Research Article

Mortalities Among Young Rabbits: Impact of Maternal Behavior and Bacterial Causes

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Abstract | Mortalities of rabbits are common during the first two months of life and considered the main reason of losses. However, research on the causes and rates of mortality according to nursing programs is limited. This study aimed to highlight the bacterial and behavioral causes of mortalities among young rabbits and control such problems. A survey on 167 specimens collected from diseased and freshly dead young rabbits in some Egyptian provinces was conducted. In addition, an experiment was carried out on 15 pregnant does divided into 3 groups: (A) opened, (B) semi closed and (C) closed nursing systems. Mean body weight, and mortalities were recorded. Moreover, 18 weaned rabbits (40 day old) were challenged intraperitoneally with *Staphylococcus aureus* (*S. aureus*) (1.5×10^8 CFU) then were divided into 3 equal groups according to their treatment strategy: (1) control group, (2) treated with antibiotics and (3) treated with antibiotic/probiotic combination. Bacteriological examination of the 167 specimens detected *S. aureus* (46.7%), *Escherichia coli* (16.7%) and *Enterobacter* (3.5%). Furthermore, mortality rates were 15.3%, 6.4%, and 25%, in groups A, B and C, respectively. The semi-closed group (B) had significantly the highest body weight throughout the observation period. In the challenge group, the mortality rate was 100% (6/6) in group (1), followed by group (2) with 66.6% (4/6), and 33.3% (2/6) in group (3). *S. aureus* was the predominant and lethal bacteria in young rabbits. In addition, the semi closed nursing system improved the health of newborn rabbits. finally, probiotic/antibiotic combination is the best choice against *S. aureus* infection. The guide lines in rearing systems , mainly semi-closed nursing system , would decrease the susceptibility to bacterial infections

Keywords | Antibiotic; Mortalities; Nursing; Probiotic; Rabbit; *S. aureus*.

Received | December 12, 2022; **Accepted** | January 20, 2023; **Published** | March 15, 2023
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Citation | Hamed DM, EL Dimerdash MZ, Ali AA, Abd El-Gaffar SA, Abdallah MS (2023). Mortalities among young rabbits: impact of maternal behavior and bacterial causes. Adv. Anim. Vet. Sci. 11(4): 578-585.
DOI | http://dx.doi.org/10.17582/journal.aavs/2023/11.4.578.585
ISSN (Online) | 2307-8316

INTRODUCTION

Rabbits, with their high fecundity, large litter size and fast growth rate, provide protein for many countries and solve the problem of protein deficiency in many regions (El-Ashram et al., 2020). Unfortunately, the high mortality rate of young rabbits can harm the domestic industry. Several factors might be involved in the survival rate of young rabbits such as biosecurity measures, maternal behavior, litter size, and neonatal birth weight (Szendrő et al., 2016, Van Praag, 2017). Indeed, the nursing system significantly affect the survival rates of young rabbits in such a way that change in nursing system from free to controlled or vice versa will have a considerable impact on

survival, welfare productivity, and health status of young rabbits (Matics et al., 2020).

On the other hand, bacterial infections can negatively affect the health status and lead to high mortality mainly in young rabbits (Zahraei Salehi et al., 2010). *Staphylococcus aureus* (*S. aureus*) is a dangerous pathogen with a high ability to reproduce in a wide range of conditions and environments, can cause a variety of diseases in both animals and humans (Penadés et al., 2020). In rabbits, *S. aureus* may remain in the sinuses or lungs and may be transmitted by direct contact or aerosol. Septicemia may be caused by skin infection and lead to anorexia, depression, fever, and death (Vancraeynest et al., 2004).

Proper antibiotic use in rabbits needs to be regulated to prevent emergence of antibiotic-resistant strains (Chai et al., 2021). Knowledge of bacterial antimicrobial spectrum helps target treatment during suspected disease outbreaks (Verma et al., 2015).

Probiotics is an alternative to antibiotic use which provide several advantages such as reduced mortalities, increase feed conversion and improve adverse clinical symptoms in experimentally infected rabbits (Abdelhady and El-Abasy, 2015). Moreover, probiotic supplementation decreasing the severity of infection and pathogen localization as well as increase the immune response, which may help in enhancing of rabbit's growth and disease tolerance (Mancini and Paci, 2021, Abd El-Hamid et al., 2022).

