

Local protocol implementation for adherence to international guidelines on antibiotic prophylaxis: a simple tool for improving antibiotic stewardship in the Hospital of Trento (Italy)

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Riassunto

È stato recentemente dimostrato come l'aderenza alle linee guida della Società Europea di Urologia (EAU) nella profilassi antibiotica nelle manovre strumentali e negli interventi in urologia garantisce una riduzione dei costi diretti ed indiretti ed una riduzione delle resistenze batteriche. Nel 2011 nell'Unità Operativa di Urologia dell'Ospedale Santa Chiara di Trento, è stato introdotto una nuova procedura per migliorare l'aderenza alle linee guida internazionali sulla profilassi antibiotica, con interessanti risultati. Sulla base di queste considerazioni è stato pianificato uno studio finalizzato a valutare l'aderenza alle linee guida EAU nella profilassi antibiotica negli interventi di prostatectomia radicale robotica a distanza di 5 anni dalla creazione del protocollo. Dal Gennaio 2017 al Dicembre 2018 sono state rivalutate tutte le cartelle cliniche di 244 pazienti sottoposti a prostatectomia radicale robotica. I dati sulla profilassi antibiotica sono stati comparati con le indicazioni delle linee guida EAU. I risultati sull'aderenza alle raccomandazioni EAU sono stati incoraggianti: corretta prescrizione dell'antibiotico 226/244 (92.6%), corretto tempo di somministrazione

159/244 (65.2%). Gli antibiotici più prescritti sono stati cefoxitina (66.3%) e cefazolina (22.9%). In 8 casi sono stati utilizzati fluorochinoloni per un'allergia ai beta-lattamici. 33 pazienti sono stati sottoposti a singola dose di antibiotico (13.5%), mentre 152 a due dosi intraoperatorie per perdite ematiche o per tempo protratto di intervento (62.3%). 59 pazienti hanno ricevuto più di 2 dosi. In termini di infezioni post-operatorie abbiamo avuto solo 2 casi (0.8%). In conclusione, il tasso di aderenza alle linee guida EAU dopo 5 anni dall'introduzione del protocollo è rimasto alto sottolineando come la nostra procedura caratterizzata dalla creazione condivisa del protocollo, meeting a cadenza regolare e audit sulla profilassi antibiotica è la strategia più corretta per migliorare l'aderenza alle linee guida internazionali.

Abstract

The adherence to European Association of Urology (EAU) guidelines on antibiotic prophylaxis is associated with direct and indirect costs saving and bacterial resistance decreasing. In 2011 a protocol for adherence to EAU guidelines for antibiotic prophylaxis for all urologic procedures has been introduced in the Department of Urology, Santa Chiara Regional Hospital, Trento (Italy), with interesting results in terms of costs saving and antibiotic overall consumption reduction. Starting from these evidences, we aim to evaluate the adherence to EAU guidelines for a marker urological surgical robotic procedure, after 5 years from protocol introduction. From January 2017 to December 2018, 244 clinical charts of patients who had undergone laparoscopic robot-assisted radical prostatectomy in the same urological institution, were retrospectively reviewed and considered for this study. Data from clinical charts have been compared to the recommendations of EAU guidelines. The adherence to EAU in terms of correct antibiotic prescription was very high 226/244 (92.6%). The most common pre-operative antibiotic used were: cefoxitin 2 g and cefazolin 2 g in 162 (66.3%) and 56 (22.9%) patients, respectively. Eight patients received ciprofloxacin due to beta-lactams allergy (3.2%). Thirty-three patients underwent a single dose of antibiotic prophylaxis (13.5%), while 152 patients underwent a second antibiotic dose during surgery

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due to blood loss or due to prolonged surgical time (62.3%). On the other hand, 59 received more than 2 doses (24.2%). Antibiotic prophylaxis has been administered within the correct timing (30–60 minutes before surgery) in 159 (65.2%). Only two patients showed post-operative infections (0.8%). In conclusion, the adherence to EAU guidelines after 5 years from protocol introduction was high, highlighting that the implementation of local protocol with regular informative meetings and audits on antibiotic prophylaxis is the right way to improve the adherence to international guidelines.

