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Antimicrobial resistance patterns in paediatric infections at Damascus Hospital, Syria: a retrospective cohort study

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Background: Antimicrobial resistance is the third top-ranking global causative of death. Ninety per cent of babies with sepsis who were admitted to the ICU in the Middle East had antibiotic-resistant bacteria. We aim to describe the epidemiology, culture findings, bacterial antibiotic resistance, as well as the outcomes of children who present with nosocomial or community-acquired infections.
Methods: A retrospective observational cohort study was conducted to analyze children with positive culture results presenting with nosocomial or community-acquired infections in Damascus Hospital, Damascus, Syria, which is considered one of the biggest hospitals in Syria.
Results: In all, 116 patients with 177 positive culture results were included in the study. However, 54 (47%) were males, and 62 (53%) were females. Ages ranged between 3 h and 13 years. Cases of positive culture results peaked at the age or period of 0–11 months, that is 59(50%). The most prevalent bacteria were *Staphylococcus aureus* (33%), *Enterobacter* (21%), *Pseudomonas aeruginosa* (15%) and *Escherichia coli* (12%). The most used antibiotics were ceftriaxone (70%), vancomycin (60%) and amikacin (25%). The highest bacterial antibiotic resistance occurred with third-generation cephalosporins, and the most antibiotic-resistant bacterium was *P. aeruginosa*. Nosocomial infections occurred in 51% of the patients. Death was the outcome of 16% of the patients.
Conclusion: The situation regarding bacterial resistance to antibiotics is critical, with the most notable examples of these resisted antibiotics being ceftriaxone, cefepime, cefotaxime, trimethoprim, gentamycin, levofloxacin and piperacillin with tazobactam, and there is no doubt that this is a major contributing factor to the high prevalence of nosocomial infections and death rates found in this study.

Keywords: antibiotic resistance, bacterial resistance, paediatrics, Syria

Introduction

The third top-ranking worldwide cause of death is due to antibiotic resistance. Antibiotic resistance is highly related to both high mortality rates and high medical costs in the healthcare system. New statistics show there were 4.95 million deaths in 2019, approximately due to bacterial antibiotic resistance. Projections revealed that death will soar to an estimated 10 million deaths by 2050 as a result of antibiotic resistance[1]. Also, 90% of babies with sepsis who were admitted to the ICU in the Middle East had antibiotic-resistant bacteria[2].

In Syria, self-diagnosing and self-medicating is a common ritual among Syrians, and seeking advice from local pharmacists is customary to avoid doctor visit expenses with a prevalence of 57%[3,4]. Over-the-counter sales of antibiotics have been reported in various countries of the Middle East; the prevalence of antibiotic self-medication ranged between 19 and 82%[5]. A

HIGHLIGHTS

- 116 patients with 177 positive culture results were included in the study.
- The most common Gram-positive bacteria was *Staphylococcus*, which was also the most common bacteria in the sample, while the most common Gram-negative bacteria was *Enterobacter*.
- The most common infection focus in the sample was urinary tract 38%, bloodstream 26%, respiratory tract 23%, cutaneous 7% and meninges 6%.
- The most antibiotic-resistant bacterium was *Pseudomonas aeruginosa*.
- The highest bacterial antibiotic resistance occurred with third-generation cephalosporins.
- The number of deaths was 37 (16%), nosocomial infection 19 (51%) and community infections 18 (49%).

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study carried out on pharmacists in the capital Damascus, found that 87% of pharmacists sold antibiotics without a prescription, 10% sold with a prescription and 3% refused to sell antibiotics without a prescription[6]; despite the law issued by the Ministry of Health in 1988 that specified that antibiotics were not among the drugs that could be sold without a prescription[7]. This has resulted in the emergence of antimicrobial resistance in both nosocomial and community infections in Syria. The current conflict in Syria has introduced epidemics of infections that have spread through vulnerable populations, including immigrants, in Syria and neighbouring countries[8]. Beyond such devastation, this local problem evolved into a global issue as several studies conducted in Europe on Syrian immigrants have revealed many multidrug-resistant pathogens bacteria. The presence of multidrug-resistant pathogens Gram-negative microbes was found in 60% of the immigrants who underwent microbiological tests[9,10].