This work was carried out for isolation and identification of the probable bacterial agents causing mortalities in young rabbits in relation to the most appropriate nursing system. Also, to investigate the protective role of antibiotics and/or probiotics combination in challenged growing rabbits.

MATERIALS AND METHODS

Ethical Approval

The experimental design, sampling and handling of animals in this study have been reviewed and accepted by the Scientific Research and Bioethics Committee of the Faculty of Veterinary Medicine, Ismailia Suez University, Egypt, approval number (201887).

Clinical Examination And Sampling

One hundred and forty diseased and freshly dead young rabbits (95 pre- and 45 post-weaned kits) were collected from rabbit farms suffering from high mortalities in Ismailia, Sharkia, and North Sinai Provinces, Egypt and submitted for both clinical and post-mortem inspection. One hundred sixty- seven samples; nasal swabs (n= 35), blood (n=16), lung tissues (n= 45), liver tissues (n= 56), and urine samples (n= 15) were collected under complete aseptic conditions. Obtained specimens were processed and submitted for bacteriological examination within 24h.

Bacteriological Isolation And Identification

Swabs and a loopful from deep tissues of each specimen were taken aseptically and directly inoculated into buffer peptone water and/or nutrient broth (Oxoid, UK) then incubated aerobically at 37 °C for 18-24 h. A loop of the medium was subculture on blood, nutrient, and MacConkey agar (Oxoid, UK) followed by incubation at 37°C for 24-48 h. Pink colonies (lactose fermenting) on MacConkey agar were transformed on the selective media eosin methylene blue (EMB) agar (Oxoid, UK). On the other hand, pure colonies with characteristic growth on blood agar media were subculture into selective medium mannitol salt agar (Oxoid, UK) and incubated at 37°C for 24 h. The bacterial identification was based on colonial characters, Gram's staining through microscopical examination, motility test, and biochemical reactions (urease, utilization of citrate, methyl red reaction, Voges–Proskauer, catalase, indole, oxidase, sugar fermentation, and nitrate reduction test) as described by (Quinn et al., 2002).

Slide Coagulase Test (Bound Coagulase Test)

On a microscope slide, a ring of *Staphylococcus* culture was mixed in a drop of saline. Rabbit plasma was then added and mixed well. Gently shake the slide, clumping within a minute indicates a positive *S. aureus* reaction (Koneman et al., 1997).

Antimicrobial Sensitivity Testing

The challenged *S. aureus* isolate was tested for antibiotic sensitivity using automatic turbidimetric method for susceptibility (Automated ID&AST SystemMA120, Render Biotech Co., China) according to company's recommendation. Use these antimicrobials; moxifloxacin, tetracycline, rifampicin, penicillin, clarithromycin, vancomycin, gentamicin, Azithromycin, Doxycycline, Levofloxacin, erythromycin, chloramphenicol, ciprofloxacin, Cefotaxim, Oxacillin, Clindamycin and trimethoprim + sulfa.

Experimental Design

Two experiments were performed to study the effects of managemental and bacterial causes of mortalities among young rabbits.

Experiment 1 (Effect Of Different Nursing Programs On Mortalities)

Fifteen 7-month-old pregnant does were housed in individual cages with nest boxes under hygienic conditions until parturition and divided into 3 groups (n=5). The nursing regime in group (A) was open nursing program (nursing at any time during day or night), Whereas in group (B) was

a semi closed nursing program (twice a day, 12 h apart). Group (C) was a closed nursing regime (once a day at 7.00 AM). Weekly mortality rate and mean body weight were recorded during the nursing period (1 month after kindling)

Experiment 2 (Intraperitoneal Experimental Challenge Of Isolated *S. Aureus* In Weaned Rabbits Treated With Probiotics And/Or Antibiotics Combinetion)

Medication Used During Experiment 2

Alamycin (Oxytetracycline- Norbrook)
Colitrim (Sulphadiazine+ trimethoprim- Pharma swede)
Bio-mos (Probiotics-Alltech) contain selected strain of *Saccharomyces cerevisiae* yeast

Expermintal Design

Eighteen weaned rabbits (40 day old) were divided into three equal groups (n=6). The three groups were infected with an infectious dose of *S. aureus* (1.5×10^8 CFU) by the intraperitoneal route (Kareem et al., 2020). Groups were categorized as follows; Group (1): rabbits were kept as non-treated (control positive). Group (2): Intramuscular treatment with a combination of 0.5 ml/1kg bwt Alamycin and 0.5 ml/1kg bwt colitrim started on day 42 and took 3 doses on 3 consecutive days. Group (3): same as Group (2) but followed by Bio-mos 2gm/L of drinking water for 7 consecutive days. Clinical signs, post-mortem examination and mortality rate were recorded.

