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SEPTIC ARTHRITIS: BACTERIOLOGICAL PROFILE AND ANTIBIOTIC RESISTANCE STATUS: EXPERIENCE OF THE AVICENNE MILITARY HOSPITAL IN MARRAKECH

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ABSTRACT

Septic arthritis is a therapeutic emergency and any delay in diagnosis has a serious impact on the patient's future, both in functional and vitality terms.

Objectives: The aim of this study is to determine the epidemiology of septic arthritis, to characterize their bacteriological profiles and to evaluate antibiotic resistance in the Avicenne military hospital in Marrakech.

Methods: This is a retrospective descriptive study over a period of 7 years from January 2014 to December 2020, focusing on the bacteriological analysis of articular liquids received in the microbiology laboratory of the Avicenne military hospital in Marrakech.

Results: Among the 496 articular liquids studied, only 25 were positive on direct examination and/or culture. The male sex was predominant with a sex ratio of 5.25. The departments involved were: 48% from the rheumatology department, 16% from the trauma department, 8% from the emergency department, 4% from the resuscitation department, and 20% from the outpatient department. A purulent aspect on macroscopic examination is the most frequent finding at 88%. Hyperleukocytosis greater than 10000 elements/mm³ is found in 60% of cases. Direct examination is positive in 60% of cases, of which 44% are gram positive cocci and 16% are gram negative bacilli.

Staphylococcus aureus is isolated in 45% of the cultures against 20% for coagulase-negative Staphylococci, 15% for streptococcus spp, 10% for Klebsiella pneumoniae, and 5% for Escherichia. Coli. However, the existence of a germ in the joint fluid is not synonymous with septic arthritis; in fact, we found 3 cases of joint fluid contamination.

The study of the resistance of these isolates revealed an absence of resistance to methicillin for Staphylococcus aureus while 33% of coagulase-negative Staphylococcus were resistant. During the study period, out of a total of 20 bacteria isolated, only one multi-resistant bacterium was isolated (ESBL-producing enterobacteria).

Conclusion: Septic arthritis is a serious infection. Bacteriological diagnosis of the articular liquid remains today the key to determine the infectious origin of arthritis and its treatment.

Keywords: Septic arthritis – Resistance- Antibiogram

I. INTRODUCTION

Septic arthritis is defined by the intra-articular proliferation of a pathogenic micro-organism in one or more joints. It is different from reactive arthritis, which are inflammatory reactions that can be induced by bacteria. Because of the rarity of arthritis of parasitic or mycological origin, the septic character is often synonymous with a bacterial etiology. [1]

The main mode of contamination is by the hematogenous way, followed by direct

inoculation and in a few cases by contiguity. [1]

The occurrence of septic arthritis is a major medical emergency. It affects the functional prognosis of the joints, but sometimes also the vital prognosis in case of septic shock. It therefore requires immediate treatment [1, 2].

The incidence of septic arthritis has been estimated in Northern Europe and Australia to be between 5.7 and 9 cases/100,000 inhabitants per year [3,4]. It is thought to be increasing, particularly due to the increase in intra-articular surgical and rheumatological procedures [5].

The increasing resistance of bacteria to antibiotics has become a major public health issue, leading to fears of therapeutic impasses. An increase in the frequency of septic arthritis caused by methicillin-resistant Staphylococcus aureus (MRSA) has been observed in various regions of the world [6].

The germs most frequently found in this type of infection are: Staphylococcus aureus, with a frequency of 40 to 54%, and Streptococcus, with a frequency of 14 to 18% depending on the series [7, 8].

The diagnosis is based on the identification of the germ in the joint fluid sample, blood cultures, and in the portal of entry or closed focus in the presence of arthritis [8]. A rigorous and persistent search for the germ is essential before any antibiotic therapy [9].

The puncture of the joint fluid is the key examination. The purulent character of the joint fluid on macroscopic examination, direct examination and culture of the samples allow the diagnosis of septic arthritis.

The objective of our study is to determine the bacteriological profile of septic arthritis isolated in the Bacteriology and Virology Department of the AVICENNE Military Hospital in Marrakech and to evaluate the state of resistance to different antibiotics over a period of 7 years between 2014-2020.

II. MATERIELS AND METHODS

This is a retrospective descriptive study conducted in the Bacteriology and Virology Department of the AVICENNE Military Hospital in Marrakech over a period of 7 years from January 1, 2014 to December 31, 2020. The samples concerned by the study are only joint puncture fluids. The samples were sent by the different departments of the hospital: rheumatology, intensive care, traumatology, emergency and maxillofacial. The collection of joint fluid is considered a valuable sample, as the isolation of a micro-organism can have important clinical and therapeutic consequences, as well as forensic consequences. It is therefore imperative to avoid contamination of this sample, which is not generally repeatable. It must be handled under microbiological safety post (MSP-2) using sterile handling techniques. Macroscopic and microscopic examination and culture are necessary to make the diagnosis.