Former studies across the world have evaluated nosocomial or community-acquired infections, but none have done so in Syria to the best of our knowledge.

Study aims

The purpose of this study is to describe the epidemiology, culture findings, bacterial antibiotic resistance, as well as the outcomes of children who present with nosocomial or community-acquired infections and have positive culture results in one of the largest hospitals in the country. Analyzing antimicrobial resistance is crucial to determining how effective our management strategies are, and providing better care for the children, especially during the ongoing conflict in Syria.

Materials and methods

Setting

This study was conducted at the Paediatric Division in Damascus Hospital (Al Mujtahid Hospital), Damascus, Syria, between 31 July 2020 and 31 July 2021. This hospital is considered one of the largest hospitals in Syria. The hospital provides medical, therapeutic and surgical services to patients. It is used to train students and graduate doctors from Syrian universities and contributes to scientific research.

Study design and procedure

This study is a retrospective descriptive cohort study. In all, 116 patients with 177 positive culture results were included in the study. The inclusion criteria for evaluation were medical records of children admitted to the paediatric division 13 years of age or less with positive culture results. Cases with positive culture results attending the paediatric accident and emergency department (70 cases), samples from any laboratory other than the hospital's, samples less than 100 000 bacteria, samples suspected of contamination and samples with more than one type of bacteria were excluded.

Data extracted from medical records in the paediatrics archive included gender, age, diagnosis, outcome (recovery or death), culture result, type of infection acquired (community or nosocomial) and types of antibiotics administered before and after culture results. Culture reports included information on the type of sample (urine, blood, sputum, cerebral spinal fluid, cutaneous swabs, lower respiratory tract secretions, respiratory tract swabs, ascites fluid, pleural fluid, pus, swabs from central and venous catheters, swabs from urinary catheter, swabs from intubation tubes and swabs from ICU ventilators), bacteria cultured and bacteria's sensitivity and resistance towards antibiotics. When culture reports were missing from medical records in the paediatric archive, the culture report was found among the archives of the bacteriology laboratory.

Identification of isolated species

The microbial identifications were based on microscopic observations of the microbe's physical features, including its size, shape and the sorts of dyes it absorbed (Gram staining).

Determination of antibiotic susceptibility

Bauer–Kirby method using Mueller–Hinton agar plates was used to determine antibiotic susceptibility. Results are compared with the annually updated interpretive criteria by the Clinical and Laboratory Standards Institute.

Data analysis

Data frequencies, percentages and means were calculated via Microsoft Excel for Windows.

Ethical approval

Ethical approval was obtained from Damascus Hospital Institutional Review Board (IRB) for accessing patients' data.

STROCSS guidelines and study registration

The study is consistent with the STROCSS (Strengthening The Reporting Of Cohort Studies in Surgery) guidelines, and it is available on Research Registry with a unique registration number: researchregistry8428 (https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6356b316a1d5490021a5e426/).

Results

Age and gender of the patients

Of 116 patients, 54 (47%) were males, and 62 (53%) were females. The ages ranged from 3 h to 13 years. Cases of positive culture results peaked at the age or period of 0–11 months, that is 59 (50%), while children aged 13 years (1%) represented a minority.

Isolated species

The bacteria that appeared in the samples were: *Staphylococcus aureus* (33%), *Enterobacter* (21%), *Pseudomonas aeruginosa* (15%), *Escherichia coli* (12%), *Proteus* (10%), *Acinetobacter* (3%), *Klebsiella* (2%), *Streptococcus* (1%), *Gram-positive bacilli* (1%), *Serratia* (1%) and *coliform* (1%). The percentage of nosocomial infections was 41%. Gram-positive bacteria accounted for 36% of the bacteria in the sample, while Gram-negative bacteria constituted 64% of the sample. Among the community-acquired infections, the percentage of Gram-positive bacteria was 40%, while the percentage of Gram-negative was 60%. Among the nosocomial infections, the percentage of Gram-positive bacteria was 29%, while the percentage of