Histopathological Examination

Lung and liver samples from the three infected groups in the second experiment were taken and fixed with 10% buffered neutral formalin solution. Five µm sections of paraffin were prepared and stained with hematoxylin and eosin, then microscopically examined for histopathological changes (Jones, 2008).

RESULTS

Occurrence Of *S. Aureus* And Other Bacterial Pathogens In The Investigated Rabbits

Bacteriological examination of the 167 specimens detected that the prevalent microbial species were *S. aureus* 46.7% (78/167), *Escherichia coli* 16.7% (28/167) and *Enterobacter* 3.5% (6/167). The identification of isolated bacteria was based on its morphological and biochemical characteristics. Biochemically *S. aureus* isolates tested positive for coagulase, catalase, protease, methyl red, Voges-Proskauer and sugar fermentation. However, they were negative for indole, oxidase and H_2S production. The occurrence of *S. aureus* in different samples was 54.2% (19/35), 50% (8/16), 53.3% (24/45), 30.3% (17/56) and 66.6% (10/45) in examined nasal swabs, blood samples, lung tissue, liver tissue and urine samples respectively. Occurrence of *S. aureus* in different samples are shown in Table 1.

Antibacterial Susceptibility Charscteristics Of Isolated *S. Aureus*

In vitro antimicrobial susceptibility testing showed that *S. aureus* isolate was inducible ß-lactamases and was highly sensitive to most antibiotics used. *S. aureus* showed resistance to only one antibiotic, cefotaxime.

The Effect Of Different Nursing Programs On Mortalities

The current results showed that the percentage of mortality in the semi-closed care group (B) was lower than the other groups. The first-week mortality rates in groups (A), (B), and (C) were 15.3% (6/39), 6.4% (2/31), and 25% (4/16), respectively. The semi-closed care group (B) had the significantly highest body weight compared to the other groups throughout the observation period. Weekly body weights in three nursing programs are shown in Table 2.

Intraperitoneal Experimental Challenge Of Isolated *S. Aureus* In Weaned Rabbits Treated With Probiotics And/Or Antibiotics Combinetion

Clinical Examination And Postmortem Picture Of Weaned Rabbits Infected With *S. Aureus*

Clinical examination of rabbits infected with *S. aureus* intraperitoneally revealed clinical symptoms include off food, arched back, grunting teeth, dropping ears, sneezing and runny nose, wet matted fur, severe diarrhea, abdominal swelling. These clinical symptoms began on 2nd day post-infection, and it was severe in infected group (1) followed by antibiotic treated group (2) while probiotic and antibiotic treated group (3) was better and began to return normal in 4th day post-infection. The most important lesions observed in dead rabbit were hyperemia and purulent pneumonia with petechial hemorrhage in the lung. Severely congested and enlarged liver with white purulent lesions on the surface. The urinary bladder is engorged with urine and pus. The clinical signs and postmortem lesion are shown in Figure (1, 2).

Regarding mortality, the infected group (1) had a mortality rate of 100% (6/6), followed by the antibiotic treatment group (2) with 66.6% (4/6). The lowest mortality rate 33.3% (2/6) was observed in the antibiotic/ probiotic treatment group (group 3). The number of mortalities in different groups are shown in Table (3)

Table 1: Occurrence of *S. aureus* in different types of samples taken from diseased and freshly dead young rabbits

Sample-types	No. of sample	Positive	%
Nasal swabs	35	19	54.2
Blood samples	16	8	50
Lung tissues	45	24	53.3
Liver tissues	56	17	30.3
Urine samples	15	10	66.6