The data were entered and processed on Excel software in order to perform frequency and percentage calculations for qualitative variables and median calculations for quantitative variables.

Joint fluid analysis is based on:

- Direct examination: includes

- A macroscopic examination which provides information on The appearance, color, viscosity and coagulation.
- A microscopic examination: with an examination in the fresh state, and an examination after staining (Gram and May-Grünwald Giemsa or methylene blue).

- Culture: the specimen should be plated in enriched media such as:

- Blood agar, aerobically incubated at 37°C.
- Chocolate agar supplemented with poly vitamins, incubated under 5% CO2 at 37°C.
- Blood agar (or Columbia agar) anaerobically at 37.
- And in an enrichment medium such as: a liquid medium like heart-brain broth and Schaedler broth

The reading of the agar plates must be careful to look for the different aspects of

colonies. It must be done at D1, D2 and D5 (and D10 for the anaerobic agar) with a regular reading of the liquid media until D14.

Once the bacterium has been identified, we carry out the antibiogram which aims to confirm the identification of the bacterium, to give an idea of the epidemiological spread of the bacterium, and to determine the antibiotics to which the bacterium is sensitive.

III. RESULTS

During the period of our study, we identified 25 cases of joint fluid infection confirmed by direct examination and/or culture, in a series of 496 cases. This corresponds to a frequency of 5%.

The distribution of these cases is variable by year, with a peak in frequency in 2019 (Figure 1).

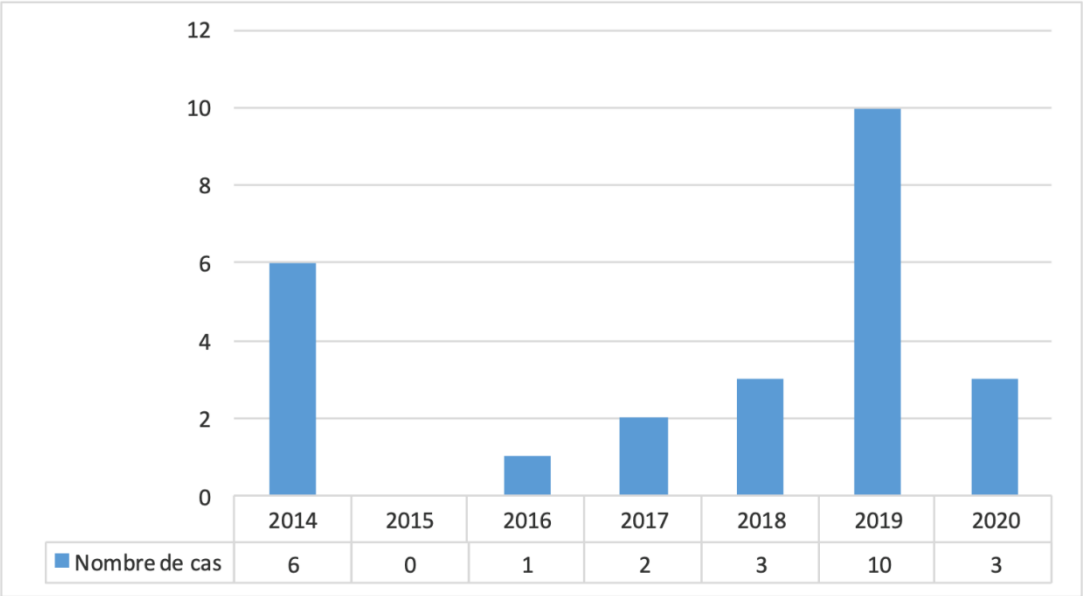

Figure 1: Distribution of cases by year of recruitment

We noticed a large male predominance with 21 men for 4 women. The sex ratio M/F is 5.25.

