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- 48 Antibiotic residues in milk and milk products: A momentous challenge for the pharmaceutical industry and medicine

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Antibiotic residues in milk and milk products: A momentous challenge for the pharmaceutical industry and medicine

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Abstract

Dairy products are nutritious food items that contain various essential nutrients, however, it has been proven that residual antibiotics have contaminated such products. These residues can cause several side effects on human health. They increase antimicrobial resistance against several threatening microorganisms, as well as significant growth in allergic reactions. Various methods, including heat treatments, have been applied to alleviate and reduce the effect of antibiotic residue level in milk and milk products. Changes in drug levels were not significantly remarkable, obliging researchers to find new approaches to prevent or reduce their risk and limit their complications on human health.

Key Words: Antibiotics residues; Milk products; Bacterial resistance; Antimicrobial drugs; Microorganisms; Health effects

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Core Tip: Little information is available regarding the use of antibiotics and their availability in dairy products as residues in Lebanon. Not a lot of care or caution is given to this sector, even though Lebanon's main income, especially in villages, is from cultivated mammals. This article mentions the availability of residual drugs in milk. It includes the different pathways of drugs upon consumption by the mammals, until excretion. As well as its side effect on human health, especially the cause of flora bacteria to become resistant to drugs.

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INTRODUCTION

Dairy products constitute a major category of human diet and are considered one of the more important sources of essential minerals needed for normal body function and growth[1]. The knowledge around the benefits of milk has been growing in the last decades paralleled with a considerable and continuous increase in consumption demand over the years[2]. This necessitates more diligent practices in the production, processing and distribution of milk and dairy products. Understanding the effect of antibiotic use or abuse in protection of milk producing cattle and how this affects the end consumer remains critical to scientists. The notion of antibiotic resistance is gaining more international merit among microbiologists and hence should be addressed when it comes to dairy products and other foods. Mammals can be highly susceptible to many diseases and infections and several microorganisms that are naturally found in nature, could easily become part of their diets, leading to several diseases[3]. Antibiotics are currently used for treating infected animals, similar to humans, by administering a prescribed dose, targeting certain known microorganisms[3]. Despite the crucial antimicrobial effect of fighting severe diseases, antibiotics still find their way from treated animal into the food products as residues[4]. These residues pose serious health alterations and problems for human health in addition to the aforementioned antibiotic resistance developed by microorganisms[4].

Institutional bodies are imposing stricter regulations by the day and even though many farmers follow a careful protocol in the use of antibiotics while following regulations, residual drugs cannot be totally prevented from passing down into consumers. Herein, we present a review on the significance and importance of testing for antibiotic residues and the challenges associated with the testing techniques. Heat treatment to reduce residual antibiotics concentrations in dairy can be a preliminary approach. Our review can provide important insight on potential effective practices to minimize the detrimental outcome of antibiotic abuse in Lebanon and other countries. Very little is known about such practices in developing and third world countries due to the lack of structured research and regulations. Heavy assessments and examinations should be carried out to ensure the safety of milk products distributed throughout these countries.

MILK AND ITS PRODUCTS

Milk is considered one of the most consumed nutritious food products in the market and along with dairy products remain essential for the human diet since they provide many minerals, vitamins, proteins and sugar, that are much needed for proper growth and development. This highly consumed product is extracted from mammals through their mammary glands, including cattle, goats and sheep [1]. Milk is mostly composed of water (87%), proteins (3%), lactose (4%-5%), fat (3%-4%), minerals (0.8%) and vitamins (0.1%)[5] along with lipids that are usually found in the form of fat globules and are considered carriers of fat-soluble vitamins, as well as flavor enhancers[5].

The demand for milk and milk products is widely discussed in political, agricultural, and economic meetings including the EU Agricultural Outlook conference. The consensus is that dairy demand will drastically increase by 2030, given the fact that milk is an affordable source of proteins and nutrients that is commonly linked to healthier life styles[2]. In one study targeting Middle Eastern and North African populations, associated higher milk consumption with increased population growth in which a 1.0% increase in population caused a 1.3% increase in consumption[6].

All dairy products share the first processing step of milk fermentation for 1-3 d at room temperature (15 °C-25 °C)[7]. These products could also be generally categorized into two groups; products considered new or those later discovered from practices in the industrial field of production and development known as "Modern Dairy Products", and products derived from ancient practices mostly used in small-scale societies and called "Traditional Dairy Products". Some of the modern products

include milk (total, skimmed, and semi-skimmed), butter, cream (fresh, double, and ice), and cheese (hard, semi-hard, soft, and fresh). Some traditional products, mainly carry Arabic names derived from different Arabic countries, including laban, labneh, ayran, kishk, and some different types of cheese such as akawieh, mish cheese, dominate cheese, and haloumi[7].