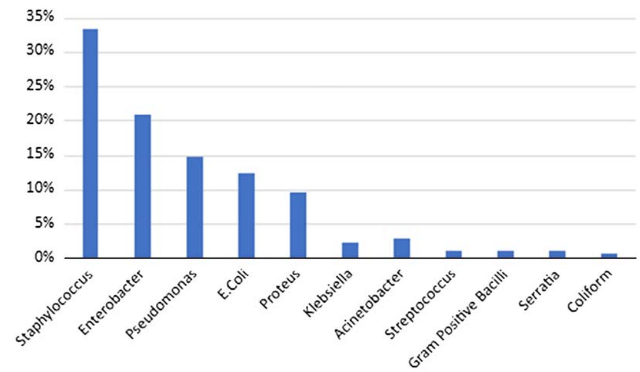

Figure 1. Prevalence of isolated species in the collected sample.

Gram-negative bacteria was 71%. *S. aureus* was the most prevalent bacteria in both nosocomial and community-acquired infections (Figs. 1, 2).

Distribution of isolated species among age groups

S. aureus was the most prevalent bacteria among all age groups. The distribution of bacteria differed across each age group: Neonatal stage (<4 weeks): *S. aureus* (38%), *Enterobacter* (25%), *E. coli* (13%), *Proteus* (13%) and *Serratia* (13%). Infant stage (1 month–1 year): *S. aureus* (24%), *Enterobacter* (21%), *P. aeruginosa* (17%), *Proteus* (14%) and *E. coli* (11%). Early childhood stage (1–6 years): *S. aureus* (42%), *Enterobacter* (19%), *P. aeruginosa* (17%) and *E. coli* (11%). Late childhood stage (6–13 years): *S. aureus* (37%), *Enterobacter* (22%), *E. coli* (15%) and *P. aeruginosa* (11%) (Fig. 3).

Distribution of isolated species in various infection foci

The most common foci of infections were the urinary tract (38%), blood (26%), respiratory tract (23%), cutaneous (7%) and meninges (6%). The most common nosocomial infections were respiratory tract (37%), blood (30%), urinary tract (25%), meninges (5%) and cutaneous (3%). The most common community-acquired infections were the urinary tract (47%) and blood (24%), followed by the respiratory tract (14%), cutaneous (11%) and meninges (5%).

The most cultured bacteria found to cause urinary tract infections (UTIs) were *Enterobacter* (27%), *E. coli* (23%) and *S. aureus* (20%). The most cultured bacteria in respiratory infections were *P. aeruginosa* (37%), *S. aureus* (22%), *Enterobacter* (15%) and *Klebsiella* (2%). Regarding cerebrospinal fluid (CSF), *S. aureus* was the most common causative (67%), followed by *streptococci* (22%) and *Gram-positive bacilli* (11%). Regarding skin infections, *S. aureus* was the most common causative (61%), followed by *E. coli* (15%), *P. aeruginosa* (8%), *Enterobacter* (8%) and *Proteus* (8%). Regarding sepsis, the most common microorganisms were *S. aureus* (48%), followed by *Enterobacter* (24%) and *Acinetobacter* (11%).

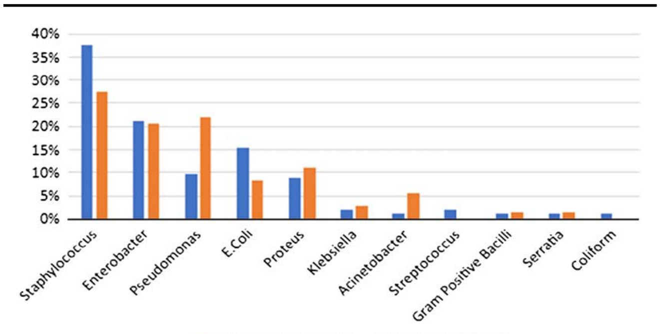

Figure 2. Distribution of isolated species in the community and nosocomial infections.