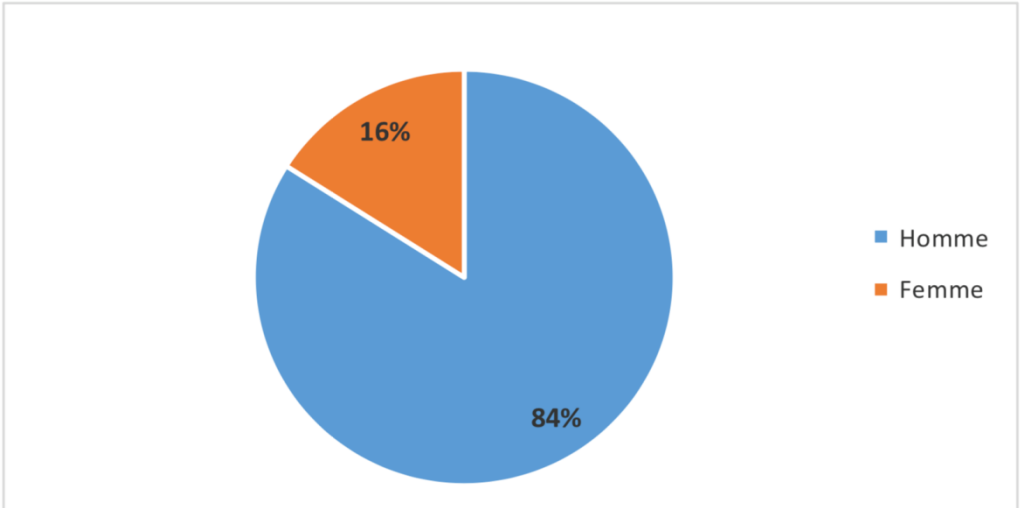

Figure 2: Distribution of cases by gender.

The rheumatology department has the highest number of cases of septic arthritis with 12 cases or 48%.

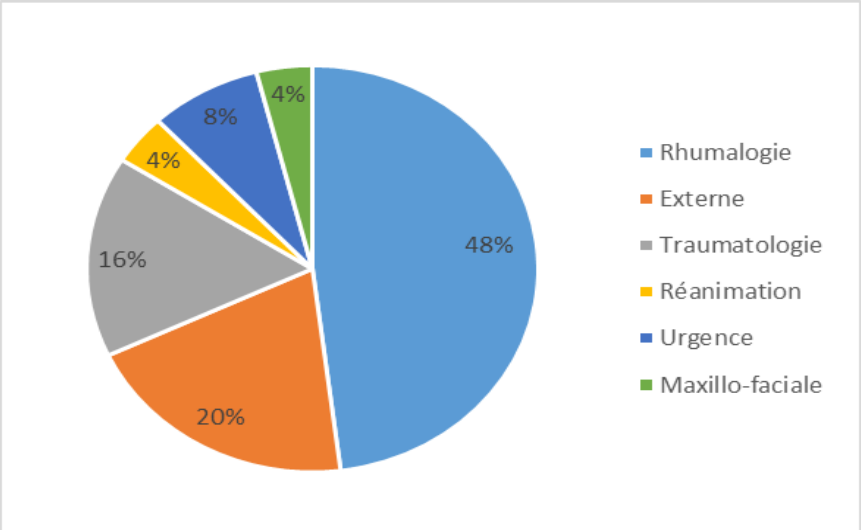

Figure 3: Distribution of cases by Departments.

Macroscopic and microscopic analysis and culture were performed on all samples to identify the causative organisms.

The macroscopic analysis of the joint fluids most frequently encountered in our sample was the purulent aspect (88% of cases). (table I)

Macroscopy	Citrin yellow	Purulent	Hematic	Clear
Number	0	22	2	1

Table I: Distribution of macroscopic aspects of positive joint fluids.

Microscopic analysis of the fresh examination showed joint fluid cytology The median was 10000/mm³ [7500-12500].

Hyperleukocytosis>10000/mm³ was found in 60% of cases (Table II).

Leukocytes (/mm3)	Number	Percentage
<1000	4	16%
[1000-2000[	2	8%
[2000-10000[	4	16%
[10000-20000[	3	12%
[20000-500000[	5	20%
[50000-100000[	4	16%
≥100000	3	12%

Table II: Leukocyte count in positive collections.

	Family	Species	number	Percentage(%)
CGP (N=16)	**Staphylocoques** N : 13	*S. Aureus*	9	45%
		S. coagulase négative	4	20%
	Streptocoques N : 3	*Streptocoque A*	2	10%
		Streptocoque G	1	5%
BGN (N=4)	**Enterobacteriaceae** N : 3	*Escherichia. Coli*	1	5%
		Klebsiellapneumoniae	2	10%
	BGN non fermentaire N : 1	*Acinetobacterhaemolyticus*	1	5%
Total			20	100%

Table III: Classification of isolated bacteria by families and species.