Introduction

Antimicrobial resistance is an actual worldwide problem with elevated health costs and greater risk of poor patients' outcomes [1]. All clinicians are asked to be aware of their responsibility for reducing the spreading of antimicrobial resistance [2]. In this sense, all clinicians need to contribute to antibiotic stewardship programs. The continuous spreading and increasing of multidrug-resistant strains could be the reason of 300,000 deaths in the 2,050 in US due to resistant bacteria [3]. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) estimate that about 33,000 people die each year as a direct consequence of an infection due to bacteria resistant to antibiotics [4]. In particular, Italy and Greece were the most affected countries, accounting for a combined 21.3% of the total [5]. In order to respond to this threat, several health care systems, such as World Health Organization and European Union have instituted antibiotic stewardship programs to promote appropriate use of antibiotics, improve patient outcomes, reduce microbial resistance, and decrease the spread of infections caused by multidrug-resistant organisms [6–8]. These programs involve enforcement and monitoring of adherence to relevant evidence-based guidelines on antibiotic use, which can have patient benefits and can lead to significant cost reductions [9]. In the hospital setting, antibiotic prophylaxis is a key point for antibiotic stewardship achieving, as highlighted by Italian Ministry of Health in the National Action Plan on Antimicrobial Resistance (PNCAR) 2017–2020 [10]. Basing on this background, antibiotic prophylaxis use should be risk adjusted according to the procedure to ensure that harms in terms of bacterial resistance in an individual and society do not outweigh the benefits [11–12]. In line with this hypothesis, Cai and co-worker demonstrated in a large cohort of patients that the adherence to European Association of Urology (EAU) Guidelines on antibiotic prophylaxis for surgical urologic procedures is able to reduce overall antibiotic consumption and the risk of resistance development among uropathogens without increasing the risk of postoperative infection and with reduced health care costs [9]. The results of this study have been obtained from 2011 in that a new protocol for adherence to EAU guidelines for antibiotic prophylaxis for all urologic pro-

cedures has been introduced in the Department of Urology, Santa Chiara Regional Hospital, Trento (Italy). Basing on this evidence, we aim to evaluate the adherence to EAU guidelines for a marker urological surgical robotic procedure, after 5 years from protocol introduction and the efficacy of this approach for reducing infectious complications after the surgical procedures.

Materials and methods

Study schedule

From January 2017 to December 2018 clinical charts of 244 patients who had undergone laparoscopic robot-assisted radical prostatectomy in the Department of Urology, Santa Chiara Regional Hospital, Trento (Italy), were retrospectively reviewed and considered for this study.

All clinical charts have been reviewed by two nurses (C.G., D.P.P) and the antibiotic data about prophylaxis have been compared with the EAU recommendations. All clinical charts have been revised in terms of:

- adherence to EAU recommendations
- type of antibiotic used
- dosage and timing of antibiotic administration
- post-operative infectious complications

All clinical charts have been discussed with urologists (T.C., I.T.) in order to evaluate the appropriateness of the evaluation and the post-operative infectious complications assessment.

Additional data were retrieved by reviewing all electronic ambulatory medical charts from the hospital information system, as previously described [9]. All data were entered into a dedicated database. Patients with incomplete clinical or microbiological data regarding important information for the study aims were excluded from the analysis.

Protocol description and clinical considerations

All patients, candidates to laparoscopic robot-assisted radical prostatectomy underwent midstream voided urine specimen collection before hospital admission and a standard culture test was performed before starting prophylaxis, in line with EAU guidelines [13]. EAU guidelines for antibiotic prophylaxis have been produced and annually revised by a board of urologists coming from the European countries and expert in the field of urological infections. The EAU guidelines are available at the website of the European Association of Urology: <https://uroweb.org/guidelines/>. All patients with positive results for the urine culture were treated according to susceptibility testing and such patients were excluded from the analysis. After discharge all patients were monitored for 1 week to evaluate all infectious complications related to the procedure after antibiotic prophylaxis. A 1 week interval was chosen to increase the likelihood of capturing all infections only attributable to the surgical procedure, as events occurring later than 1 week were deemed unlikely to be related to infection at the time of surgery [14]. All events were eval-

uated at the routine follow-up visit 30 d after discharge [14]. The resistance patterns of all isolated microorganisms were closely followed and empirical therapy was adjusted accordingly. We defined an infection related to a procedure as either the presence of symptoms related to UTI and confirmed by microbiological analysis, or surgical site infection (SSI). Deep and superficial SSIs were defined according to the criteria of the Centers for Disease Control and Prevention/National Healthcare Safety Network [15]. The Clavien-Dindo classification was used for postoperative complications [16]. In order to improve and check the adherence to this protocol, regular informative meetings and audits have been performed every 6 months. Moreover, a revision of all clinical charts in terms of antibiotic prophylaxis has been regularly performed by the same urologist (T.C.). All audits have been planned when a serious discrepancy has been found between the antibiotic prophylaxis prescription and the protocol recommendation during the regular revision of the clinical charts. A detailed report about the antibiotic prophylaxis has been discussed during the audits.