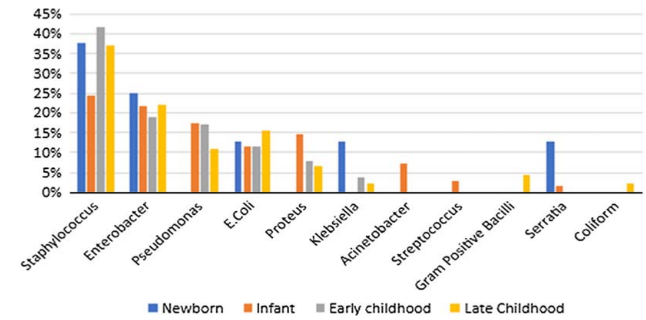

Figure 3. Distribution of isolated species among age groups.

Antibiotics usage and susceptibility

The following three antibiotics were used as pretreatments: ceftriaxone 70% and was appropriate in 34% of the cases; vancomycin 60% and was appropriate in 56% of the cases; amikacin 25% and was appropriate in 53% of the cases.

The most antibiotic-resistant bacterium was *P. aeruginosa,* while the least antibiotic-resistant bacterium was *S. aureus*. The highest resistance occurred with third-generation cephalosporins (Table 1).

Mortality rates and causative species

The mortality was 37 (16%), 19 (51%) were due to nosocomial infection and 18 (49%) were due to community-acquired infections. The age group associated with the most deaths was the infant (43%), followed by early childhood (27%), late childhood (22%) and newborn (8%). Respiratory tract infections were the leading cause of death (59%), followed by UTIs (22%), blood (11%) and cutaneous (5%); no deaths were associated with meninges. Mortality by pathogen: *P. aeruginosa* (27%), *Enterobacter* (26%), *E. coli* (16%), *S. aureus* (11%), *Serratia* (5%), *Proteus* (5%), *Klebsiella* (5%) and *Gram-positive bacilli* (5%).

Discussion

This is the first study that describes the outcomes of children with positive culture results presenting with nosocomial or community-acquired infections in Syria to the best of our knowledge.

The percentage of nosocomial infections in our study was 41%, which is very high compared with a Chinese study, 2.56% in 2019, and decreased to 1.39% in 2020[11]. A similar study in Iran reported the incidence of nosocomial infections as 3%[12].

S. aureus was the most common isolated bacteria in both nosocomial and community-acquired infections. *E. coli* was the

Table 1

Antibiotic resistance pattern of the most prevalent isolated pathogens in the collected sample.

	Staphylococcus aureus, number of resistant/number of tested (%)	*Escherichia coli*, number of resistant/number of tested (%)	*Enterobacter*, number of resistant/number of tested (%)	*Proteus*, number of resistant/number of tested (%)	*Pseudomonas aeruginosa*, number of resistant/number of tested (%)
Amikacin	15/49 (31)	5/16 (31)	14/30 (47)	6/10 (60)	16/24 (67)
Augmentin	7/23 (30)	6/10 (60)	10/12 (83)	9/11 (82)	14/14 (100)
Cefuroxime	12/16 (75)	3/4 (75)	10/10 (100)	3/3 (100)	15/15 (100)
Ceftazidime	17/21 (81)	7/8 (88)	7/8 (88)	4/4 (100)	11/12 (92)
Ceftriaxone	32/52 (62)	17/18 (94)	28/28 (100)	13/14 (93)	24/24 (100)
Cefaclor	11/24 (46)	7/7 (100)	10/11 (91)	5/5 (100)	13/13 (100)
Cefepime	23/37 (62)	12/16 (75)	20/24 (83)	8/8 (100)	20/23 (87)
Cefixime	16/20 (80)	10/10 (100)	17/19 (89)	11/11 (100)	5/6 (83)
Cefotaxime	32/48 (67)	15/16 (94)	22/24 (92)	10/11 (91)	18/18 (100)
Trimethoprim	32/43 (74)	18/18 (100)	29/33 (88)	11/12 (92)	16/17 (94)
Cefpodoxime	26/27 (96)	7/7 (100)	14/14 (100)	9/9 (100)	0/0
Ciprofloxacin	13/25 (52)	13/15 (87)	10/17 (59)	5/6 (83)	7/9 (78)
Colistin	20/33 (61)	1/11 (9)	4/20 (20)	7/7 (100)	5/19 (26)
Nitrofurantoin	2/11 (18)	3/11 (27)	9/18 (50)	8/9 (89)	6/6 (100)
Gentamycin	19/29 (66)	11/12 (92)	16/25 (64)	13/15 (87)	10/14 (71)
Imipenem	7/33 (21)	3/8 (38)	9/24 (38)	4/7 (57)	12/18 (67)
Levofloxacin	21/42 (50)	11/18 (61)	11/28 (39)	5/14 (36)	12/15 (80)
Piperacillin/ tazobactam	10/22 (45)	4/8 (50)	10/15 (67)	7/12 (58)	18/20 (90)
Nalidixic acid	9/9 (100)	9/12 (75)	15/16 (94)	8/9 (89)	4/4 (100)
Norfloxacin	2/2 (100)	1/1 (100)	3/4 (75)	0/0	1/1 (100)
Pefloxacin	8/10 (80)	4/4 (100)	2/5 (40)	2/3 (67)	7/8 (88)
Clarithromycin	3/5 (60)	0	6/6 (100)	3/3 (100)	9/9 (100)
Vancomycin	15/46 (33)	0	0/0	0/0	0/0