Table 2: Weekly body weight of young rabbits in the three nursing programs

Body weight	Group (A) Open nursing	Group (B) Semi-closed nursing	Group (C) Closed nursing	*p*-value
Birth weight	$44.03^{b}\pm1.18$	$49.38^{a}\pm1.33$	$45.33^{ab}\pm1.49$	0.032*
1st week	$86.68^{a}\pm2.24$	$97.32^{a}\pm11.49$	$95.00^{a}\pm10.02$	0.647
2nd week	$185.50^{b}\pm4.09$	$244.94^{a}\pm23.58$	$205.17^{ab}\pm16.17$	0.071
3rd week	$287.86^{b}\pm8.74$	$396.16^{a}\pm30.04$	$315.67^{ab}\pm39.73$	0.027*
4th week	$592.22^{b}\pm41.80$	$741.32^{a}\pm37.63$	$583.67^{b}\pm27.91$	0.027*
6th week	$1054.94^{b}\pm40.25$	$1305.72^{a}\pm49.50$	$1046.10^{b}\pm85.84$	0.009**
8th week	$1581.66^{b}\pm65.31$	$2107.48^{a}\pm63.58$	$1712.50^{b}\pm32.50$	<0.001**

* (a- b) Means with different superscripts in the same raw data are significant at ($p\leq0.01$).

Table 3: Number of mortalities in different challenged groups

Day	Group1 (Infected only)	Group2 (Infected and treated with antibiotics)	Group3 (Infected and treated with antibiotic +probiotic)
1st day	-	-	-
2nd day	2	2	1
3rd day	3	1	-
4th day	-	-	-
5th day	-	-	-
6th day	-	-	-
2nd week	1	-	1
3rd week	-	1	-
Total	6	4	2

Group (1): rabbits were kept as non-treated (control positive). Group (2): Intramuscular treatment with a combination of 0.5 ml/1kg bwt Alamycin and 0.5 ml/1kg bwt Colitrim for 3 consecutive days. Group (3): same as Group (2) but followed by Bio-mos 2gm/L of drinking water for 7 consecutive days. All groups infected with an infectious dose of *S. aureus* (1.5×10^{8} CFU) by the intraperitoneal route.

Histopathological Result

The lung tissue of the *S. aureus* infected group showed se vere peri bronchitis and congested blood vessels with focal peri bronchial leukocytic infiltrations. Vascular thrombi and vasculitis were also observed. Diffused interstitial inflammatory reaction and focal alveolar emphysema. Animals in group (2) exhibited mild to moderate lesions manifested by mild congestion of interalveolar capillaries and focal leukocyte infiltration with mild alveolar emphysema and mild focal necrotic lesions. Group (3) had mild inflammatory cell infiltrations and congestion with mild focal thickening of interalveolar septa (Figure 3). Liver tissue from *S. aureus*-infected rabbits showed severe hepatic vascular congestion with perivascular edema. Diffuse degeneration of hepatocytes and focal necrosis were also observed. Large abscess formation was also observed, and the abscess was formed of necrotic tissue, and pus cells and surrounded by a thick wall of granulation tissue. Group (2) had local degeneration, mild hyperemia of blood vessels and mild hyperplasia of bile ducts. Group (3) exhibited normal hepatic cord with localized to discrete hepatocytes and mild hyperemia (Figure 4).

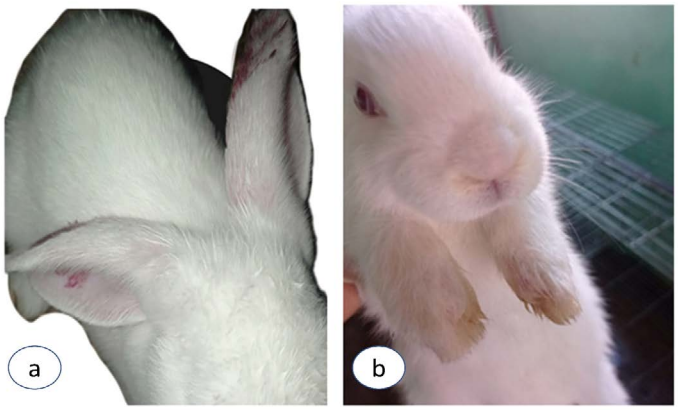

Figure 1: Clinical signs of *S. aureus* infected rabbit at 3rd day PI showing clinical signs of arched back (a) and wet matted fur (b).