Ethical and statistical considerations

This was deemed a service evaluation by the local ethics committee and thus did not require approval, due to the nature of the study and due to the fact that all personal data have been censored. Informed consent was not required since all procedures were performed according to routine standards with no data collection additional to routine care [9]. The study was registered as an audit within the institution. Results for categorical variables are presented as percentages and those for continuous variables are presented as the mean and standard deviation.

Results

Two-hundred and forty-four clinical charts have been selected from a total of 246. Two clinical charts have been excluded for data lack. Data obtained by the revision of the two missed clinical charts did not show any significant difference from these included in the analysis. The **table 1** shows the clinical and pathological characteristics of all patients at pre-surgery evaluation.

Antibiotic type, dose and timing

The most common pre-operative antibiotic used were: cefoxitin 2 g and cefazolin 2 g in 162 (66.3%) and 56 (22.9%) patients, respectively. Eight patients received ciprofloxacin due to beta-lactams allergy (3.2%). Thirty-three patients underwent a single dose of antibiotic prophylaxis (13.5%), while 152 patients underwent a second antibiotic dose during surgery due to blood loss or due to prolonged surgical time (62.3%). Fifty-nine patients received one or more doses of antibiotics after surgery (24.2%). However, the **table 2** shows characteristics of the antibiotic prophylaxis.

Table 1. Clinical and pathological characteristics of all patients at pre-surgery evaluation.

Patients n°	244
Age - mean (\pm SD)	65 (\pm 11.3)
Charlson Comorbidities Index - median (range)	1 (0-2)
PSA - mean (\pm SD)	8.3 (\pm 6.8)
Gleason Score at biopsy - median (range)	7 (6-8)
cT	
1	0
2	195 (79.9)
3	49 (20.1)
4	0
cN	
0	211 (86.4)
1	33 (15.6)
cM	
0	244 (100)
1	-
History of UTI	
yes	10 (4.1)
no	234 (95.9)
Indwelling catheter	
yes	1 (0.4)
no	243 (99.6)
Previous antibiotic use in the last 6 months	
yes	37 (15.2)
no	207 (84.8)

Table 2. Antibiotic prophylaxis: antibiotic, dosing, timing.

Antibiotic	
<u>Beta-lactams</u>	231 (94.7)
Cefazolin	56
Cefoxitin	162
Ceftriaxone	1
Amoxicillin – Clavulanic acid	12
<u>Fluorquinolones</u>	11 (4.5)
Ciprofloxacin	8
Levofloxacin	3
<u>Other</u>	2 (0.8)
Vacomycin	
Meropenem	
Dose and timing	
<u>Timing</u>	
<30 minutes prior to incision	61 (25.0)
30-60 minutes prior to incision	159 (65.2)
>60 minutes prior to incision	21 (8.6)
After incision	3 (1.2)
<u>Dose</u>	
Only one dose prior to incision	33 (13.5)
One dose prior to incision and one intraoperative dose	152 (62.3)
Post-surgery (one or more doses)	59 (24.2)

Adherence to EAU guidelines and post-operative infectious complications

The adherence to EAU in terms of antibiotic prescription was very high 226/244 (92.6%). Moreover, in terms of tim-

Table 3. Antibiotic prophylaxis: comparison to EAU recommendations.

EAU recommendations	Antibiotic prophylaxis used	Adherence
<i>Antibiotic</i> Trimethoprim/sulfamethoxazole (TMP/SMX) Cephalosporin group 2 or 3 Aminopenicillin/BLI	- 231	242 (99.2)
In case of allergy <i>Fluoroquinolones</i> Ciprofloxacin Levofloxacin	11	
<i>Dose and timing</i> <i>Timing</i> 30-60 minutes prior to incision	159	159 (65.2)
<i>Dose</i> Only one dose prior to incision One dose prior to incision and one intraoperative dose	185	185 (75.8)

ing, antibiotic prophylaxis has been correctly administered (from 30 to 60 minutes before surgery) in 159 (65.2%), as well as in terms of antibiotic used 242/244 (99.2%). Only in two cases the antibiotic molecules were not adherent to the EAU guidelines. In these two cases, the antibiotic choice has been guided on the results of a previous urine cultures. On the other hand, in terms of antibiotic duration, the adherence to EAU guidelines was lower 185/244(75.8%). The **table 3** shows the comparison between EAU recommendations and antibiotic prescription in our series.

Only two patients showed post-operative infections (0.8%). The two patients reported a superficial skin infection that required antibiotic treatment without any surgical revision. The patients did not require any hospital admission for the infectious complication resolution.

