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Staphylococcus lugdunensis, a serious pathogen in Periprosthetic Joint Infections

Comparison to *S. aureus* and *S. epidermidis*

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ABSTRACT:

Objectives: The aim of the study was to assess characteristics of Periprosthetic Joint Infections (PJI) due to *S. lugdunensis* (SL) compared to S. *aureus* (SA) and S. *epidermidis* (SE) PJI.

Methods: We conducted a retrospective multicentric study including all consecutive cases of SL PJI (2000-2014). We recorded 88 cases of staphylococcal PJI divided in 28 SL, 30 SA, 30 SE identified by Vitek2 or ApiStaph (Biomerieux®).

Results: Clinical symptoms were more often reported in SL group and mean delay between surgery and infection was shorter compared to SA and SE group.

Regarding antibiotic susceptibilities SL strains were susceptible to antibiotics and 61% of the patients could be treated with levofloxacin-rifampicin. Outcome was favourable in 89% patients with SL, 83% SA, 97% of SE PJI.

Conclusion: SL is an emerging pathogen with a pathogenic power quite similar to SA. This coagulase negative staphylococcus must be precisely identified to choose the adapted surgery and antibiotics in PJI.

Keywords: *Staphylococcus lugdunensis*, periprosthetic joint infections

Introduction:

Periprosthetic joint infections (PJI) are the main complication of knee and hip prosthetic arthroplasty. One to 3% of the patients undergoing prosthesis implantation are concerned by these infections (1, 2). Staphylococci (*Staphylococcus aureus* (SA) and coagulase negative staphylococci (CNS)) are the major pathogens involved in these infections (2, 3). *Staphylococcus lugdunensis* (SL) is a CNS considered part of the normal flora of human skin as well as other CNS (4). It is widely spread on the skin, especially in inguinal and perineal areas (5). SL was first described in 1988 (6) and was shown to have morphological, biochemical and pathogenic properties close to SA. These common properties can lead to misidentification of SL: It may be positive for clumping factor and thus could show positive latex agglutination tests, like SA. SL is also ornithine decarboxylase positive, like other CNS and therefore be mistaken for another CNS. Recent evolution in bacteriological techniques has led to a considerable improvement in species identification. Automatized systems and mass spectrometry have solved the misidentification problems especially for CNS.

Virulence factors of SL are shared with SA such as ability to adhere on host proteins (fibronectin, fibrinogen), slime production, secretion of various toxins (7). Moreover, the gene "agr" (accessory regulator), ica operon, fbl, atlL, vwbl and slush factors involved in bacteria virulence has been identified in SL strains. All these common properties show that SL is an aggressive pathogen and may be responsible for serious infections (8, 9). SL is also described as a bacteria able to produce biofilm due to atlL autolysin, especially in prosthetic device-associated infections (10).

The pathogenic role of SL was emphasized in 1991 when a total of 155 SL specimens were isolated from different sites in 143 patients (4). In this study, patients included often

presented necrotized wounds, empyema or abscesses. SL is well described as an aggressive pathogen involved in brain, thoracic, cutaneous and soft tissues abscesses (11-13).

SL can cause endocarditis on native valves, septicemia, deep tissue infections, peritonitis (4, 9) but few studies reported SL bone and joint infections.

SL shares several properties with SA: SL may produce in particular a bound coagulase via a clumping factor. But unlike SA, it doesn't produce a free coagulase. Short coagulase test (rapid agglutination test) may be positive for SL because of the same surface proteins shared with SA. For these reasons it can be misidentified and the management of PJI treatment may be influenced. SL is more virulent and clinical manifestations are more similar to SA than CNS.

Since its first description in 1988 by Freney et al. (6, 11), SL has been acknowledged as an agent causing severe infections such as endocarditis (14, 15), soft infections, peritonitis, breast and cerebral abscesses, vascular graft infections, septicemia (4, 12, 13) and toxic shock syndromes (16).

As far as we know, less than 30 cases of prosthetic joint infections (PJI) due to SL have been reported in literature.

The objective of this study was to assess the differences between SL versus SA and SE in terms of clinical symptoms, delay between surgery and infection, antibiotic susceptibilities and clinical outcomes.