most common in a Chinese study[13]. *S. aureus* was the most cultured bacteria (67%) from CSF. This is likely to be high due to the presence of only nine CSF-positive bacterial cultures. *S. aureus* was also the most common causative of meningitis in a study conducted in China. The number of few positive CSF bacterial cultures reflects the effect of pretreatments with antibiotics before the CSF sample collection[14]. *S. aureus* was the most causative of cutaneous infections. This is attributed to the role these bacteria play in the skin's microbiota. Also, they were found to be the most prevalent source of blood infections. This was also the case in the previously mentioned Chinese study.

There is an extremely high bacterial resistance to most antibiotics, especially: ceftriaxone, cefepime, cefotaxime, trimethoprim, gentamycin, levofloxacin, and piperacillin with tazobactam. This indicates a huge problem that hospitals must face across Syria. Our results are higher in comparison with a study conducted in China[12]. The least antibiotic-resistant bacteria were *S. aureus*. Vancomycin has been the mainstay of treatment for susceptible infections such as methicillin-resistant *S. aureus*[15].

P. aeruginosa was the most resistant to antibiotics among the bacteria. Eradication of *P. aeruginosa* has become increasingly difficult due to its remarkable capacity to resist antibiotics. Strains of *P. aeruginosa* are known to utilize their high levels of intrinsic and acquired resistance mechanisms to counter most antibiotics. In addition, adaptive antibiotic resistance of *P. aeruginosa* is a recently characterized mechanism, which includes biofilm-mediated resistance and formation of multidrug-tolerant persister cells and is responsible for recalcitrance and relapse of infections[16]. The least antibiotic-resistant bacteria were *S. aureus*.

Enterobacter was the most isolated bacteria found in UTIs. In community-acquired infections, UTIs are the most common because of the close correlation between the incidence of UTIs and the poor hygiene currently observed due to poor living conditions in Syria. This low level of personal hygiene affects females more than males because of the anatomical differences between them that make females more vulnerable to UTIs. Females who were exposed to community-acquired UTIs constituted 69% of all children with UTIs. Also, the high rate of community-acquired UTIs and their recurrence can be explained by the widespread treatment of UTIs outside hospitals without doing bacterial cultures, the lack of patient follow-ups post-recovery, and the lack of investigation of urogenital abnormalities when examining the ill child in Syria. In our study, *Enterobacter* was fully resistant to cefuroxime, cefpodoxime, clarithromycin and ceftriaxone, as ceftriaxone is considered an alternative antibiotic for septicaemia, pneumonia and UTI caused by *Enterobacter* in children. *Enterobacter's* resistance rate to cefepime was 83%, while to piperacillin and tazobactam was 67%; these antibiotics are considered the antibiotics of choice for septicaemia, pneumonia and UTI caused by *Enterobacter* in children[15].