Discussion

Main findings

All clinicians have an imperative responsibility to contribute to antibiotic stewardship programs, by using all instruments and tools useful for achieving the goal. Here, we demonstrated that the implementation of local protocol for antibiotic prophylaxis based on the EAU guidelines on urological infections, seems the right way to improve the adherence to international guidelines and improve the principles of antimicrobial stewardship, showing a high adherence to EAU recommendation in terms of antibiotic prescription (92.6%) and timing of administration (99.2%). -Moreover, the implementation of local protocol, with regular informative meetings and audits, guarantees to maintain the adherence to EAU guidelines after 5 years from protocol introduction.

Results in the context of current literature

Recently, Cai et al. demonstrated that the adherence to antibiotic prophylaxis guidelines results in antibiotic resist-

ance reduction without any impact on post-operative infectious complications in agreement with previous studies [9, 17-18]. Adherence to guidelines usually entails lower use of broad-spectrum antibiotics, leading to a lower risk of selection of resistant strains [19]. Here, for the first time we demonstrated, in a urological setting, that the local implementation of a local protocol with regular informative meetings and audits, guarantees to maintain the adherence to EAU guidelines after 5 years from protocol introduction, reducing the antibiotics use and save costs, without any impact on infectious complications prevalence. A similar experience has been performed in pediatric area, by Breakell R. et al. who demonstrated that implementation of the NICE bronchiolitis guideline supported by a simple educational intervention can effectively reduce the number of inappropriate chest radiographs and antibiotic prescribing in bronchiolitis and enhance compliance with the NICE guideline [20]. In this study, the authors performed an implementation of the NICE guideline, accompanied by an educational intervention, by using regular staff educational interventions, consisting of e-mail consultations, sessions of presenting and discussing audit data and presentations of the NICE guideline with all levels of medical and nursing staff [20]. They, also, reported an overall NICE guideline compliance about 63% [20]. Here, we reported a high adherence to international guidelines (92.6%). The higher adherence showed in our study comparing with the Breakell's study is probably due to the fact that here we analyzed the results obtained from patients who had undergone the same urological procedure (laparoscopic robot-assisted radical prostatectomy) in a single Institution. In our study we found that the high adherence to EAU guidelines is in terms of antibiotic molecules and dose. We found that the most common pre-operative antibiotic used were beta-lactams, in line with EAU recommendations. The use of fluoroquinolones is limited to that patients who reported allergy to beta-lactams. Haifler and co-workers demonstrated that a single preopera-

tive dose of antibiotics does not increase the rate of post-operative infectious complication compared with prolonged antibiotic treatment, highlighting that complying with the international guidelines may reduce morbidity and medical costs [21]. In this study, the most common antibiotic used is an association of cephalosporin and aminoglycoside [21]. Moreover, in a retrospective study performed by Shin et al. the most common antibiotic prophylaxis used is second-generation cephalosporin, highlighting the efficacy of this antibiotic class in radical prostatectomy [22]. On the other hand, the timing of antibiotic administration shows the lower adherence to guidelines, even if the guideline compliance is high (65.2%). EAU guidelines suggest to administer antibiotic prophylaxis about 30-60 minutes before surgery. The lower guidelines compliance is probably due to logistic factors related to the incorrect evaluation of the operative theater starting time. However, future analysis are ongoing in order to evaluate it. Finally, our protocol is perfectly in line with the recent alert by the European Medical Association (EMA) and European commission (EC) that implemented stringent regulatory conditions regarding the use of fluoroquinolones (e.g. Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin, Ofloxacin) in urology [23]. In line with the regulation from EMA, all national authorities have been urged to promote the correct use of all classes of antibiotics, in order to reduce the adverse effects and bacterial resistance increasing [24].

Limitations of this work

The single Centre feature and the small number of patients enrolled in this study should be considered a limitation to consider. However, the high adherence to the EAU guideline and the low prevalence of infectious complications is the key message and a strong point of this study. Future multicenter and prospective studies should be planned in order to confirm these results.

Conclusions

Here, by using a retrospective, single Centre, observational study, we find that the adherence to EAU guidelines after 5 years from protocol introduction was high with limited number of infectious complications after surgical procedures and antibiotic consumption reduced, highlighting that the implementation of local protocol for antibiotic prophylaxis is the right way to improve the adherence to international guidelines. Finally, our experience is part of a local implementation program of antibiotic stewardship started few years ago in Azienda Provinciale per i Servizi Sanitari of Trento. This program included education initiative on antimicrobial stewardship and audits in all clinical Departments. Our program is structured in line with the statement included in the “United towards Global Health: common strategies for common challenges”, in the part of supporting the development of evidence-based strategies, tools and interventions to fight antimicrobial resistances [25].

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