We found four patients with a WBC count <1000/mm³ :
- The 1st patient (case 5) had a leukocyte count of 700/mm³ predominantly PNN (70%),
- The 2nd patient (case 10) had a WBC count of 120/mm³ with lymphocyte predominance (80%).
- The 3rd patient (case 16) had a white blood cell count of 600/mm³, predominantly PNN (52%),
- The 4th patient (case 20) had a leukocyte count of 127/mm³ with lymphocyte predominance (79%).

In our study, the search for microcrystals was negative.

In the 25 samples retained, the number of positive cases on direct examination was 15, a frequency of 60%.

The direct examination after Gram staining shows the presence of gram positive cocci (GPC) in 44% of the samples taken, while gram negative bacilli (GNB) are present in 16% of the samples.

Concerning culture, the number of positive cases is 20 (80%), distributed over 7 different species. The distribution by families shows the predominance of Staphylococci (65%), followed by Enterobacteriaceae (15%), Streptococci (15%) and non-fermentative BGN (5%).

We realized an antibiogram for the germs isolated in our population (S.aureus, coagulase negative Staphylococcus, Streptococcus, Enterobacteriaceae) in order to appreciate the degree of resistance to the antibiotics usually tested for these bacteria.

Concerning the spectrum of resistance and sensitivity of Staphylococcus aureus, we have noticed no case of resistance to methicillin, 89% of the strains are sensitive to Gentamicin, 44% are sensitive to Kanamycin and just 33% are sensitive to Tobramycin. Concerning Erythromycin, 11% are resistant, and 67% of strains are sensitive to Clindamycin.

Almost the majority of strains are sensitive to glycopeptides with a percentage of 89% for Vancomycin and 78% for Teicoplanin.

And for the other families of antibiotics, 33% of the strains are sensitive to Fusidic Acid, 33% of the strains are sensitive to Rifampicin, and 67% of the strains are sensitive to Fosfomycin.

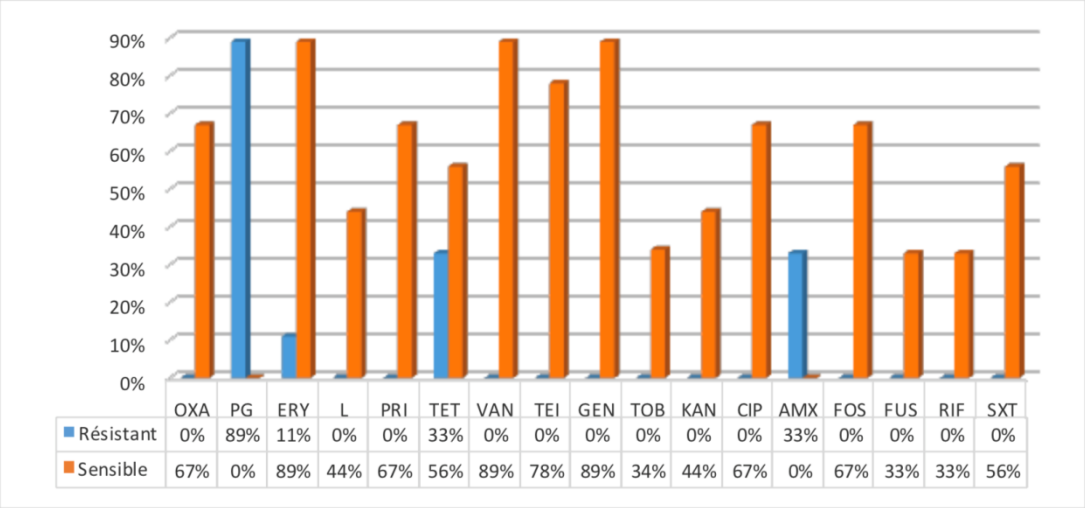

Figure 4: Antibiotic resistance profile of Staphylococcus aureus isolates

Concerning the resistance and sensibility of coagulase-negative staphylococcus, we have noticed that 33% of the strains are resistant to meticillin and that one third of the strains are resistant to penicillin G.

We found 67% of the strains are sensitive to Gentamicin and Kanamycin while 33% are resistant to both Gentamicin, Kanamycin and Tobramycin, all strains are sensitive to Vancomycin as well as Teicoplanin.

We found that 67% of the strains are sensitive to Erythromycin, while 33% are resistant. And for Clindamycin 33% of strains are resistant.

And for the other families of antibiotics, 67% of the strains are resistant to Fusidic acid, 33% of the strains are sensitive to Rifampicin, and 33% of the strains are resistant to Fosfomycin.