E. coli resistance to all cephalosporins ranged between 75% and 100% despite being the antibiotic of choice for both nosocomial and community-acquired UTI, septicaemia and pneumonia caused by this bacterium in children, while its resistance to ceftriaxone, which is the antibiotic of choice for meningitis caused by *E. coli* in children, was 94%[15].

P. Aeruginosa was fully resistant to many antibiotics too. Its resistance rate to cefepime was 87%, on piperacillin and tazobactam 90% and to ceftazidime 92%, which are the antibiotics of choice for the treatment of UTIs, nosocomial septicaemia and pneumonia caused by this bacterium in children[15].

Proteus resistance rate to cefotaxime was 91%, cefepime 100% and ciprofloxacin 83%. All previously mentioned antibiotics are considered the antibiotics of choice for UTIs, septicaemia and meningitis caused by this bacterium in children[15].

Sadly, the number of deaths was 37(16%): nosocomial infections 19(51%) and community-acquired infections 18(49%). Our results are excruciatingly higher compared with nosocomial infections in China (0.02%).

Clinical implications must be taken into consideration to come up with acceptable solutions for this significant challenge. The high prevalence of *S. aureus* pathogens, which may indicate insufficient hospital sanitation procedures, was one significant issue. We therefore strongly advise that the hospital's sanitation and disinfection procedures, as well as personnel adherence to them, be reviewed. Furthermore, it seems impracticable to administer an antibiotic pretreatment before receiving the results of the culture due to the extremely high resistance rates. In addition to the significant financial investment needed to complete this ineffective activity, administering inappropriate antibiotics is a leading contributor to staggeringly high rates of microbial antibiotic resistance. Moreover, educational programs targeting doctors, pharmacists and the community will aid the rational use of antimicrobials; similar programs have been implemented in various countries.

Limitations

We acknowledge that there are some limitations to this study, mainly with the retrospective aspect of data collection. Struggles with data collection included: disorganized medical paper records, missing culture reports, subjective aspects and illegible handwriting. Regarding the identification of isolated bacteria, only primitive methods have been used, such as direct microscopic observation. This is because the hospital cannot afford more advanced methods due to the bad economic situation in Syria.

Conclusion

The situation regarding bacterial resistance towards antibiotics is dire, as most of the isolated species showed extreme resistance towards most antibiotics and most notably: ceftriaxone, cefepime, cefotaxime, trimethoprim, gentamycin, levofloxacin and piperacillin with tazobactam. The high resistance rates make an antibiotic pretreatment before learning the findings of the culture seem impractical. Additionally, using inappropriate antibiotics might not only be ineffective in treating infection, but also have undesirable side effects, in addition to the high funding required to achieve this counterproductive task. Through sensible usage, the effectiveness of the remaining antibiotics, to which the bacteria are susceptible, must be preserved. The judicious use of antibiotics should be aided by educational initiatives aimed at community members, medical professionals and pharmacists, as such initiatives have been put in place in several other nations and proved effective in lowering microbial antibiotic resistance.

There is an extremely high bacterial resistance to the antibiotics of choice and there is no doubt that this is one of the main reasons for the high rate of deaths in the study; therefore, the efficacy of the remaining antibiotics to which the bacteria are sensitive must be maintained through rationalization of its use. Strict precautionary measures must be implemented to ban the illegal dispensation of antibiotics.

Ethical approval

Ethical approval was obtained from Damascus Hospital Institutional Review Board (IRB). Please note that the ethical approval of this study was granted without an ethical committee reference number.

Patient consent

This study is an observational, descriptive and retrospective study; accessing all the medical records used was approved by the Damascus Hospital Institutional Review Board, and no written consents were required.

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Author contribution

F.K.: conceptualized and designed the study, wrote the study protocol, performed the statistical analysis, participated in data collection, did a literature search and drafted the manuscript; A.H., A.T. and F.M.: participated in the study design; A.H. and A.A.: participated in data collection; M.A.: did a literature search and revision of the draft. All authors read and approved the final draft.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry.
2. Unique identifying number or registration ID: researchregistry8428.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6356b316a1d5490021a5e426/

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Data availability

All data related to this paper's conclusion are available and stored by the authors. All data are available from the corresponding author at a reasonable request.

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