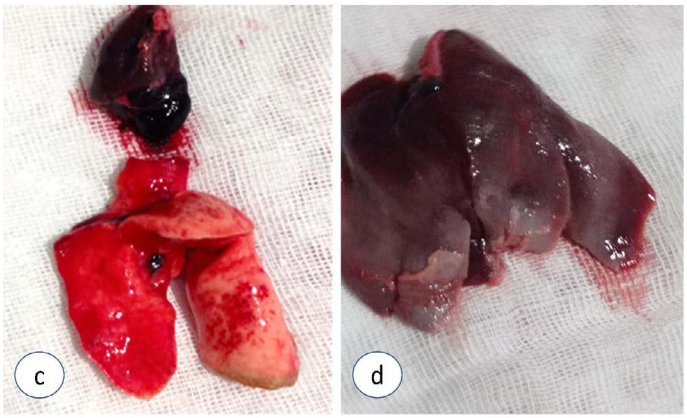

Figure 2: Postmortem lesion of *S. aureus* infected rabbit showing lung congestion with petechial hemorrhage (c) and liver was severely congested, enlarged with white purulent lesions on the surface (d).

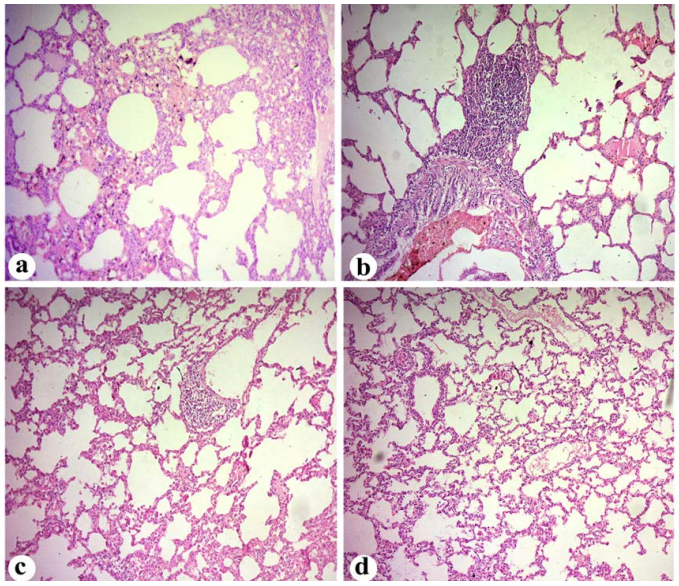

Figure 3: Lung of rabbit infected with *S. aureus*: (a & b) showing an interstitial inflammatory reaction, hemorrhages, and focal peribranchial leukocytic infiltrations. (c) lung treated with an antibiotic, showing mild focal peribranchial aggregations along with mild interstitial pneumonia. (d) lung treated with antibiotic+ probiotic. showing mild thickening of interstitial tissue and mild congestion. H&E. X 100.

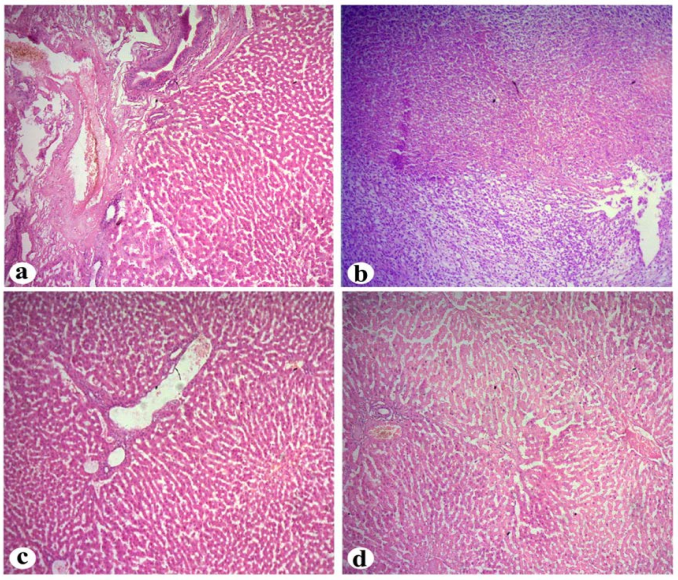

Figure 4: Liver of rabbit infected with *S. aureus*: (a & b) showing congestion, hyperplasia of bile ducts, perivascular edema, focal degeneration, and necrosis of hepatocytes, and in (b) large abscess formation. (c) liver treated with an antibiotic, showing mild hyperplasia of bile ducts and congestion of portal blood vessels. (d) liver treated with antibiotic+ probiotic. showing pronounced improvement of hepatic tissue. H&E. X 100.