Materials and methods:

Study population:

We conducted a retrospective and descriptive study from 2000 to 2014 including patients from 3 orthopedic centers in the same area. Eighty eight cases of monomicrobial staphylococcal PJI were analyzed: 28, 30, 30 consecutive infections due to respectively SL, SA and SE.

Patients and samples:

Data information collected were: age, gender, medical history, infection localization, clinical signs, surgical type, antibiotic therapy, duration of treatment, outcome post treatment, delay between surgery and bacterial identification. These data are summarized in Table 1.

All patients included were suffering from PJI. The diagnosis was based on multidisciplinary criteria and assessed by clinical, biological, microbiological, histopathological and radiological arguments (17).

PJI diagnosis was established on the presence of 1 major criterion or 3 minor criteria:

Major criteria were: at least 2 positive periprosthetic cultures with phenotypically identical organisms or a sinus tract communicating with the joint.

Minor criteria were: a C reactive protein value >10mg/L , a histological analysis of periprosthetic tissue asserted a septic process (18).

The surgical technique was chosen by the orthopedic surgeon in concertation with the infectious diseases specialist (17):

-Irrigation-debridement (ID) was the technique used for an early PJI with less than one month between prosthesis implantation and clinical symptoms of infection.

-One stage surgery (OSS) was considered for patients with chronic PJI with an adequate state of bone and tissues. A Gentamicin bone cement (Palacos-Genta®) was used each time as possible.

-A 2-stage revision (TSR) was indicated for patients not candidates for ID or OSS. These patients presented a chronic PJI, with eventually bone and soft tissues defects. This strategy was used for patients who could undergo at least 2 surgeries.

A local spacer impregnated with gentamicin was used until the placement of a new prosthesis.

The outcome of patients was based on at least a 1-year follow up. This consisted of a multidisciplinary consult (surgeon and infectious disease physician) including a clinical and radiological evaluation and a CRP blood analysis.

A favorable outcome was established on a good clinical recovery, a satisfying joint mobility, and no sign of inflammation.

To perform the microbiological diagnosis, intraoperative bone tissue, synovial membranes, articular fluid samples were performed. Our recommendations were to stop antibiotics 15 days prior to surgery in order to obtain growing bacteria in culture.

At least 3 intraoperative deep samples per patient were collected. After collecting, samples were transferred to the microbiological laboratory in less than 1 hour.

Bacteriological culture:

For each suspect site: solid and tissues specimens were collected on sterile balls vials; articular fluids were inoculated in blood culture bottles. All samples were incubated under

aerobic with CO2 and anaerobic atmosphere for 15 days. Gram staining was performed for each sample on day one.

Solid and tissues were then crushed by vortexing in 1 mL of saline solution for 10 minutes.

Standard cultures were performed on columbia blood agar, polyvitex chocolate agar and thioglycolate solution (Oxoid®, Dardilly, France). Articular fluids were inoculated in blood culture bottles and on solid agar media.

Media were observed daily for microbial growth. Bacteriological criteria for positive diagnosis of infection were: at least 1 positive sample for SA positive cultures; at least 2 positive samples for SE and SL positive cultures.

We selected only monomicrobial cultures with SA, SL and SE. Seven polymicrobial infections including SL were excluded. In these cases PJI involved cutaneous flora bacteria : coagulase negative staphylococci, corynebacteria, or Propionibacterium *acnes*. The exclusion of polymicrobial infections was necessary to know what bacteria conducted to PJI. Thus all clinical, biological and treatment's related results were specifically attached to a single bacteria species: SA, SL or SE.

In case of positive culture:

Identification was performed by automatized technique on Vitek2 (Biomérieux®) or manual technique on ApiStaph (Biomérieux®, Marcy l'Etoile, France).

When identification results were conflicting, complementary tests were performed to confirm species identification:

-SA: positive latex agglutination

-SL: typical salty smell, positive pyrrolidonylarylamidase (L-PYR) test

-SE: colistin resistance detected by a disk diffusion test

Antimicrobial susceptibilities were tested on Vitek2 (Biomérieux®) according to the Committee of Antibiotic susceptibility from the French Society of Microbiology

recommendations (19). Methicillin resistance was interpreted from oxacillin CMI. Staphylococci strains were considered as susceptible when CMI was included between 0.5 and 2 µg/mL. Methicillin susceptibility conflicting results were verified by a cefoxitin disk (Biorad®, Marnes-la-Coquette, France).