Like humans, animals are highly susceptible to many different diseases. They could get sick due to exposure to different microorganisms if protective measures are not in place. Despite Lebanon's small size, it is known that there is a fair proportion of the population that relies on milk and dairy products as a source of income[3]. Microbial infections and other diseases present major challenges to indigenous local farmers as well large industrial producers. Furthermore, mastitis is the most common fatal disease in dairy cattle which results from bacterial infection from the external environment, such as contaminations from non-sterile milking equipment, milking personnel, or dirty stalls[8].

Mastitis is one of many other reasons why antimicrobial use has gained attention in dairy farms[9]. Hence, antimicrobials are introduced to cows when the animal is sick to assure the wellbeing of both the cattle and humans down the food chain[10].

ANTIBIOTICS

Antibiotic treatment in animals is generally used either to help and protect the animals' welfare, or in some cases, used for the farmers' benefit to increase the animals' weight beyond the normal[11]. In the case of the animal's wellbeing, antibiotics are used in one of two fashions; either prophylactically, through the injection of medications or vaccines to prevent any possible illness, especially severe ones, or therapeutically to aid in infighting a certain illness or organism that is considered a health threat[11].

Antibiotics used for animals should be limited as much as possible for obvious reasons including serious accumulation in higher consumers. They are regulated within certain "safe" levels to prevent side effects, such as the development of antibiotic resistance in animals. For this reason, certain parties should be involved to ensure the maintenance of the efficiency and safety use of veterinary antibiotics [11].

Different medicines with antimicrobial activity are used depending on their target bacteria and mode of action. Some happen to have similar characteristics and act on the same pathogens. Others are used over a wide range, effective on more than one microorganism[12]. Penicillin is a commonly used drug for humans and several animals and is considered one of the first discovered and used drugs. It is a medication used against many types of microorganisms. Similar to penicillin, cephalosporins are a group of bactericidal molecules that also possess antibiotic properties[12]. Tetracycline is another common drug used for different purposes, mostly administered when penicillin cannot be used[12]. Aminoglycoside is a drug used therapeutically and prophylactically; it works against Gram-negative bacterial infections[7]. Streptomycin is a common type of aminoglycoside used in dairy cows[12]. Moreover, potentiated sulphonamides are a combination of both antibiotics, sulphonamides, and trimethoprim, used for the treatment of different bacterial infections[12].

Nonetheless, if not controlled, microorganisms can make their way to the human body through food, human-animal contact, or the environment. When bacteria are successfully targeted, antibiotics would then be discharged out of the animal's body. However, antibiotics are not completely released from the animal and a certain amount of these drugs remains concentrated in some tissues or products (such as milk) that will eventually be consumed by the human[11].

Antibiotic abuse

Antibiotic misuse, also called antibiotic abuse, is the inappropriate use of antibiotics in levels higher than required. In many areas, there is no proper inspection for the use of drugs, especially in third world countries. For instance, many local farms in Lebanon within different villages are left with no auditing or oversight. Unlike other countries, farmers mostly do not need a prescription and are most likely not supervised by a vet upon antibiotic administration, making it more likely to either use drugs in overdosage or for the inappropriate target. This lack of knowledge regarding antibiotics' use and their mechanisms could cause negative consequences for both, animals and humans[13].

Other than AMR, residues could cause disorders of the intestinal flora, severe allergic reactions, and hypersensitivity[4].

Antibiotics absorption, distribution, and excretion

Upon authorized use of antimicrobials within the respected doses, and its administration to the animal, a major part of this drug is detoxified and excreted. Since antibiotics could easily transfer from the mammary gland to the milk, it is thus the main cause for residues presence in milk and its products[14]. Antibiotics progress through the animal's body after their introduction and are absorbed and distributed into different parts of the body. They are then eliminated by being metabolized to perform their normal function or secreted out of the body.

Several studies have been aimed at understanding the metabolism and retention of antibiotics in both animals and consumers. One study assessed the distribution of antibiotics after the intramammary

infusion of different antibiotics, and physical properties were examined instead of the molecular configuration of the antibiotics[15]. It was concluded that absorption of drugs is highly dependent on the lipid-solubility of the introduced drug and on the dissociation constant (pK_a). The pK_a determines the concentration of the undissociated form of the drug in milk, as well as the rate of the drug passage from milk to the blood. The degree of lipid-solubility is determined by comparing the lipid-to-water partition coefficient ($K_{o/w}$). The higher the $K_{o/w}$, the faster the drug is absorbed. When comparing both factors, it seemed that the rate of fusion from milk to drug was dependent on the degree of lipid-solubility of each drug, thus pK_a became the main factor affecting absorption of drug from the udder[16]. In addition, it also appeared that some antibiotics could bind to proteins which will eventually affect the rate of absorption of the drugs[15].