DISCUSSION

Weaning is transitory and stressful for rabbits in which beneficial cecal microflora is not yet established (Ismail et al., 2017). Pre-weaning management of rabbits is critical due to the possibility of high mortality, however, research on the causes and mortality of rabbit farms during pre- and postweaning is limited (El-Ashram et al., 2020). Bacteriological tests proved that *S. aureus* was one of the most common pathogens in dead rabbits, similar to the results obtained by Abd El Gwad et al. (2004) who detected *S. aureus* in breeders, causing mastitis, uterine irritation, and abscess or dermatitis in growing rabbits, resulting in the death of young rabbits and newborns. As well as Roshdy et al. (2021) mention that *S. aureus* is one of the important pathogens causing the death of rabbits in different inspection farms. The widespread of *S. aureus* is due to its frequent presence in the environment, and nasal carriers play an important role as a source of infection for *S. aureus* transmission (Becker and Von Eiff, 2011).

Judging from the types of samples tested, the detection of *S. aureus* was 54.2% (19/35), 50% (8/16), 53.3% (24/45),

30.3% (17/56), 66.6% (10/15) in nasal swabs, blood samples, lung tissue, liver tissue, and urine samples examined, respectively. The results are partially similar to those of Attili et al. (2020) who reported higher colonization rate from nose/ear, the nose is considered important site of *S. aureus* colonization, as rabbits spend a lot of time cleaning themselves, eating, and they can use the nose to reach almost every part of the body.

Some laboratory tools are important for the detection of Staphylococci. The catalase test is one of the most important routine tests to differentiate *Staphylococcus* and Streptococcus. Coagulase assay divides staphylococci into two groups with different virulence and coagulase Positive one is considered the main pathogen (Otto, 2013). In general, most of the *S. aureus* isolates in this study were coagulase-positive. Similar results were previous obtained (Martins et al., 2013), reporting that all *S. aureus* strains isolated from chicken carcasses were coagulase positive.

Antimicrobial resistance of *S. aureus* isolates derived from rabbits is relatively rare because of the relatively low usage of certain toxic antimicrobials in rabbits (Pipová et al., 2012). *In vitro* antimicrobial susceptibility testing showed that the recovered *S. aureus* isolates were highly sensitive to nearly all the antibiotics used. The results of this study are consistent with those of Indrawattana et al. (2019) who mention that most *S. aureus* isolates were sensitive to gentamycin, amikacin, and doxycycline.

Rabbit does visit their babies every day only to suckle without providing any other maternal care (González-Mariscal et al., 2016). Therefore, the choice of the nursing mode of newborn rabbits plays significant role in reducing the mortality rate and improving the survival rate of newborn rabbits. Moreover, switching from free to regulated nursing affects the doe's behavioral habits (Matics et al., 2020). To our knowledge, there is scanty previous work examining mortality according to nursing programs. In this study, the mortality percentage in the semi-closed care group (B) was lower than the other groups. The first-week mortality rates in groups (A), (B), and (C) were 15.3% (6/39), 6.4% (2/31), and 25% (4/16), respectively. González-Mariscal et al. (2013) noted that a doe visits her kits at about the same time each day, which is unique among mammals. As well, Matics et al. (2020) showed that when changing from free nursing care to controlled one, doe behavioral patterns became nervous (scratching, head contact, and wire biting), which was frequently observed in the hours before the nest box was opened.

In terms of body weight in the three nursing programs, the semi-closed group (B) had the highest body weight compared with the other groups throughout the observation period. This result might be attributed to increased breastfeeding and /or litter size in kits in semi-closed systems, similarly El-Ashram et al. (2020), reported insufficient milk supply was more prominent in those with large litter sizes that resulted in greater competition for the nipples of does during feeding and increased milk consumption, which did not allow weak and small kits to consume adequately.