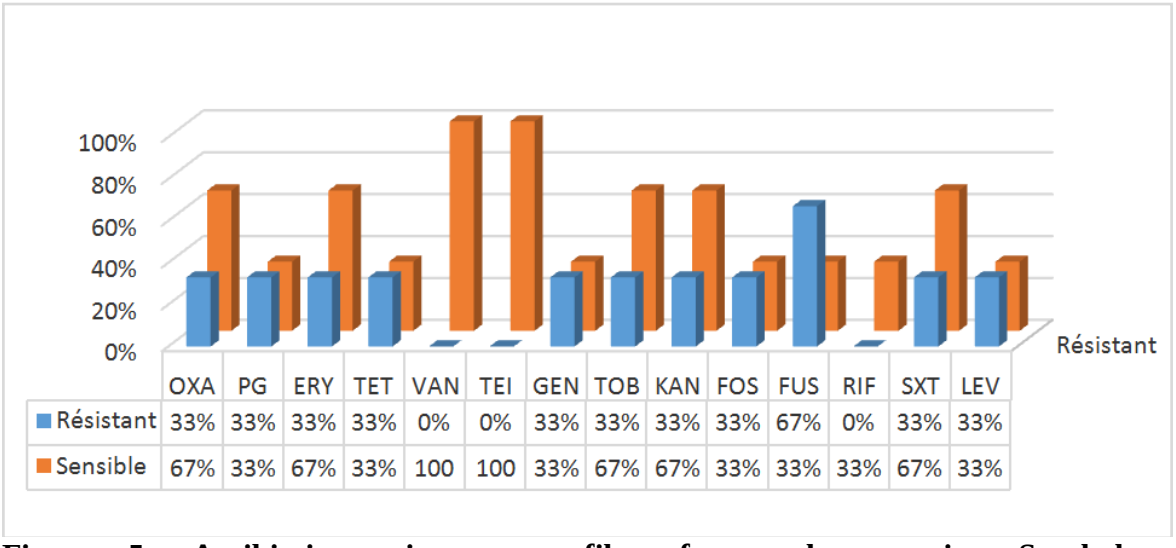

Figure 5: Antibiotic resistance profile of coagulase-negative Staphylococcus isolatescoagulase-negative Staphylococcus isolates.

For the streptococcus family, the sensibility and resistance spectrum analysis showed a sensibility of 50% to Peni G and Amoxicillin. The majority of the strains are sensitive to Clindamycin and Erythromycin. All strains are sensitive to fluoroquinolones and vancomycin.

And for the other families of antibiotics, all strains are sensitive to Trimethoprim + Sulfamethoxazole, and 50% are resistant to Amikacin.

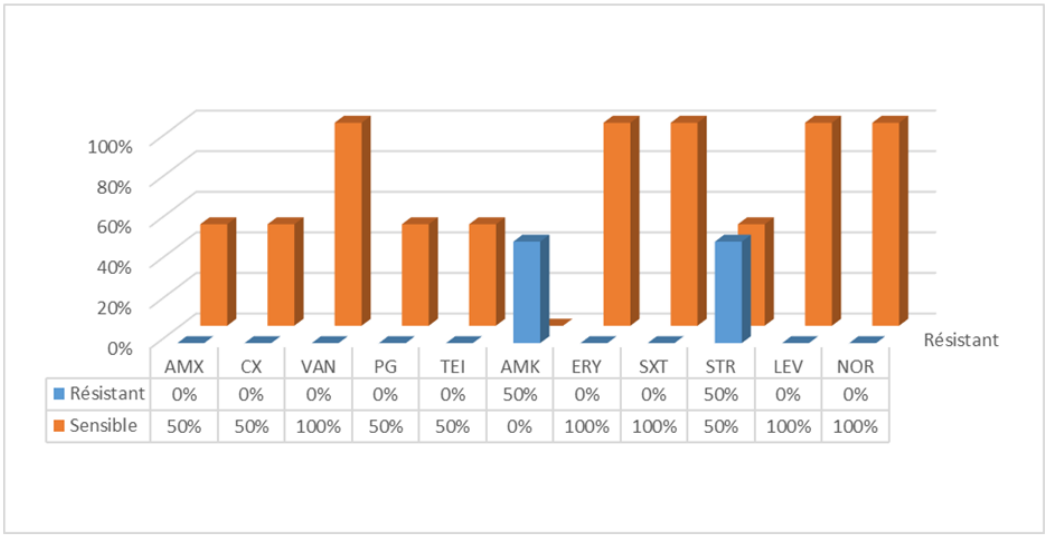

Figure 6: Antibiotic resistance profile of Streptococcus isolates

Concerning the Klebsiella pneumoniae strain, we have seen a total resistance to Amoxicillin, as well as 50% of the strains are resistant to Amoxicillin + Clavulanic acid, Cefixime, Cefotaxime, Cefepime, and Trimethoprim + Sulfamethoxazole, while most of the strains remain fully sensitive to Gentamicin, Amikacin, Imipenem, Norfloxacin and Ciprofloxacin.