Another study involved four lactating goats that were injected with radioactive-labeled antibiotics by intramammary infusions. After milk samples were collected, antibiotic concentrations were evaluated and collected from several dairy products; skim milk, whey, cream and casein were compared to whole milk, using either microbiological or radiochemical assay methods[15]. In the case of cream, concentrations were shown to be inversely proportional to the concentration of the drug in the product[17]. The percentage of drugs distributed in the different milk components differs depending on the type of antimicrobial used[16]. Whereas, when comparing residues within the same product, high concentrations showed lower residues with a percentage close to that of water in cream, while low concentrations of certain drugs displayed a higher level in the product[17]. The concentration of drugs in casein was highly dependent on the percentage of antibiotics consumed. In the case of skim milk, concentrations depended on the interaction of drugs with the proteins. Other studies showed that the concentration of drugs in casein is usually higher than in whey since proteins in casein are largely higher than in whey, thus antibiotics would concentrate with the proteins[17].

Yet, other studies showed that after intramammary injection of penicillin into one of the quarters of the cow, the antibiotic was detected in the other 3 quarters[18]. It could be concluded that the drug is capable of interstitial migration from one area to another. Moreover, a study was performed to analyze the absorption, distribution, and excretion of two drugs; penicillin G and dihydrostreptomycin, a type of aminoglycoside[18]. Six cows free of clinical mastitis were treated each by injecting 100000 units of penicillin G and 100 mg of dihydrostreptomycin into three quarters (1, 2, and 4). This treatment was repeated twice for each cow after a 2-wk rest. Results showed that in the case of two quarters treatments, penicillin G was found in untreated quarters after 8 h' rest[18]. There was also a diffusion of the drug into untreated quarters in the case of dihydrostreptomycin. Five cows out of six were found to have drug residues in untreated quarters[8,18]. Blood, milk, and urine samples were collected from each cow and results revealed the presence of both drugs in the three different samples; the highest level was detected in the blood, followed by the milk, and urine. This indicates that drug crossover from treated to untreated quarters is not only directly through the blood; there could be another pathway or mechanic for this distribution[8,18].

In the case of antibiotic excretion, the percentage of drugs released from the cow during milking clearly decreases as the time of administration is longer. Antibiotics are excreted partly which would still hold complications during manufacturing and later for human health after consumption. Depending on the type of antibiotics, 70%-80% of the drug is found in the first milking after administration[19]. That explains why first milking should be discarded when cattle are treated with antibiotics.

Bacterial resistance

The misuse and overuse of antimicrobial agents is the main reason for the increase in antimicrobial resistance (AMR). The concept has evolved quickly and is a big concern worldwide since it could impact health in general and for decades[20]. Bacteria have remarkable genetic flexibility that allows them to respond to any environmental threats. Constant exposure of the drug to certain microorganisms could lead to reduced effectiveness due to changes developed by the organism itself. A bacterium can acquire resistance by either modifying its DNA during cell replication referred to as mutation, or by inserting the organism's gene into its own, becoming part of the bacteria's genetic material thus becoming resistant to the drug. Therefore, upon introduction of the drug again, only non-resistant organisms are affected while resistant bacteria remain unaffected and preferentially proliferate. Each organism acquires resistance differently, depending on its type. For instance, the resistance mechanisms of β -lactams differ depending on the type of bacteria. For Gram-negative, it is modified in a way to produce β -lactamases, while in Gram-positive bacteria, it is achieved by resistance by modifying its target site; the penicillin-binding proteins[20].

To provide a complete classification of antibiotic resistance, they can be categorized depending on their biochemical pathway related to the drug[20]. Modifying the antibiotic molecule can be done by either producing enzymes that inactivate the drug, or by destroying the molecule itself, thus preventing the drug from interacting with its target. For example, aminoglycoside modifying enzymes can modify the hydroxyl or amino group of the aminoglycoside drug, reducing or eliminating the drug's activity. Another mechanism is preventing the reach of the antibiotic to its target, achieved by reducing the penetration of the antimicrobial compound[20]. The third mechanism includes the modification of the binding sites.