Statistical analysis:

Continuous variables were displayed as median and inter-quartiles. Categorical variables are presented as count and proportions. In univariate analysis, continuous data were compared among 3 groups of patients according to the type of Staphylococcus of using a Kruskall Wallis test. Qualitative variables were compared with $\chi 2$ test (or Fisher exact test when necessary). The statistical analysis was performed using Stata® 11.2 software (statacorp, Texas, USA).

Results:

Population study:

We reported 28 cases of SL PJI between 2000 and 2014, followed in 3 orthopaedic centers of the same area. SL clinical and surgical data are detailed in table 1.

Age, sex, prosthesis sites, clinical, biological signs and surgery type in the 3 groups are summarized in table 2.

The populations of the 3 groups were comparable statistically regarding age (p=0.34) and gender (p=0.196).

SL patients: Eight patients (29%) had comorbidity factors: 4 (14%) cardiovascular diseases, 1 (4%) inflammatory rheumatism, 1 (4%) diabetes mellitus, 2 (7%) had a cancer treated history.

The C reactive protein (CRP) was evaluated in this group and median CRP value was 42mg/L.

SA patients: Nine (30%) patients had comorbidity factors: 5 (17%) cardiovascular diseases, 1 (3%) cancer treated, 1 (3%) inflammatory rheumatism, 1 (3%) diabetes mellitus, 1 (3%) type C hepatitis.

SE patients: Thirteen (43%) patients presented comorbidity factors: 5 cardiovascular diseases, 1 treated cancer, 5 diabetes mellitus.

CRP data in SA and SE PJI are not presented as they were only available for a few patients.

Surgical intervention:

The median delay between surgery and infection and the surgery type for the 3 groups are presented in table 2. In SL PJI the median delay was statistically shorter than in the other groups (p=0.0449).

Bacteriological results:

Bacteriological results on deep per-operative samples in the 3 groups are presented in table 2 and no significant difference was found between the 3 groups regarding the number of positive (p=0.449) and total samples (p=0.413). SL culture results and antibiotic resistance profiles are detailed in table 3. Comparison of antibiotic resistances is presented in table 4. SL was significantly the most susceptible species regarding Penicillin G, meticillin, fluoroquinolones, clindamycin (p=0.000) and rifampicin (0.038). Antibiotics resistance profiles in the 3 groups are compared on figure 1.

Medical therapy:

All patients underwent an empiric intravenous antibiotic regimen with vancomycin or daptomycin following surgery. After approximatively one week of parenteral antibiotics, an oral relay therapy was set up during a mean duration of 7 weeks in the 3 groups. Main oral medical treatments are presented in table 4. Antibiotics prescribed in SL and SA PJI were mostly fluoroquinolones associated with rifampicin. Because SE strains were more resistant compared with SA and SL, second line antibiotics like linezolid were used more. Comparison of oral medical treatment in the 3 groups is shown on figure 2.

Outcome of patients:

The outcome was evaluated after a follow up starting at the end of treatment and during at least 12 months for all patients. Outcome results are presented in Table 2 and were statistically comparable in the 3 groups (p=0.233).

Nine unfavorable outcomes were reported in the total population. The global success rate of surgery technique defined by the lack of relapses was respectively 85%, 97% and 86% for ID, OSS and TSR.

DISCUSSION:

To our knowledge, it is the first study comparing clinical and bacteriological characteristics of 28 consecutive SL cases of PJI, compared to other staphylococci PJI.

SL colonization is described on the skin, especially in inguinal and perineal areas (5). This localization may play a role in a potential dissemination by a hematogenous or subcutaneous way which could lead to bone and joint infections. Several studies about SL bone and joint infections have reported osteomyelitis (4, 22), septic arthritis (23), PJI (4, 24).

They all have described the invasive side of these SL infections. In our study, we reported significantly more clinical symptoms like pain, fever and local inflammation signs in SL and SA compared with SE series. In our series, C-reactive protein at diagnosis time was not reported for all patients (especially for those with SE PJI). It was available for half of the patients with SL PJI and the mean value was 42 mg/L, which is much higher than the value usually reported in SE PJI (25).