Only one strain is producer of an extended spectrum betalactamase.

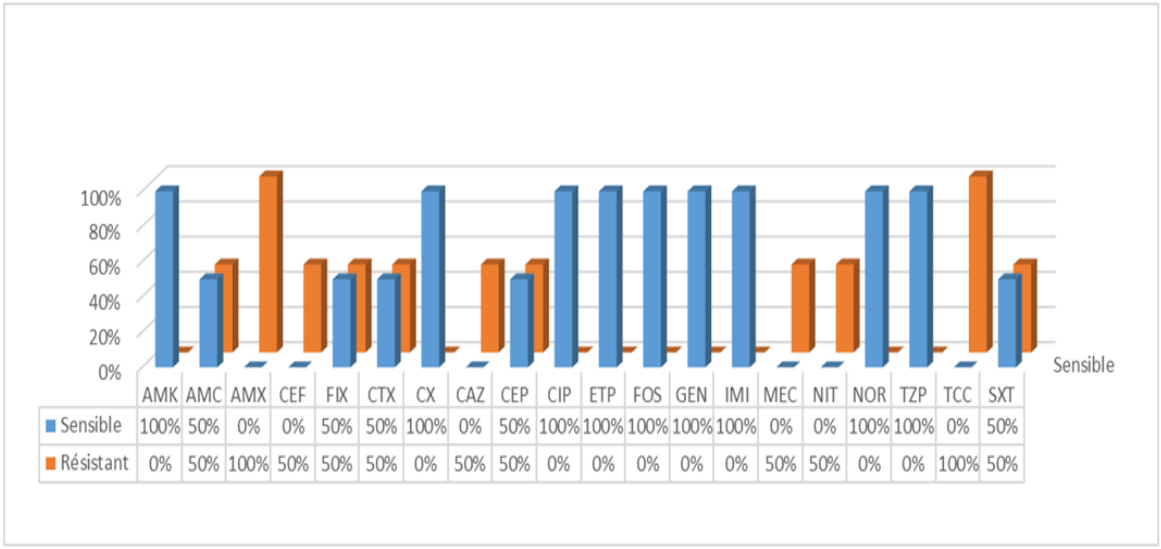

Figure 7: Antibiotic resistance profile of Klebsiella pneumoniae isolates

For the Escherichia coli strain, the antibiogram showed a multi-sensitive strain.

During the study period, out of a total of 20 isolated bacteria, only one multi-resistant bacterium was identified. The prevalence of

multi-resistant bacterial infections is therefore 5%.
- We did not find any methicillin (Oxacillin) resistant Staphylococcus aureus.
- The EBLSE strains isolated were represented by Klebsiella pneumoniae (case 10), thus representing 33.33% of the Enterobacteriaceae.

IV. DISCUSSION

Septic arthritis is a rare disease. The incidence varies between 2 to 10 per 100,000 population per year in the general population [10].
In our study, the prevalence of septic arthritis was 5% in relation to 496 joint fluid samples received between 2014 and 2020, which is consistent with a study conducted at the Avicenne military hospital in Marrakech Rheumatology department, the prevalence of septic arthritis was 5.11% in relation to 313 joint fluid samples received between 2012 and 2017[11]. A lower rate was found in the Rheumatology Department of EL Ayachi Hospital, according to a retrospective study that had included 45 cases of septic arthritis [12]. A higher rate was found at the Military Hospital Mohammed V of Rabat (HMIM V), the prevalence of septic arthritis was about 8.3% in relation to 168 joint fluid samples received in the period between 2007 and 2009[13].

Series	Year	City	Prevalence de l'AS
EL Hassani S et al [12]	2001	Rabat	0,7%
N. Bennis et al [13]	2013	Rabat	8,3%
S.Falahi [11]	2018	Marrakesh	5,11%
Our study	2022	Marrakesh	5%