Drug identification

Milk should be tested, before collection and delivery to the truck, to ensure its safe use. It is imperative to test for antimicrobial residues before processing, to ensure its compliance to accepted doses[21]. If antibiotics tested exceed the maximum residue limit (MRL), then milk collected should be disposed, and not used for consumption or product manufacturing[14]. There are several techniques available for residual drug identification, yet liquid chromatography has demonstrated to be the most generally effective, definite and of maximum sensitivity. Milk samples are usually found to be rich in more than one type of antibiotic, thus tests are usually done to identify the type of each drug, and its concentration [21]. One group of researchers analyzed a set of milk samples to identify the presence of several antibiotics using the liquid chromatography technique. The antibiotics investigated were cloxacillin, dihydrostreptomycin, tetracycline, oxytetracycline, chlortetracycline, chloramphenicol, neomycin, novobiocin, bacitracin, erythromycin, oleandomycin, ampicillin, streptomycin, and oxacillin[21]. Different analytical grade reagents were used to extract each antibiotic present, such as hydrochloric acid, citric acid, ammonium chloride, and others. The solvents used were as follows: (1) Chloroform-acetone-impregnation liquid (5:5:2); (2) ethanol-water-ammonia (8:1:1); (3) methanol-chloroform (9:1); (4) methanol-acetone (3:2); and (5) methanol-ammonium chloride (3%). The three adsorbents used to coat the thin layer plates were kieselguhr F254, silica gel 60, and cellulose. The organisms used for testing were *Bacillus ceurus*, *Bacillus subtilis* (*B. subtili*), *Micrococcus flavus* and *Sarcina lutea*. The approach involved 6 different plates of either a control or the mentioned microorganisms being targeted by each drug[21]. Table 1 represents the scheme followed to implement the chromatography technique.

Furthermore, Table 2 shows the R_f values of the antibiotics on different plates. This is indicative that the minimum concentrations of such antibiotic are still detected by liquid chromatography and can be identified using this method. Penicillin was not tested since its presence could be determined by using the *B. calidolactis* test. It was eliminated or removed from the samples by adding an enzyme; penicillinase, which would cause its degradation. Other techniques that could be used for the identification of antibiotic residues in the milk include paper chromatography, high-tension electrophoresis, gas chromatography, mass spectrometer and thin-layer chromatography. Some of these techniques were shown to be of little and inefficient use because of their need for highly concentrated solutions with antibiotics or only being efficient for certain drugs[21].

Yet another technique that could be used is known as the Screening Test for Antibiotic Resides (STAR) protocol. STAR protocol is a five-plate test (FPT), which involves agar diffusion for the identification of antibiotics in food. It is a qualitative screening test used to detect bacterial growth inhibitors. Five agar plates are used to detect antibiotics using sensitive known bacterial strains. The formation of inhibition zones would prove the presence of the antibacterial substance[22].

Near-infrared absorption (NIR) spectroscopy is also used for residue identification. Using a detector, this technique can analyze and record different wavelengths of each substance present in the solution. The intensity of each wavelength computed is equivalent to the concentration of the substance or drug. A study was conducted using the NIR technique for different types of antibiotics, it was proven to be fast and accurate, thus proving the method's great potential[23].

As a result, the chromatographic technique could be considered as the most efficient one in detecting the highest number of antibiotic residues because of its higher sensitivity and specificity and higher quantification capability (Sachi *et al*[14]).

Heat treatment

During processing, the milk is exposed to different thermal, chemical, or mechanical shocks. This includes boiling at high temperatures, the addition of acidic substances, and reduction in water activity, cooling or freezing, drying, or evaporation. These changes could alter the product's characteristics[24].

A study was performed to assess the effect of high temperature and pH on tetracycline and azithromycin concentrations. *B. subtilis* was used to test the presence of these drugs in 13 milk samples. The results showed that high concentrations of residues were present in the samples; high enough to inhibit the growth of *B. subtili* and to kill the microflora culture during milk fermentation. The effect of heat treatments on the degradation or reduction of residues varied amongst different temperature treatments and pH[25].

In the case of azithromycin, a significant decrease of the azithromycin constant κ was observed at 70 °C after 3 h incubation, followed by a higher reduction during 24 h incubation (Table 3). Similarly, a high decrease of constant κ was also observed at 100 °C after incubation[25]. On the other hand, a significant increase in the tetracycline constant κ was observed during incubations. Tetracycline constant κ showed a fast decline at 70 °C and 100 °C after 24 h incubation (Table 4). Results showed that the stability of both drugs, tetracycline, and azithromycin, is highly dependent on temperature[25]. Using *B. subtili* culture, no inhibition areas were observed, proving that azithromycin lost its antimicrobial activity after treatments of 70 °C and 100 °C for 24 h. In the case of tetracycline, the Inhibition zone was reduced but not inhibited upon the increase of temperature[25].

