)		
Variable	**n**	**%**	**n**	**%**	**p-value**
Intravenous route					
peripheral vein	88	75.2	79	67.5	0.25
central venous catheter	29	24.8	38	32.5	
Nutrition					
oral	60	51.3	46	39.3	0.17
zero/parenteral	45	38.5	58	49.6	
catheter (probe)***	12	10.3	13	11.1	

* April 04 to July 20, 2005. ** September 24 to December 20, 2007. *** nasoenteral, nasogastric, oroenteral or gastrostomy.

TABLE 3 - Courses of treatment submitted to sequential antibiotic therapy and length of hospital stay after sequential antibiotic therapy, in the periods of pre-intervention (April 04 to July 20, 2005) and of intervention (September 24 to December 20, 2007), Clinical Hospital of Uberlândia, State of Minas Gerais, Brazil.

	IV antibiotic		OT antibiotic after the intravenous form (SAT)		Length of hospital stay after the start time of SAT
Period	antibiotic used	time (days)	antibiotic used	tme (days)	(days)
Pre-intervention	CLIND+CEFT	12	LEVO	5	6
	CIPRO	2	CIPRO	7	7
	LEVO	2	LEVO	9	53
	ST	10	ST	6	6
Intervention	CEFE	4	LEVO	5	18
	CEFE	6	MOXI	1	1
	LEVO	3	LEVO	11	15
	LEVO	7	LEVO	3	13
	LEVO	1	LEVO	9	9

OT: oral treatment**; SAT: s**equential antibiotic therapy; **CLIND**: clindamycin; **CEFT**: ceftriaxone; **LEVO**: levofloxacin; **CIPRO**: ciprofloxacin; **ST:** sulfamethoxazole + trimethoprim; **CEFE**: cefepime; **MOXI**: moxifloxacim.

DISCUSSION

The studied populations at different periods, had similar demographic and clinical characteristics, with the predominance of intra-abdominal, and respiratory and urinary tracts infections[10,15]. The predominance of these infections is common to most hospitals[10,15]. The largest percentage of cases of respiratory infections found in PIP was higher than that in the IP, and this might be related to the period of the year when this study was conducted. Respiratory infections become more frequent in colder and drier weather[18,19].

The data of this study, although collected from a single hospital, raise suspicions that in Brazil the SAT is little performed in many hospitals.

In the present study, the eligibility of patients has not been assessed regarding clinical stability criteria. However, it is known that by the third day of treatment, nearly half of the hospitalized patients are already eligible for SAT[17,20].

Some studies showed the effectiveness of the use of guidance protocols for SAT promotion. Al-Eidan et al.[21], in the UK, observed that the use of a protocol led to a reduction in the length of time that IV antibiotics were used for patients with community-acquired pneumonia. The authors attributed the success of the program to three main reasons: the system used to assess patient's risk factors; the predetermined criteria to exchange the antibiotic to OT, when the patient's condition stabilized or improved and a clear and simple presentation of an algorithm for infection management. Even before the use of the protocol, the average time (geometric mean) for IV antibiotics was 5.7 days, which shows a great discrepancy from the data of this present study. Although the authors evaluated only community-acquired pneumonia, this is not a consistent reason for this discrepancy. McLaughlin et al.[10]. in a Glasgow's hospital, also in the UK, pointed out that the guidelines intervention adapted for the locality, increased substantially the use of SAT. Likewise the study conducted by Al-Eidan et al.[21] shows that the SAT was already performed in most patients, even before the intervention. Sevinç et al.[15], in a study performed in a large university hospital in the Netherlands, noted that a guideline reduced the average duration of intravenous treatment from 6 to 4 days. The reduction time (6 to 4 days) was even shorter than the one of this present study (14.79 to 11.75 days), but the reduction was proportionately much greater.

Although not evaluated for each individual case whether patients were able to receive the antimicrobial agent by OT, the number of cases of patients who underwent SAT was extremely small. Moreover, half of the patients have clinical stability about 3 days after start the antibiotic treatment[17,20,22]. It is clear from the current literature that there need not be a total resolution of parameters before oral switch can occur, but that the optimal timing has yet to be determined[4,23].

There was no explanation for the shorter hospital length of stay in the second period of the study, but it is not due the implementation of SAT because it doesn´t occurred.

In this present study, in the few cases of the use of SAT, a quinolone or a sulfonamide was used, perhaps because these antibiotics are available in both oral and intravenous presentation. They also have a good spectrum for nosocomial germs and they have very good bioavailablility by OT. For quinolones, the serum concentration is similar to that achieved by IV use[24]. However, in this present study, the quinolones were used in several other courses of treatment in which the SAT was not used. The third generation cephalosporins have been widely used, and currently there are no oral formulations available for these in the market[12]. This may also be a limitation for SAT. SAT is safe, effective and economical when performed at the appropriate time[4,7]. So there is no reason to disregard its use in a public hospital of a still developing country like Brazil.

The ability to tolerate and absorb the antibiotic administered orally can be easily assured when the patient is receiving and tolerating nutrition and/or other drugs, by OT[24]. This shows that gastrointestinal intolerance to the drug may not be the cause of the permanent use of IV antibiotics in these cases.