Table IV: Comparison of the prevalence of septic arthritis

Internationally, the incidence is variable. In Western Europe, the incidence is approximately 4 to 10 new cases per 100,000 inhabitants per year [14].
In England, it is estimated at 4 cases per 100,000 inhabitants per year [8],
In France, 15 cases of septic arthritis are hospitalized each year according to a study conducted at the Gabriel Montpied Hospital in Clermont Ferrand [1],
In the Netherlands (Amsterdam), the incidence of septic arthritis in adults is estimated at 5.7 cases per 100,000 inhabitants/year [15].
In Australia, it is estimated at 10 cases per 100,000 inhabitants/year [3].
In our study, we noted a large male predominance, which is consistent with studies done in Marrakech, Rabat and Congo [11,13,16].
The origin of the patients according to the services during our study was essentially the services of rheumatology, traumatology and resuscitation, which is consistent with the results of the study conducted at the Military Hospital Mohammed V of Rabat (HMIM V).
The results of our study show a purulent aspect in 88% of cases, which is in line with the results of the study conducted at the HMIM V, the rheumatology department at the HMA and according to a study conducted in Tunisia where the purulent aspect was predominant [13,11,17].
Cytological examination of the joint fluid provides an etiological orientation. Normal synovial fluid is poor in cells, the number of leukocytes does not usually exceed 200 elements/mm³. It consists mainly of neutrophils, lymphocytes and cells of the synovial lining[18].
According to a national study conducted at HMIM V, microscopic study showed that 85.5% of positive specimens, displayed a

leukocyte count > 20000 elements/mm3 against only 7.1% having a leukocyte count < 1000 elements/mm3[13].

A study conducted in Mali, microscopic analysis showed that 42.85% of positive samples, displayed a leukocyte count > 50000 elements/mm3 and 14.29% were < 10000 elements/mm3[19].

And according to another study conducted at HMA Rheumatology department during the period 2012-2017, The microscopic study showed that 25% of the positive specimens, displayed a leukocyte count > 100000 elements/mm3 against only 37% having a leukocyte count < 25000 elements/mm3[11].

In our study, four cases had the number of leukocytes less than 1000 elements/mm3, (case 5: 700 elements/mm3, case 10: 120 elements/mm3, case 16: 600 elements/mm3, case 20: 127 elements/mm3), this can be explained by the coagulation of leukocytes due to the non-compliance with the collection conditions: the forgetfulness of collecting the joint fluid in heparinized or citrated tubes and a standard sterile bottle.

Thus, synovial white blood cells alone are not sufficient to exclude or confirm AS. Similarly, synovial polynuclear cells, even >90%, did not significantly increase the probability of AS in native joints. And the leukocyte formula can give etiological orientations. When the fluid is predominantly neutrophilic, it is most often of bacterial origin, and when it is lymphocytic one should think of a mycobacterium in priority[20].

In our study, out of 496 samples received, the number of cases positive on direct examination was 15, i.e. a frequency of 3.03%.

According to a Moroccan study conducted at the HMIM V, out of 168 samples received, the number of direct examination positive cases was 31, i.e. a frequency of 18.45% [13].

A study conducted at the HMA during the period 2012-2017, out of the 313 samples received, the number of direct examination positive cases is 12 or a frequency of 3.83%[11].

Synovial fluid culture remains important for identification of the pathogen and for determining its resistance profile.

It is observed that synovial fluid culture has a better sensitivity than direct examination (non-gonococcal arthritis: 66-95% positive cultures; gonococcal arthritis: 25-50% positive cultures) and therefore remains the test of choice[13].

In our study, Staphylococcus aureus is the most identified germ, with a frequency of 45%.

And according to a study conducted at HMIM V, Staphylococcus aureus represented 64.28% of the species identified[13]. This predominance was also observed in a study conducted at the G.-Montpied hospital on the distribution of germs responsible for septic arthritis in naïve joints over a period of 30 years, and during all three decades Staphylococcus aureus was the leading germ in terms of frequency: 62.20% in the first decade, 53.67% in the second decade and 54.95% in the third decade. The predominance is also consistent in several data in the literature [21-22], and it is the most frequently responsible for septic arthritis, representing 2/3 of the germs identified [1].

Several studies have found an increase in the frequency of MRSA septic arthritis[23, 24, 25].

According to Dubost's study, the frequency has not changed over the last 30 years (1979-2008), MRSA accounts for 13% of Staphylococcus aureus septic arthritis[26].

And in another study carried out in Switzerland on native adult septic arthritis over a 10-year period (1999-2008), 9.6% of Staphylococcus aureus isolates are resistant to methicillin. The proportion of MRSA in all clinical S. aureus isolates increased from 4% in 1999 to 12% in 2008 [27].

The HMIM V study shows that 11% of S. aureus were resistant to methicillin[13].

In our study, we did not identify any methicillin-resistant Staphylococcus aureus.

Series	Year	Country	Prevalence des MRSA
Olivier Clerc et al [27]	2011	Swiss	9,6%
N. Bennis et al [13]	2013	Morocco	11%
Jean-Jacques Dubost et al [26]	2014	France	13%
Notre étude	2022	Morocco	0%

Table V: Comparison of MRSA prevalence.