Table 1 Chromatographic scheme

Thin-layer plate	Adsorbent	Amount of sample applied in μL	Solvent	Test organism
1	Kieselguhr	30	A	<i>B. cereus</i>
2	Silica gel	30	B	<i>M. flavus</i>
3	Silica gel	30	C	<i>S. lutea</i>
4	Silica gel	30	C	<i>B. subtilis</i>
5	Silica gel	30	D	<i>M. flavus</i>
6	Cellulose	10	E	<i>B. cereus</i>

B. cereus: *Bacillus cereus*; *M. flavus*: *Micrococcus flavus*; *S. lutea*: *Sarcina lutea*; *B. subtilis*: *Bacillus subtilis*.

Table 2 R_f values of antibiotics on the different plates

Antibiotic	Plate					
	1	2	3	4	5	6
Cloxacillin	-	-	0.70	0.70	-	0
Dihydrostreptomycin	-	-	-	-	-	0.40
Tetracycline	0.35	0	0	0	0	-
Oxytetracycline	0.20	0	0	0	0	-
Chlortetracycline	0.60	0	0	0	0	-
Chloramphenicol	0	0.70	0.65	0.65	0.80	-
Neomycin	-	-	-	-	-	0
Novobiocin	-	0.80	0.80	0.80	0.80	-
Bacitracin	-	0.45	-	-	-	-
Erythromycin	0.20	0.70	0.35	0.35	0.25	-
Oleandomycin	0.20	0.70	0.35	-	0.25	-
Ampicillin	0.35	-	0.50	-	-	-
Streptomycin	-	-	-	-	-	0.50
Oxacillin	0	-	0.60	0.60	-	-

CONCLUSION

Milk contains many important nutrients that are required daily. Milk components take part in the body's metabolism by providing essential amino acids, vitamins, minerals, and fatty acids. The presence of drug residues in dairy products is harmful and not acceptable to many individuals or food industries. The use of antibiotics should be controlled and handled under the control of specialists. Antibiotics are absorbed by animal tissues and later distributed into different fluids and tissues. A high concentration is later excreted after a few hours, but a significant amount would still be found concentrated in different parts, including milk and meat. Heating treatments do not cause significant residual reduction among all drugs. High temperatures are effective against azithromycin, where it causes a drastic reduction, while it is less effective against tetracycline. There are no techniques effective on all drugs and that significantly decrease antibiotic residue level. Antibiotic usage in animals cannot be completely banned since their absence could be harmful to both the animal and human health. More research should be conducted to identify new programs that could possibly reduce and control their usage or their concentration in milk and milk products.

Table 3 Azithromycin degradation constant rate k values at different temperatures[10]

Time in h	4 °C	37 °C	70 °C	100 °C
1	1000 ± 8 ^e	50 ± 1 ^a	50 ± 2 ^a	200 ± 3 ^a
3	333 ± 3 ^d	966 ± 9 ^d	4033 ± 22 ^e	3900 ± 18 ^e
6	250 ± 2 ^c	933 ± 8 ^d	2000 ± 15 ^d	2033 ± 16 ^d
12	116 ± 2 ^b	516 ± 7 ^c	1025 ± 8 ^c	1000 ± 6 ^c
24	62 ± 2 ^a	270 ± 4 ^b	537 ± 5 ^b	533 ± 4 ^b

^aDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard error of triplicate samples.

^bDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard error of triplicate samples.

^cDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard error of triplicate samples.

^dDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard error of triplicate samples.

^eDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard error of triplicate samples.

Table 4 Tetracycline degradation constant rate k values at different temperatures[10]

Time in h	4 °C	37 °C	70 °C	100 °C
1	20 ± 4 ^a	50 ± 6 ^a	30 ± 6 ^a	60 ± 15 ^a
3	256 ± 32 ^e	400 ± 46 ^e	630 ± 81 ^e	860 ± 61 ^e
6	163 ± 17 ^{cd}	290 ± 23 ^{cd}	360 ± 17 ^{cd}	510 ± 46 ^d
12	116 ± 26 ^c	225 ± 12 ^c	300 ± 26 ^c	340 ± 32 ^c
24	50 ± 8 ^b	135 ± 20 ^b	160 ± 18 ^b	160 ± 02 ^b

^aDifferent letters indicate statistically significant differences at $P < 0.05$ according to a Turkey's honest significant difference *post hoc test*. Values are mean ± standard deviation of triplicate samples.

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FOOTNOTES

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