Clinical examination of rabbits infected with *S. aureus* intraperitoneally revealed clinical symptoms include off food, arched back, grunting teeth, dropping ears, sneezing and runny nose, wet matted fur, severe diarrhea, abdominal swelling as reported by Kareem et al. (2020). The clinical signs were more severe in infected group (1) followed by less severity in antibiotic treated group (2) while probiotic/antibiotic treated group (3) were least affected and began to return normal in 4th day post-infection. Meanwhile, *S. aureus* in this study showed sensitivity against different antibiotics. Therefore, the recommended antibiotic for rabbits' treatment is needed to be effective, cheap, available, and less used in human to prevent the further emergence of resistant strains. Tetracyclines are commonly used in the field of veterinary medicine, primarily for the treatment of respiratory and skin diseases as well as systemic infections (Prescot, 2000). Furthermore, Indrawattana et al. (2019) reported that most *S. aureus* isolates were sensitive to doxycycline. Trimethoprim/sulfa can be a treatment option for staphylococcal infections (Adra and Lawrence, 2004). The combination of antibiotics in this experiment was able to improve health status and reduce mortality of the rabbits. The most important lesions observed in dead rabbits were hyperemia and purulent pneumonia with petechial hemorrhage in the lung. Severely congested and enlarged liver with white purulent lesions on the surface. The urinary bladder is engorged with urine and pus our results agreed with Abd El Gwad et al. (2004). *S. aureus* infection is usually acutely purulent and spreads to deeper surrounding tissues or metastasizes to other sites involving other organs, which is life-threatening disease (Lowy, 1998). Moreover, the lung tissue of the *S. aureus* infected group showed congested blood vessels and severe peribronchitis with focal peribronchial leukocytic infiltrations. Vascular thrombi and vasculitis were also observed. Liver tissue showed severe congestion of hepatic vessels with perivascular edema. Diffuse degeneration of hepatocytes and focal necrosis was also observed the livers tissue revealed severe congestion of hepatic blood vessels along with perivascular edema. The results are consistent with previous report RZ et al. (2013). Large abscess formation was also observed in infected liver tissue, and the abscess was formed of necrotic tissue, pus cells and surrounded by a thick wall of granulation tissue. *Staphylococcus* is a common disease that can lead to fatal systemic sepsis or localized purulent inflammation

of various organs (Prabhu, 2010). Regarding mortality, the infected group (1) had a mortality rate of 100% (6/6), followed by the antibiotic treatment group (2) with 66.6% (4/6). The lowest mortality rate 33.3% (2/6) was observed in the antibiotic/ probiotic treatment group (3). These results matched with Raza et al., (2015) who found that *S. aureus* caused 100% mortality in experimentally challenged rabbits at 15d post challenged with same route of inoculation. The use of probiotics in this experiment was able to reduce mortality, since probiotics had a positive effect on clinical symptoms for *S. aureus* infection in weaned rabbits (intraperitoneal injection). At the same time, mortality rate was reduced, and adverse clinical symptoms of infected rabbits were improved (Abdelhady and El-Abasy, 2015). Probiotics are live commensal microorganisms as an alternative therapeutic option to fight pathogens at sites of adhesion, restore epithelial barrier function, improve nutrient utilization, enhance microbial balance, and enhance epithelial immune responses, thereby preventing infection and subsequent pathological damage (Al-Khalaifah et al., 2020, Raheem et al., 2021).

CONCUSION

This study revealed that the most prevalent bacterial species in samples from diseased and dead rabbits were *S. aureus*. Furthermore, the semi-closed nursing system achieved the lowest mortality rate and the best weight gain in young rabbits. Finally, when rabbits were challenged with *S. aureus,* the best treatment strategy is to administer antibiotic/probiotic combination rather than antibiotic alone. This study shed the light on the different infectious and management factors that contribute to early mortalities in young rabbits.

ACKNOWLEDGMENTS

We thank Prof. Dr/ Amina Dessouki Prof. of Pathology, Faculty of Veterinary Medicine, Suez Canal university for her effort in reading and comments of histopathological examination in this study and Makkah lab. for sensitivity test assay.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

NOVELTY STATEMEMENT

Open rearing system is proved to be a risk factor for disease transmission in rabbits.

AUTHORS' CONTRIBUTION

Completion and design of this study was carried out by DMH, MZE, AA and SA. SA was fully involved in data collection and experimental implementation. Data analysis, interpretation, and critical revision were carried out by DMH, MZE, AA, SA and MSA. Manuscript writing done by MSA and DMH gave conceptual ideas and reviewed. In general, all authors made every effort to present this manuscript properly.

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