The delay between surgery and infection was significantly shorter in SL and SA PJI compared to SE PJI. Others studies also reported a short delay in SL PJI. This result confirms that the clinical course of SL PJI is close to SA infections (23, 26).

The type of surgical interventions performed for SL and SA PJI was ID and TSR. In all other studies published, the most frequent surgical type chosen is TSR with placement of an antibiotic spacer (24, 26, 27). The success rate of SL PJI treatment was globally the same whatever the type of surgery. Three patients had unfavorable outcomes (one after ID and 2 after TSR).

In our study, SL was responsible for knee PJI more than hip PJI, as was SA. On the contrary, SE was more involved in hip PJI. These data may confirm the suggestion of Shah and coll. That SL could infect knees preferentially (26).

Although SL shares many properties with SA, one of the main differences between the two species is the antimicrobial susceptibility. We found that SL strains were all susceptible to meticillin, and half was resistant to Penicillin G. These results are different to some previous studies especially for Penicillin G resistance (4, 11, 26). These results seem to indicate that the adapted parenteral βlactam to treat SL PJI should be antistaphylococcal beta-lactam agent.

As in previous studies, we found a high rate of susceptibility (90-100%) to quinolones, rifampicin and clindamycin (22, 23, 26, 27). No strain was resistant to linezolid or SXT. SA strains were quite susceptible to meticillin (87%) but we reported 17% of resistant strains to quinolones and 27% to clindamycin. Comparatively, 77% of SE strains were resistant to meticillin, 60% to quinolones and 20% to rifampicin, the first line antibiotics used to treat PJI.

Thus SA and SL strains in our study were much more susceptible than SE as reported in other publications on staphylococci bone and joint infections (28).

The treatment of SL PJI was the combination quinolones + rifampicin for 61% of the patients. This is the reference treatment in meticillin susceptible CNS PJI advised by French and International guidelines (17, 29). This combination was chosen as a first line treatment in SA PJI too, but only for 40% of patients in SE PJI. More second line antibiotics like linezolid, SXT, cyclins, clindamycin or fusidic acid often used for treatment of PJI due to the resistance of SE.

Duration of treatment was on average 7 weeks in the 3 groups. It seems that the good outcome of patients was based on the early (<1 month) surgery associated with an adapted antibiotic combination more than the duration of treatment. Previous studies reported a mean duration of 4 to 8 weeks (22-24).

Moreover 97% of patients with SE PJI had a favorable outcome compared to 89% and 83% respectively in SL, SA PJI (p=0.233). These results are not significant in this population but it may suggest nevertheless the high pathogenic power of SL.

In our study number of SL PJI collected was only 28 and seemed not statistically sufficient to assert all our observations. Our results would warrant confirmation on prospective studies conducted on wider SL PJI samples.

To conclude, SL is classified in CNS but the clinical aspect of SL PJI, the precocity of the infection and the relapses observed are similar to SA PJI. Regarding microbiological diagnosis, the species of CNS must be precisely identified in PJI joint to the adapted antibiotic susceptibilities, even if only one deep sample is positive in culture.

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Table 1: Characteristics of patients and clinical information in SL PJI:

Patient	gender	Age (years)	medical history	prosthesis site	clinical signs	surgery type
1	F	49	0	knee	P	ID
2	M	79	CV	knee	P	ID
3	F	75	0	hip	P	ID
4	M	87	CV	knee	FE P, SLI	OSS
5	F	63	0	foot	FE P Fi	ID
6	F	68	0	shoulder	FE P SLI	ID
7	M	63	0	hip	P	TSR
8	F	67	CV	hip	P	TSR
9	M	37	0	knee	FE P	OSS
10	M	55	CV	knee	FE P	ID
11	F	83	0	hip	FE P, SLI	ID
12	M	40	0	knee	FE P, SLI	ID
13	F	70	0	knee	FE SLI P	TSR
14	M	70	0	knee	FE P, SLI	TSR
15	M	40	0	hip	FE P, SLI	ID
16	F	82	DM	hip	FE DP	ID
17	M	48	RD	hip	SLI	ID
18	F	78	0	knee	Fi	TSR
19	F	66	K	knee	L	TSR
20	M	64	K	hip	L	TSR
21	M	66	0	knee	SLI FE P	OSS
22	M	41	0	hip	SLI P	TSR
23	F	87	0	knee	Fi	TSR
24	F	71	0	knee	SLI FE P	TSR
25	F	61	0	knee	FE D SLI	OSS
26	F	78	0	knee	D	OSS
27	F	84	0	knee	D	TSR
28	M	71	0	hip	FE D SLI	OSS