Thus, once there is a clear reason to use the SAT, an important issue is to know how to act in order to succeed in changing the behavior of physicians. It was noted that the proposed intervention, although it may be useful in some circumstances, was not so in this study. This shows that several factors, which are not clear to the observer, may interfere with the effectiveness of the interventions. A systematic review of strategies for continual medical education suggests that multiple interventions (*bundles*), performed with leadership and monitoring, are most effective for information transmission[25]. However, it is very difficult to prove which of these multiple interventions is truly effective.

One alternative would be to add to the guidelines, an explanation for the prolonged use of IV antibiotics by the physicians so that the pharmacist could easily provide them. Forms filled in by physicians justify the permanence of an intravenous antibiotic therapy for more than 48/72h as happens in the studies conducted in university hospitals in Manchester, England[17] and in Lausanne, Switzerland[26]. In this context, the performance of the clinical pharmacist and of the infectious disease physician of the HICS, are important to assess the justifications and to provide continuous feedback to the physicians.

It is concluded that, in the presented conditions, the evaluated intervention strategy is not effective in the sense of promoting the SAT. It is also concluded that in the studied hospital, SAT is rarely performed and that the length of time of IV antibiotic use is very long.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Kunin CM. Resistance to antibiotic drugs a worldwide calamity. Ann Intern Med 1993; 118:557-561.
2. Presidência da República [Internet]. Lei nº 8.080, de 19 de setembro de 1990. [cited 2009 June 19]. Available from: http://www.planalto.gov.br/ccivil_03/Leis/L8080.htm.
3. Rede Nacional de Monitoramento da Resistência Microbiana em Serviços de Saúde - Rede RM [Internet]. [cited 2009 May 11]. Available from: http://www.anvisa.gov.br/servicosaude/controle/rede_rm/index.htm.
4. Barlow GD, Nathwani D. Sequential antibiotic therapy. Curr Opin Infect Dis 2000; 13:599-607.
5. Zarb P, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): value of a point-prevalence survey of antimicrobial use across Europe. Drugs 2011; 71:745-755
6. Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. Arch Intern Med 1995; 155:1273-1276.
7. Tan JS, File Jr TM. Management of community-acquired pneumonia: a focus on conversion from hospital to the ambulatory setting. Am J Respir Med 2003; 2:385-394.
8. Lopes HV. Terapia antimicrobiana seqüencial ou "switch" terapia. Rev Panam Infectol 2004; 7:45-46.
9. Quintiliane R, Grant E, Quintiliane Jr R. Traditional (intravenous to oral) antibiotic therapy. J Med Liban 2000; 48:233-240.
10. McLaughlin CM, Bodasing N, Boyter AC, Fenelon C, Fox JG, Seaton RA. Pharmacy -implemented guideline on switching from intravenous to oral antibiotic: an intervention study. Q J Med 2005; 98:745-752.
11. American Thoracic Society Guidelines. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001; 163:1730-1754.
12. Cunha BA. Intravenous to oral antibiotic switch therapy. Drugs Today 2001; 37:311-319.
13. Ehrenkranz NJ. Containing costs of antibiotics in the hospital: a critical evaluation. Am J Infect Control 1989; 17:300-310.
14. Nathwani D, Tillotson G, Davey P. Sequential antibiotic therapy-the role of quinolones. J Antimicrob Chemother 1997; 39:441-446.
15. Sevinç F, Prins JM, Koopmans RP, Langendijk PNJ, Bossuyt PMM, Dankert J, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. J Antimicrob Chemother 1999; 43:601-606.
16. Di Giammarino L, Bihl F, Bissig M, Bernasconi B, Cerny A, Bernasconi E. Evaluation of prescription practices of antibiotics in a medium-sized Swiss hospital. Swiss Med Wkly 2005; 135:710-714.
17. Williams S, Alexander K, Rushton S, Cooke J. A new approach to optimising hospital antimicrobial use. Hosp Pharm 2005; 12:321-324.
18. Toyoshima MTK, Ito GM, Gouveia N. Morbidade por doenças respiratórias em pacientes hospitalizados em São Paulo/SP. Rev Assoc Med Bras 2005; 51: 209-213.
19. Pomilla PV, Brown RB. Outpatient treatment of community-acquired pneumonia in adults. Arch Intern Med 1994; 154:1793-1802.
20. Ramirez JA. Switch therapy in adult patients with pneumonia. Clin Pulm Med 1995; 2:327-333.
21. Al-Eidan FA, McElnay JC, Scott MG, Kearney MP, Corrigan J, McConnell JB. Use of a treatment protocol in the management of community-acquired lower respiratory tract infection. J Antimicrob Chemother 2000; 45:387-394.
22. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, et al. Time to Clinical Stability in Patients Hospitalized With Community-Acquired Pneumonia: Implications for Practice Guidelines. JAMA 1998; 279: 1452-1457.
23. Siegel RE. Strategies for early discharge of the hospitalized patient with community-acquired pneumonia. Clin Chest Med 1999; 20:599-605.
24. Kuti JL, Le TN, Nightingale CH, Nicolau DP, Quintiliani R. Pharmacoeconomics of a pharmacist-managed p rogram for automatically converting levofloxacin route from i.v. to oral. Am J Health Syst Pharm 2002; 59:2209-2215.
25. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Can Med Assoc J 1997; 157:408-416.
26. Senn L, Burnand B, Francioli P, Zanetti G. Improving appropriateness of antibiotic therapy: randomized trial of an intervention to foster reassessment of prescription after 3 days. J Antimicrob Chemother 2004; 53:1062-1067.