Concerning glycopeptides, the majority of Staphylococcus aureus isolates were sensitive to Teicoplanin and Vancomycin. This sensitivity is comparable with a study done at HMIM V which showed a sensitivity of 100% of isolates to Teicoplanin and Vancomycin[13].

In our study, 3 species of coagulase-negative Staphylococcus were implicated in septic arthritis: Staphylococcus caprae, Staphylococcus sp, and Staphylococcus haemolyticus.

Nationally, a study conducted at HMA over a 5-year period (2012-2017) showed that 2 out of 16 cases of septic arthritis were caused by coagulase-negative Staphylococci specifically: Staphylococcus epidermidis and Staphylococcus caprae[11].

Coagulase-negative Staphylococci are a heterogeneous group and their behavior towards antibiotics varies between species. They are generally more resistant to antibiotics than Staphylococcus aureus, as confirmed by our results.

Some of them show natural resistance which is useful to identify them, which is why we note in our series a 33% resistance to Fosfomycin while Staphylococcus aureus appears totally sensitive to the same antibiotic.

Among our isolates, 33% of coagulase-negative Staphylococci were resistant to Oxacillin. According to a Moroccan study conducted at the HMIM V in Rabat, 70% of coagulase-negative Staphylococci were resistant to Oxacillin [13].

In Morocco, a tuberculosis endemic country, Rifampicin is rarely prescribed for the treatment of osteoarticular infections, although resistance to it is low. According to a Moroccan study conducted at HMIM V, 33% of coagulase-negative Staphylococci were resistant, whereas in our study there was no resistance.

Several strains of Streptococcus are involved in the appearance of septic arthritis, with an increase in Streptococcus B, G and non-groupable [15, 28, 29]. They are considered to be bacteria of cutaneous origin, and are often, according to the literature, dominant in perioperative infections [30].

In our study, the species found were group A and G streptococci.

According to Dubost, Gram-negative bacilli are involved in 7-14% of septic arthritis [26], a frequency comparable to other series [31, 32, 33]. Their frequency increases discreetly and non-significantly over time. This could be the consequence of an increasingly older population with more comorbidities.

The table below shows the different BGN species found according to the series.

Studies	*E. coli*	*H.influenzae*	*Klebsiella*	*Acinetobacter*	others
Ryan MJ et al [35]	61	69	8	3	79
Kaandorp CJE et al [15]	9	8	1	0	12
Our study	1	0	2	0	0

Table VI: Comparing the different BGN species found in septic arthritis.

Among our isolates, extended-spectrum beta-lactamase (ESBL)-producing strains isolated were represented by Klebsiella pneumoniae (case 10), accounting for 33.33% of enterobacteria.

In two Moroccan studies, no ESBL-producing strains were isolated[13,11].

According to a study done in Switzerland, over a period of 10 years (1999-2008), no ESBL-producing strains were identified[27].

Based on a study conducted at Taiwan Regional Hospital over a 3-year period (January 2008 and December 2011), we isolated two ESBL Enterobacteriaceae: Escherichia coli and klebsiella pneumoniae [34].

V. CONCLUSION

Septic arthritis is a serious infection, and any delay in diagnosis or treatment may lead to locoregional or even systemic septic complications and mortality.

Therefore, the sample must be taken as soon as possible, under strict aseptic conditions, at best in a surgical setting, in a sterile bottle containing an anticoagulant, and without any prior antibiotic therapy.

The microbiological examination of the joint fluid is based on: a macroscopic analysis, followed by a microscopic analysis: which allows to see the cytology of the joint fluid, to detect microcrystals, in order to classify the arthropathy as mechanical or inflammatory and to carry out the direct examination, and finally to start the culture and to carry out the antibiogram when the latter is positive.

A purulent macroscopic appearance and a cellularity >10,000 elements/mm^3 immediately points to the diagnosis of septic arthritis. Direct examination is very useful when it is positive; it allows the clinician to be oriented in an emergency situation, but it is not very sensitive compared to culture, which remains the reference examination.

Staphylococcus aureus is the most common infectious organism and is responsible for the vast majority of septic arthritis. There has been little change in the susceptibility of the causative organisms of septic arthritis, and in particular there has been no increase in MRSA.

Given the complexity of the causative organisms and the problem of resistance, the safest approach is for clinicians and microbiologists to work closely together to ensure the best possible management of the patient.

Vigilance by clinicians and microbiologists is required to report the emergence of new epidemiological phenomena, as well as to ensure compliance with prevention guidelines and the judicious use of antibiotics in both hospital and community settings.

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