RD : Rhumatoid disease, K : cancer, DM : Diabetes mellitus, CV: cardiovascular disease

SLI: inflammation local signs, FE: fever, Fi: fistula, L: loosening, P: pain

ID: irrigation and debridement, OSS: one stage surgery, TSR: two stage revision

0: no medical history

Table 2: Comparison of populations in SL, SA and SE PJI:

		S. lugdunensis (28)	**S. aureus (30)**	**S. epidermidis (30)**	**p value**
	age (years)	67.5 [58-78]	60.5 [44-75]	67 [61-77]	p=0.34
	number of males (n/%)	13 (46.4%)	20 (66.7%)	20 (66.7%)	p=0.196
prosthesis site	knee	16 (57%)	18 (60%)	11 (36,7%)	p=0.145
	hip	10 (36%)	9 (30%)	16 (53%)	p=0.158
	other	2 (7%)	3 (10%)	3 (10%)	
clinical signs	fever	15 (53.6%)	9 (30%)	4 (13.3%)	p=0.004
	local signs of inflamation	13 (46.4%)	7 (23.3%)	4 (13.3%)	p=0.015
surgery type	irrigation and debridement	11 (39.3%)	10 (33.3%)	5 (16.7%)	p=0.144
	one stage surgery	6 (21.4%)	12 (40%)	16 (53.3%)	p=0.044
	two stage revision	11 (39.3%)	8 (26.7%)	9 (30%)	p=0.568
surgery/infection	delay surgery/infection (weeks)	12 [3-56]	44 [12-144]	84 [44-192]	p=0.0449
Samples	number of positive samples	3.5 [1.5-5]	4 [3-5]	4 [3-5]	p=0,449
	total number of samples	5 [2-6]	4 [3-5]	5 [4-6]	p=0,413
Treatment	duration (weeks)	7	7	7	
Outcome	positive (number of patients)	89%	83%	97%	p=0.233

Table 3: microbiological results, treatment and outcome of patients:

patient	antibiotic resistances	treatment	duration (weeks)	positive/total samples	outcome
1	PENI FOS	FQ RIFAM	6	2/5	FAV
2	PENI	FQ RIFAM	6	5/5	FAV
3	PENI	FQ RIFAM	6	2/2	FAV
4	PENI RIFAM	FQ CLINDA	6	4/4	FAV
5	PENI MLS	FQ RIFAM	6	1/1	FAV
6		SXT RIFAM	6	4/5	FAV
7	PENI FOS	LNZ	3	2/6	FAV
8	PENI	LNZ	4	6/7	FAV
9		FQ RIFAM	6	2/2	FAV
10	PENI	FQ RIFAM	6	3/6	FAV
11		FQ RIFAM	6	2/2	FAV
12	PENI	FQ CLINDA	8	2/2	FAV
13		FQ RIFAM	6	5/5	UNFAV
14	PENI	FQ RIFAM	9	5/5	FAV
15		FQ RIFAM	8	5/5	FAV
16	PENI MLS FQ TET	FQ RIFAM	10	5/5	UNFAV
17	FOS MLS	FQ RIFAM	6	6/7	FAV
18	FOS	OXA	17	3/4	FAV
19	FOS	OXA FA	65	3/5	FAV
20	FOS	OXA	4	4/5	FAV
21		AMC RIFAM	17	1/1	FAV
22	FOS	FQ RIFAM	16	2/2	FAV
23	FOS FQ	CLINDA	13	4/5	FAV
24	PENI	FQ CLINDA	16	2/2	FAV
25		FQ RIFAM	6	9/9	FAV
26	PENI AF	FQ RIFAM	6	6/6	FAV
27		FQ RIFAM	8	6/6	UNFAV
28	PENI FOSFO	FQ RIFAM	8	2/7	FAV

FAV: outcome favourable

UNFAV: outcome unfavourable

Table 4: Comparison of antibiotics resistance and treatment in the 3 groups:

	SA	SE	SL	p value
Resistance Penicillin G	22 (73.3%)	30(100%)	14 (50%)	p=0.000
resistance meticillin	4 (13.3%)	23 (76.7%)	0	p=0.000
resistance fluoroquinolones (FQ)	5 (16.7%)	18 (60%)	1 (6.6%)	p=0.000
resistance rifampicin (RIF)	1 (3.3%)	6 (20%)	1 (3.6%)	p=0.038
resistance clindamycin	8 (26.7%)	19 (63.3%)	3 (10.7%)	p=0.000
treatment FQ+RIF	25 (83.3%)	12 (40%)	17 (60.7%)	p=0.003
treatment Linezolid	2 (6.7%)	12 (40%)	2 (7.1%)	p=0.001

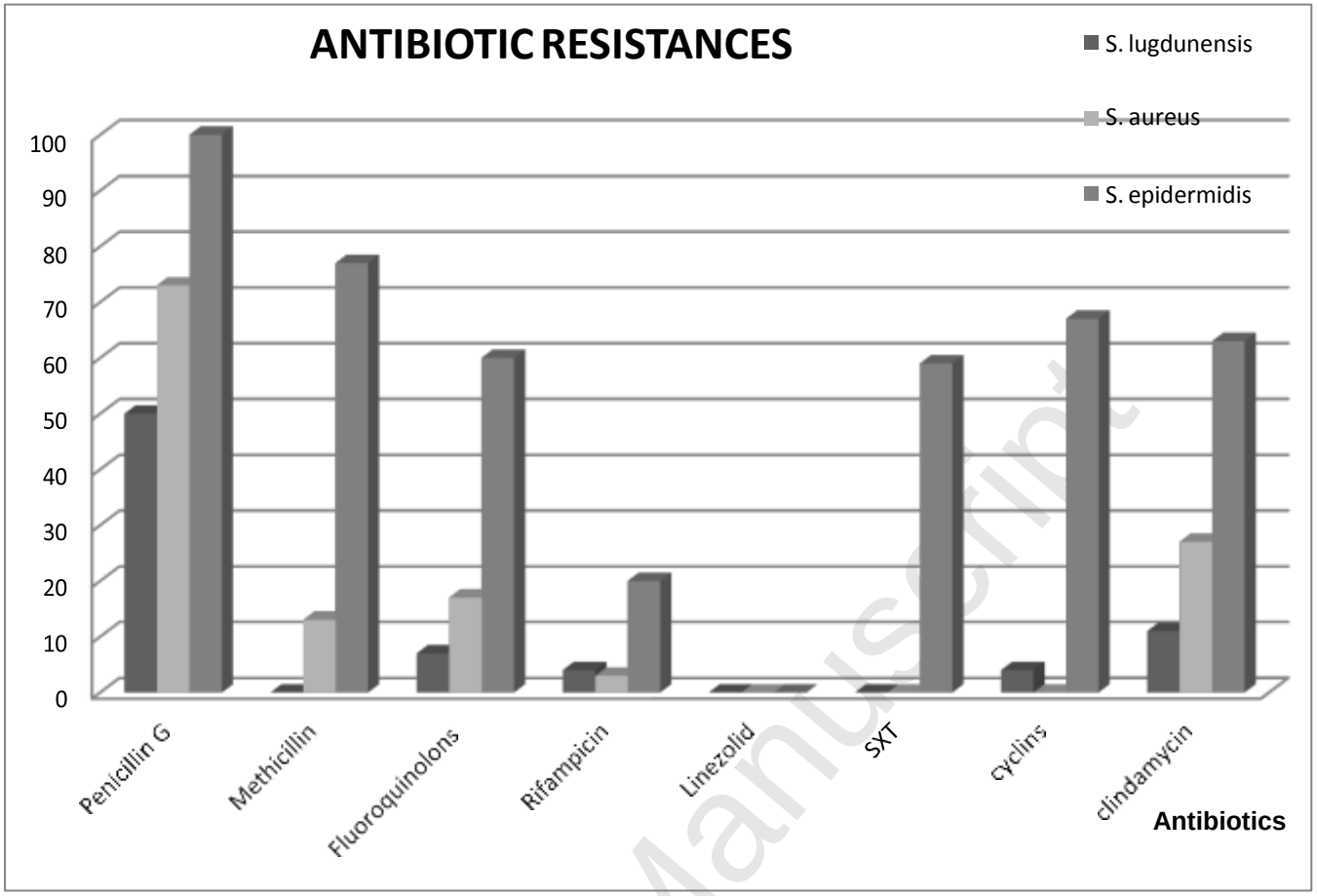

Figure 1: Antibiotic resistances of SL, SA and SE strains

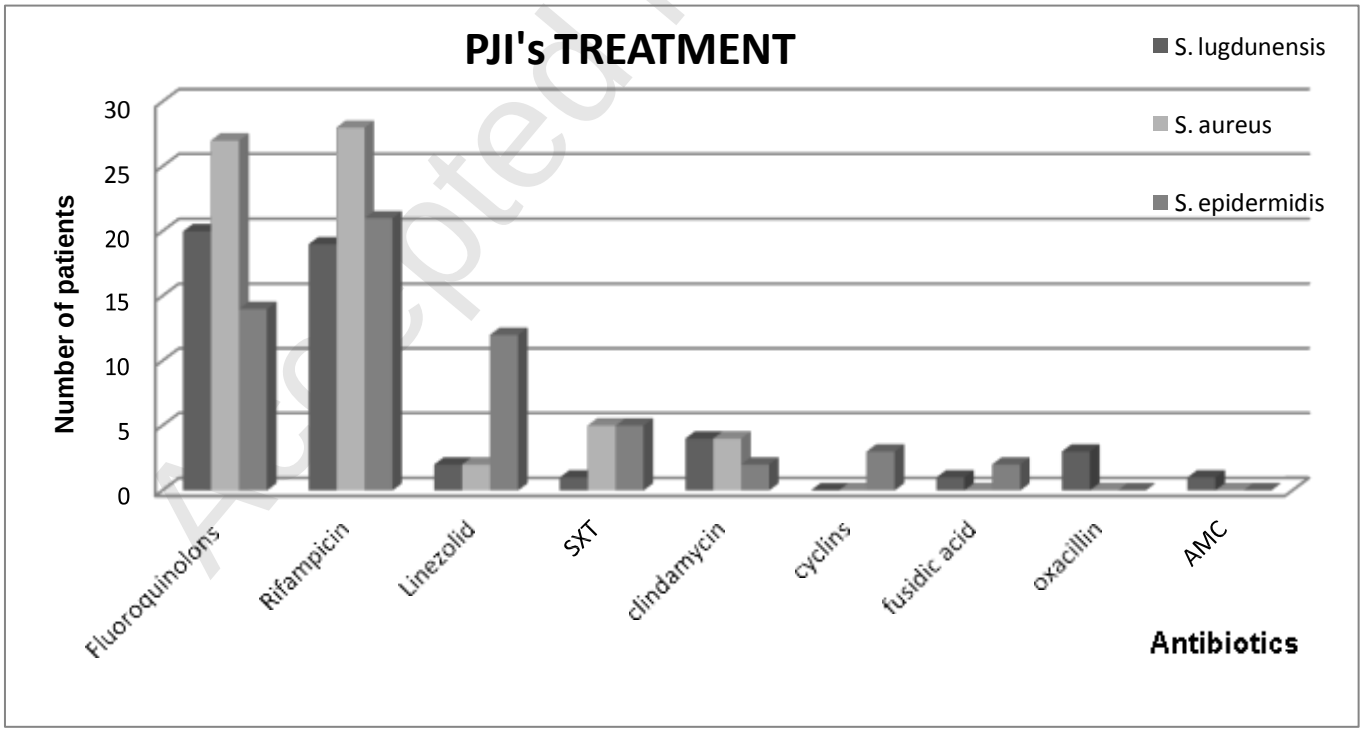

Figure 2: Antibiotic treatment in SL, SA and SE PJI